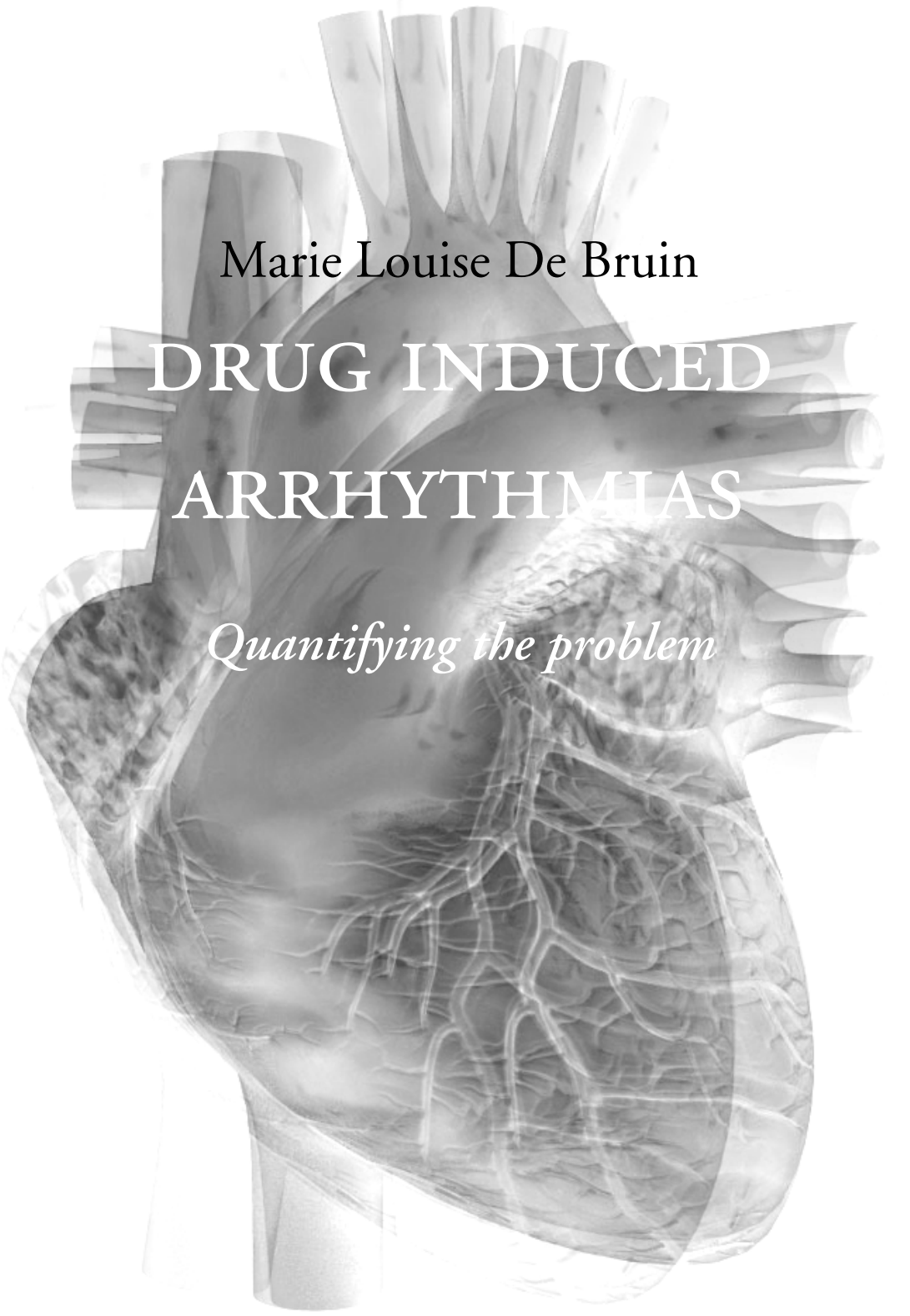


Marie Louise De Bruin

DRUG INDUCED ARRHYTHMIAS

Quantifying the problem

Cover design: Tom Frantzen

CIP-gegevens Koninklijke Bibliotheek, Den Haag

De Bruin, Marie Louise

Drug-induced arrhythmias, quantifying the problem / Marie Louise De Bruin
Thesis Utrecht - with ref.- with summary in Dutch
ISBN: 90-808203-3-4

DRUG-INDUCED ARRHYTHMIAS, QUANTIFYING THE PROBLEM

Geneesmiddel-geïnduceerde hartritmestoornissen,
kwantificering van het probleem
(met een samenvatting in het Nederlands)

Proefschrift ter verkrijging van de graad van doctor aan de Universiteit van Utrecht op gezag van de Rector Magnificus Prof. dr W.H. Gispen, ingevolge het besluit van het College voor Promoties in het openbaar te verdedigen op woensdag 1 december 2004 des namiddags om 14.30 uur

door

Marie Louise De Bruin
Geboren op 1 april 1974 te Haarlem

PROMOTORES

Prof. dr H.G.M. Leufkens
Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands

Prof. dr A.W. Hoes
Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands

The work in this thesis was performed at the Department of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences (Utrecht) and the Julius Center for Health Sciences and Primary Care (Utrecht), in collaboration with the PHARMO Institute (Utrecht), the Netherlands Pharmacovigilance Centre Lareb ('s-Hertogenbosch), the WHO-Uppsala Monitoring Centre (Uppsala, Sweden) and the Academic Medical Center (Amsterdam).
The research presented in this thesis was funded by the Utrecht Institute for Pharmaceutical Sciences, and an unrestricted grant from the Dutch Medicines Evaluation Board. The study presented in chapter 3.1 was funded by an unrestricted grant from Janssen Pharmaceutica NV, Beerse, Belgium.

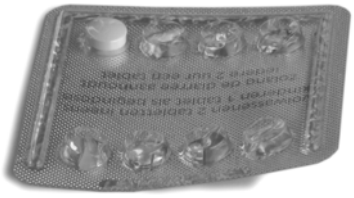
Financial support from the Netherlands Heart Foundation for the publication of this thesis is gratefully acknowledged.

Voor mijn ouders

CONTENTS

Chapter 1

INTRODUCTION



A 59-year-old man presented himself to the emergency department after playing handball, complaining of shortness of breath for 45 minutes associated with dizziness and upper extremity tingling. His medical history was significant only in relation to hypertension. He had had palpitations 10 years ago and was prescribed verapamil with complete resolution of symptoms. He still was taking verapamil 40mg twice daily, and two days previously he had taken two tablets of terfenadine 60mg for one day, for nasal congestion associated with hay fever. Initial physical examination revealed a well-developed, well-nourished man in mild distress. The patient was placed on a cardiac monitor, which revealed three episodes of Torsade de Pointes associated with shortness of breath and dizziness, but without loss of consciousness. He was given 2g magnesium which led to resolution of the arrhythmia. The QT-interval reverted to 0.36ms from 0.46ms during the episodes of Torsade de Pointes. The possibility of the arrhythmia being caused by a myocardial infarction, silent ischemia, electrolyte disturbance or liver disease was excluded. It was considered likely that the terfenadine lengthened the patient's QT-interval sufficiently to allow the increased sympathic tone produced from playing handball to trigger Torsade de Pointes [1].

This publication in 1997 was probably a pivotal case report that triggered public awareness about the seriousness of drug-induced arrhythmias. Syncope during initiation of quinidine therapy was already recognised in the 1920s [2], and cardiac effects of first-generation antihistamines [3, 4], antidepressants [5] as well as antipsychotics [6] had been described in the 1960s and 1970s. In addition, in the late 1980s and early 1990s the first few drugs had already been withdrawn from the market for their proarrhythmic potential (Table 1). However, this case report was the first proof that an apparently harmless drug, being sold without prescription, and used to treat a mild condition such as hay fever could cause a potentially fatal adverse reaction, even when the drug is taken in the recommended therapeutic dose, and without concomitant use of metabolism inhibiting drugs.

Since the publication of this case report, seven drugs, including terfenadine, have been taken off the market in parts of the world or worldwide, because of their potential to prolong the QTc-interval or even cause Torsade de Pointes arrhythmias

(Table 1). Over the last decade QTc-interval prolongation and Torsade de Pointes have been the single most common cause of withdrawal from or restriction of the use of drugs on the market, and it appears to be the latest 'epidemic' in drug regulatory affairs [7].

Although they have gained much attention during recent years, drug-induced arrhythmias have been in existence for centuries. Recently, Mari et al [8] hypothesised that Napoleon may have died from Torsade de Pointes arrhythmias. At the time of his death, the Emperor was exposed to three agents that could block cardiac potassium channels (arsenic, quinidine and antimony) as well as to two agents (mercury chloride and antimony potassium tartrate) which may cause gastrointestinal potassium loss predisposing to Torsade de Pointes.

Table 1 *Reasons for regulatory action of drugs with proarrhythmic potential* [7]

Drug	Indication	Year	Reason(s) for regulatory action
Prenylamine	Angina pectoris	1988	TdP*
Terodiline	Bladder instability	1991	QTc-prolongation and TdP
Encainide	Cardiac arrhythmia	1991	Proarrhythmic effects
Flosequinan	Heart failure	1993	Excess mortality, possibly due to arrhythmias
Terfenadine	Allergy	1998	QTc-prolongation and TdP
Sertindole	Schizophrenia	1998	QTc-prolongation and potential for TdP
Astemizole	Allergy	1999	QTc-prolongation and TdP
Grepafloxacin	Infection	1999	QTc-prolongation and TdP
Cisapride	Gastroparesis	2000	QTc-prolongation and TdP
Droperidol	Psychosis	2001	QTc-prolongation and TdP
Levacetylmethadol	Opioid dependence	2001	QTc-prolongation and TdP

**TdP: Torsade de Pointes*

WHY ARE DRUG-INDUCED ARRHYTHMIAS OF CONCERN?

Although drug-induced arrhythmias are very rare [9], they are nevertheless of concern. The following facts are central to the regulatory concern:

- Drug-induced arrhythmias are potentially fatal [10]
- They concern a broad range of widely used drugs, from different therapeutic classes [11, 12], and the number of drugs concerned continues to increase
- For the majority of the drugs, proarrhythmic potential was recognised only after approval [13], at a time when the drugs were already widely prescribed
- Most of the drugs are prescribed for otherwise relatively benign or low risk conditions, and some of the drugs are even available without prescription [14]
- Drug-drug interactions may substantially increase the proarrhythmic risk in some instances [15]

Regulators usually have to weigh the potential proarrhythmic risks of treatment against the benefits in the context of the potentially large numbers of exposed patients and availability of therapeutic alternatives, and have to estimate the public health impact of their decisions. When therapeutic alternatives are available, or the drugs causing concern are used to treat mild diseases (as in the case of astemizole and terfenadine), the decision to withdraw a drug from the market may be straightforward. Nevertheless, when the therapeutic equality of the alternatives is debatable (for example in the case of sertindole), or the disease treated is much worse than the potential adverse reaction (such as arsenic trioxide [16]), regulatory decision-making is much more complex.

In order to take appropriate regulatory measures, it is essential to have detailed information about several relevant aspects of the adverse reaction. The clinical problem should be described while some understanding of the physiological mechanism underlying the drug-induced disease would be useful, although this often remains unknown. In addition, epidemiological research is needed to quantify the magnitude of the problem and to identify patient groups at increased risk of the adverse reaction.

Figure 1 *ECG of an 83 year old female who developed Torsade de Pointes while on fluoxetine therapy*

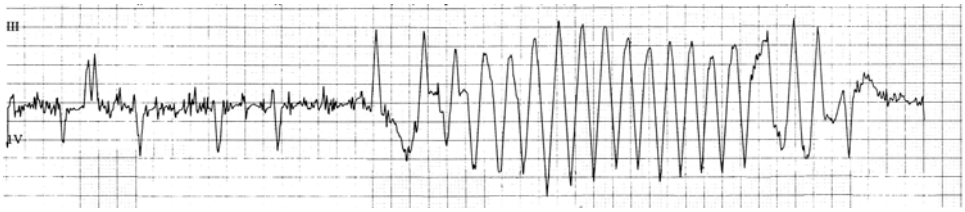
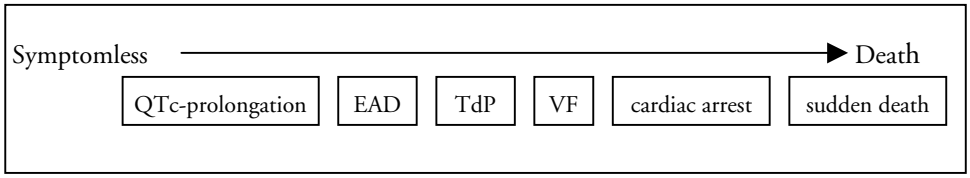


Figure 2 *Torsade: Rope molding, cable molding. A Norman molding enrichment like a twisted rope; any ornamental twist [17]. Example: Blauwbrug, Amsterdam*

Figure 3 *Drug-induced arrhythmias according to severity of clinical manifestations*



EAD: early afterdepolarisations, TdP: Torsade de Pointes, VF: ventricular fibrillation

CLINICAL MANIFESTATIONS, TREATMENT AND PHYSIOLOGICAL MECHANISM

Syncope during initiation of quinidine therapy was already recognised in the 1920s. It took until 1964, however, before this adverse reaction was recognised as polymorphic ventricular tachycardia [18]. In 1966, Dessertenne [19] introduced the term Torsade de Pointes to describe the peculiar appearance of a unique polymorphic form of ventricular tachycardia on the surface electrocardiogram [2] (Figure 1). The word 'Torsade' refers to an ornamental motif imitating twisted hairs or threads, as seen on classical architectural columns (Figure 2). 'Pointes' refers to points or peaks [20].

Although Torsade de Pointes can occur in many situations (such as heart block, as originally described), it is usually seen in patients with one of the congenital long-QT syndromes or in association with drug therapy [2].

Clinical manifestations of Torsade de Pointes, which is usually a transient tachyarrhythmia, may include palpitation. When Torsade de Pointes is sustained, symptoms caused by impaired cerebral circulation such as dizziness, syncope and/or seizures may be manifested. Torsade de Pointes subsequently degenerates into ventricular fibrillation in approximately 20% of cases and, not uncommonly, sudden death may occur. The overall mortality is approximately 10-17% [7].

Emergency therapy for drug-induced arrhythmias includes discontinuation of the culprit drug as well as other medications which may prolong the QTc-interval, suppression of early afterdepolarisations with magnesium sulphate, potassium chloride or lidocaine, and sedation. If needed, the basic heart rate can be increased, the patient can be defibrillated and β-blockers may be administered [21].

The mechanism underlying drug-induced arrhythmias has been (partly) unravelled in recent years. Through blockade of the HERG (human ether a go-go related gene) potassium channels in cardiac myocytes, drugs may decrease the rapid component of the delayed rectifier K^+ current (I_{Kr}), leading to a prolonged action potential, which manifests itself as a prolonged QTc-interval on the surface electrocardiogram [20]. HERG is the human variant of the 'ether a go-go' (EAG) locus of the *Drosophila melanogaster*. Fruit flies with a mutation in the EAG exhibit leg-shaking behaviour during ether anaesthesia, just like go-go dancers [22]. Prolongation of the cardiac action potential may be followed by early afterdepolarisations (EAD), which can in turn generate spontaneous or 'triggered' upstrokes [2]. When accompanied by the presence of a notably increased dispersion of repolarisation, this may induce re-entry and provoke Torsade de Pointes [20].
The effect of drugs on cardiac potassium channels is thought to be acute and dose-dependent. The effect disappears after the drug has been cleared from the body [23].

EPIDEMIOLOGY OF DRUG-INDUCED ARRHYTHMIAS

More than 200 pharmaceutical compounds have been associated with Torsade de Pointes arrhythmias in spontaneous adverse drug reaction reports gathered by the WHO Drug Monitoring Centre [9]. These drugs are often divided into anti-arrhythmic and non-antiarrhythmic drugs. As part of their therapeutic effect, anti-arrhythmic drugs (such as dofetilide and quinidine) prolong the QTc-interval [7]. Cardiac arrhythmias as a side effect of these drugs are not unexpected, and drug therapy is mostly started under electrocardiographic surveillance [24]. Cardiac arrhythmias induced by non-antiarrhythmic drugs are rare and not normally expected by the prescribing physicians. In this thesis we will almost exclusively focus on non-antiarrhythmic drugs.
In recent years several review articles on drugs which may cause cardiac arrhythmias were published. Some authors gave their expert opinion, summarising their current knowledge on the topic concerning a variety of drugs [9, 20, 25]. Others tried to classify drugs into categories according to clinical relevance or available evidence of the association between drug-use and adverse event [11, 26-29], a goal which is also pursued by the researchers of the center for education on research and therapeutics (CERT) at the University of Arizona Health Sciences Center, USA. CERT Arizona started two internet based registries for drug-induced arrhythmias (www.qtdrugs.org

and www.torsades.org) and provides an up-to-date list of medications reported to cause drug-induced arrhythmias [30]. For most drugs substantial evidence for a causal relationship between drug exposure and cardiac arrhythmias is still lacking. Since different definitions for relevant drug-induced arrhythmias are applied, the lists of drugs with proarrhythmic effects are rather heterogeneous (Appendix 1). Only six drugs are included in all five available lists: erythromycin, droperidole, haloperidole, pimozide, thioridazine and pentamidine. Most of these drugs are still on the market and widely used [11, 12].

For the majority of the studies in this thesis we use a list adapted from the listing of De Ponti et al [11]. Six of the 37 drugs are excluded because De Ponti et al state that clinical data do not provide a strong signal for the proarrhytmogenity of these drugs. This list was chosen because it applied the most objective method, i.e. a structurised literature search, using predefined terms.

Incidence of drug-induced arrhythmias

Proarrhythmic drugs may cause electrocardiographic changes, cardiac arrhythmias and sudden death. All these conditions can be studied as epidemiological outcomes. Changes from baseline QTc-interval following the administration of the drug have been studied extensively. However, the clinical relevance as well as the correct measurement of this early proarrhythmic signature is currently under debate [31].

The incidence of ventricular arrhythmias and sudden death among patients taking non-antiarrhytmic drugs is quite low. Estimations of the incidence of cardiac arrhythmias attributable to drug-use are often based on reporting rates of adverse drug reactions per total amount of drugs sold. Spontaneous reporting rates vary from 1 per 100,000 prescriptions for cisapride to 1 per 700,000 and 1 per 33 million prescriptions for astemizole and ciprofloxacin respectively [32-35]. Due to underreporting, spontaneous reports represent only a fraction of the true adverse events [36, 37]. Therefore, the true incidence of cardiac arrhythmias may be up to a factor 10 higher: 1 per 10,000 prescriptions. The incidence of chloramphenicol-induced aplastic anaemia, hydrochlorothiazide-induced pancreatitis, and angiotensin receptor blocker-induced eosinophilic nephritis are of similar magnitude [38].

SCOPE AND OUTLINE OF THE THESIS

Within the broad field of drug-induced arrhythmias, only a limited number of pharmacoepidemiological issues can be addressed in this thesis. The work concentrates on:

- Different methods of assessing the etiologic association between drug exposure and the occurrence of cardiac arrhythmias
- Identification of patients with an increased risk of drug-induced arrhythmias
- Development and testing of tools to protect patients against drug-induced arrhythmias
- Exploration of ways of incorporating molecular strategies into pharmacoepidemiological research on drug-induced arrhythmias
- Biases affecting results from pharmacoepidemiological database studies

In the past, studies on drug-induced arrhythmias were often performed on an ad-hoc basis after a safety issue arose [39-41]. Those studies mainly focused on the presence of an association, rather than on the magnitude of the effect and identification of high-risk groups. Quantification of the association and identification of high-risk groups will be the main focus of this thesis. In addition, methodological aspects and validity issues of epidemiological research on a rare adverse reaction, such as drug-induced arrhythmias, will be addressed in several chapters. This thesis will focus on non-antiarrhythmic drugs, for which the incidence of the adverse reaction is very low, poorly accepted, and due to its rarity a challenge to study.

In chapter 2 the risk of drug-induced arrhythmias is quantified using various data sources and several definitions of cardiac arrhythmias. Groups of patients prone to develop the adverse reaction are identified. In chapter 2.1 the association between antihistamine drugs and cardiac arrhythmias is determined using data from a spontaneous reporting system. In chapter 2.2 cardiac arrhythmias which require hospitalisation are studied, and in chapter 2.3 cardiac arrest requiring cardiopulmonary resuscitation in a hospital setting is studied as the outcome of interest.

Chapter 3 focuses on groups of patients at increased risk of drug-induced arrhythmias. In chapter 3.1 the influence of official warnings for potentially hazardous drug-drug interactions concerning proarrhythmogenicity among cisapride users on prescribing practice is studied. The study presented in chapter 3.2 aims to develop a decision tool to be applied in general practice to predict the risk of serious

ventricular arrhythmias and sudden death among diabetic patients taking non-antiarrhythmic proarrhythmic drugs.

Chapter 4 provides new insights into molecular strategies in research on drug-induced arrhythmias. In chapter 4.1 the feasibility of a pharmacogenetic study using spontaneous reporting data as a source to identify case patients is discussed. The study presented in chapter 4.2 links the preclinical molecular HERG-blocking properties of drugs to postmarketing drug safety data.

Chapter 5 addresses the validity of pharmacoepidemiological research on drug-induced arrhythmias and may be used to improve future research on this topic. Chapter 5.1 reports on the validity of hospital discharge diagnoses of cardiac arrhythmias, and in chapter 5.2 the potential influence of non-differential misclassification of exposure on the results of studies on drug-induced arrhythmias is discussed.

Chapter 6 provides a general discussion on options in study design, when studying rare, potentially fatal, adverse reactions, using drug-induced arrhythmias as a case example.

BIBLIOGRAPHICAL REFERENCES

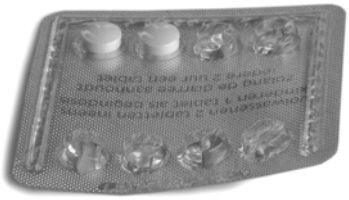
1. June RA, Nasr I. Torsades de pointes with terfenadine ingestion. *Am J Emerg Med.*1997;15:542-3.
2. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med.* 2004; 350: 1013-22.
3. Burrell ZL, Gittinger WC, Martinez A. Treatment of cardiac arrhythmias with hydroxyzine. *Am J Cardiol.* 1958; 1: 624-8.
4. Kahn A, Blum D. Possible role of phenothiazines in sudden infant death. *Lancet.*1979;314:364-5.
5. Freeman JW, Mundy GR, Beattie RR, Ryan C. Cardiac abnormalities in poisoning with tricyclic antidepressants. *Br Med J.* 1969; 2: 610-11.
6. Alexander CS. Cardiotoxic effects of phenothiazine and related drugs. *Circulation.* 1968; 38: 1014-5.
7. Shah RR. Pharmacogenetic aspects of drug-induced torsade de pointes: potential tool for improving clinical drug development and prescribing. *Drug Saf.* 2004; 27: 145-72.
8. Mari F, Bertol E, Fineschi V, Karch SB. Channelling the Emperor: what really killed Napoleon? *J R Soc Med.* 2004; 97: 397-9.
9. Darpo B. Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. *Eur Heart J Supplements.* 2001; 3 (suppl K): K70-K80.
10. Fung MC, Wu JH, Kwong K, Hornbuckle K, Muniz E. Evaluation of the profile of patients with QTc prolongation in spontaneous adverse event reporting over the past three decades - 1969-1998. *Pharmacoepidemiol Drug Saf.* 2000; 9: S24-S5.
11. De Ponti F, Poluzzi E, Vaccheri A, et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. *Br J Clin Pharmacol.* 2002; 54: 171-7.
12. Curtis LH, Ostbye T, Sendersky V, et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *Am J Med.* 2003; 114: 135-41.
13. Shah RR. Drug-induced prolongation of the QT interval: why the regulatory concern? *Fundam Clin Pharmacol.* 2002; 16: 119-24.
14. Sampey CS, Follin SL. Second-generation antihistamines: the OTC debate. *J Am Pharm Assoc (Wash).* 2001; 41: 454-7.
15. Michalets EL, Williams CR. Drug interactions with cisapride: clinical implications. *Clin Pharmacokinet.* 2000; 39: 49-75.
16. Unnikrishnan D, Dutcher JP, Garl S, Varshneya N, Lucariello R, Wiernik PH. Cardiac monitoring of patients receiving arsenic trioxide therapy. *Br J Haematol.* 2004; 124: 610-7.
17. LaChiusa C. *Buffalo Illustrated Architecture Dictionary.* Available at: http://ah.bfn.org/a/DCTNRY/r/rope.html; Accessed October 19, 2004.

18. Selzer A, Wray HW. Quinidine syncope. Paroxysmal ventricular fibrillation occurring during treatment of chronic atrial arrhythmias. *Circulation.* 1964; 30: 17-26.
19. Dessertenne F. La tachycardie ventriculaire à deux foyers opposés variables. *Arch Mal Coeur Vaiss.* 1966; 59: 263-72.
20. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart.* 2003; 89: 1363-72.
21. Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. *Prog Cardiovasc Dis.* 2003; 45: 415-27.
22. Karle CA, Kiehn J. An ion channel 'addicted' to ether, alcohol and cocaine: the HERG potassium channel. *Cardiovasc Res.* 2002; 53: 6-8.
23. van Haarst AD, van 't Klooster GA, van Gerven JM, et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. *Clin Pharmacol Ther.* 1998; 64: 542-6.
24. Freeland S, Worthy C, Zolnierz M. Initiation and monitoring of class III antiarrhythmic agents. *J Cardiovasc Electrophysiol.* 2003; 14: S291-5.
25. Doig JC. Drug-induced cardiac arrhythmias: incidence, prevention and management. *Drug Saf.* 1997; 17: 265-75.
26. De Ponti F, Poluzzi E, Montanaro N. Organising evidence on QT prolongation and occurrence of Torsades de Pointes with non-antiarrhythmic drugs: a call for consensus. *Eur J Clin Pharmacol.* 2001; 57: 185-209.
27. Crouch MA, Limon L, Cassano AT. Clinical relevance and management of drug-related QT interval prolongation. *Pharmacotherapy.* 2003; 23: 881-908.
28. Redfern WS, Carlsson L, Davis AS, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development.*Cardiovasc Res.* 2003; 58: 32-45.
29. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA.* 2003; 289: 2120-7.
30. Remich SA, Kilborn MJ, Woosley RL. The role of Internet-based registries in tandem with genetic screening for the study of drug-induced arrhythmias. *Curr Ther Res.* 2001; 62: 787-95.
31. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. *Prog Cardiovasc Dis.* 2001; 43: 1-45.
32. Barbey JT, Lazzara R, Zipes DP. Spontaneous adverse event reports of serious ventricular arrhythmias, QT prolongation, syncope, and sudden death in patients treated with cisapride. *J Cardiovasc Pharmacol Ther.* 2002; 7: 65-76.
33. Frothingham R. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. *Pharmacotherapy.* 2001; 21: 1468-72.

34. Lindquist M, Edwards IR. Risks of non-sedating antihistamines. *Lancet.* 1997; 349: 1322.
35. Ahmad S, Wolfe S. Cisapride and torsades de pointes. *Lancet.* 1995; 345: 508.
36. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ('black triangle') drugs in general practice: observational study. *Br Med J.* 1998; 317: 119-20.
37. Lumley CE, Walker SR, Hall GC, Staunton N, Grob PR. The under-reporting of adverse drug reactions seen in general practice. *Pharmaceut Med.* 1986; 1: 205-12.
38. Fenichel RR, Malik M, Antzelevitch C, et al. Drug-induced torsades de pointes and implications for drug development. *J Cardiovasc Electrophysiol.* 2004; 15: 475-95.
39. Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med.* 1999; 107: 356-62.
40. Staffa JA, Jones JK, Gable CB, Verspeelt JP, Amery WK. Risk of selected serious cardiac events among new users of antihistamines. *Clin Ther.* 1995; 17: 1062-77.
41. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999; 47: 307-13.

Chapter 2

QUANTIFICATION OF THE RISK OF DRUG-INDUCED ARRHYTHMIAS



Chapter 2.1

NONSEDATING ANTIHISTAMINE DRUGS AND CARDIAC ARRHYTHMIAS, BIASED RISK ESTIMATES FROM SPONTANEOUS REPORTING SYSTEMS?

Marie L De Bruin [1], Eugene P van Puijenbroek [1,2], Toine CG Egberts [1,3], Arno W Hoes [4], Hubert GM Leufkens [1]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaco-epidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands
[3] Hospital Pharmacy Midden-Brabant, TweeSteden and St. Elisabeth Hospital, Tilburg, the Netherlands
[4] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands

British Journal of Clinical Pharmacology. 2002; 53: 370-374

SUMMARY

Objective: This study made use of spontaneous reports of adverse events to estimate the risk of developing cardiac arrhythmias due to the systemic use of nonsedating antihistamine drugs and compared the risk estimate before and after the regulatory action to recall the over-the-counter status of some of these drugs.

Methods: All suspected adverse drug reactions (ADRs) reported until July 1999 to the Netherlands Pharmacovigilance Foundation Lareb were used to calculate the ADR reporting odds ratio, defined as the ratio of exposure odds among reported arrhythmia cases, to the exposure odds of other ADRs (noncases), adjusted for gender, age, reporter, year of reporting and comedication, stratified for the periods before and after the government decision in the Netherlands.

Results: Seven hundred and thirty-seven cases of arrhythmia were reported, of which there were 43 instances where patients were using nonsedating antihistamines. In general, nonsedating antihistamines are associated with cardiac arrhythmia to a higher extent in comparison with other drugs (ADR reporting odds ratio 2.05, 95%CI 1.45 to 2.89). The association between arrhythmias and nonsedating antihistamine drugs calculated before 1998 was not significantly higher than 1 (OR 1.37, 95%CI 0.85 to 2.23), whereas the risk estimate calculated after the government decision significantly differed from 1 (OR 4.19, 95%CI 2.49 to 7.05).

Conclusion: Our data suggest that nonsedating antihistamines may have an increased risk of inducing arrhythmias. Our findings, however, strongly suggest that the increased risk identified can, at least partly, be explained by reporting bias as a result of publications on - and mass media attention paid to - antihistamine-induced arrhythmias.

INTRODUCTION

Cardiac arrhythmia, notably associated with QTc-interval prolongation, has been one of the most important adverse drug reactions leading to regulatory action in recent years. Prolongation of the QTc-interval may lead to fatal ventricular arrhythmias, such as Torsade de Pointes [1], and is associated with increased mortality [2, 3]. Therefore, prevention of drug-induced QTc-prolongation is of utmost importance.

The use of nonsedating antihistamines, widely used to treat allergies, has been associated with arrhythmias in various case reports [4-7]. The absolute risk of developing ventricular arrhythmias as a result of the use of these drugs is found to be very low: approximately 1 per 57,000 prescriptions [8].

One of the available strategies to identify rare adverse events is to evaluate spontaneous reports of adverse drug reactions (ADRs) using the concept of 'reaction proportion signalling' first described by Finney [9] and consequently applied by several others [10-12]. This method includes the calculation of an adverse drug reaction reporting odds ratio, which is used as an estimate of the risk of developing a certain event for patients using the index drug(s), relative to patients using reference drug(s). A large odds ratio indicates that the studied drug represents a disproportionate share of the reports of the adverse reaction of interest compared with the share of reports of other adverse reactions [9]. In other words, the drug is associated with the specific adverse reaction. The validity of the method has, however, been criticised on account of the fact that reports on adverse reactions on a voluntary basis can be biased. So far, most concern has been expressed in relation to the persistent feature of underreporting. However, attention in the media may also result in selective reporting of certain adverse events [13]. In the Netherlands, a great deal of attention was paid to antihistamine-induced arrhythmias at the beginning of 1998 when the Dutch government, in accordance with many other countries decided that, for safety reasons, the former over-the-counter drugs terfenadine and astemizole could no longer be obtained without a prescription.

This study made use of the Dutch spontaneous reporting system of adverse events to estimate the risk of developing cardiac arrhythmias due to the use of nonsedating antihistamine drugs and compared the risk estimate before and after the government decision to recall the over-the-counter status of some of these drugs to assess whether increased media attention influenced the risk estimates.

METHODS

Source

The Netherlands Pharmacovigilance Centre Lareb runs the spontaneous adverse drug reaction reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Its objective is to collect and analyse reports of the adverse reactions of medicines and hence signal new adverse drug reactions as soon as possible [14].

ADRs are provided by health care professionals on a voluntary basis and provide relevant clinical information about the patient (age, gender), ADR, medication used at time of the event ('suspected' and 'concomitant'), source (physician or pharmacist) and year of reporting. Each report is reviewed by a qualified assessor (physician or pharmacist) and is coded according to the Adverse Drug Reaction Terminology of the World Health Organisation (WHO-ART) [15]. All ADRs reported from January 1986 until July 1999 to the Netherlands Pharmacovigilance Centre Lareb were used for this study.

Selection of cases and noncases

The method of 'reaction proportion signalling' compares the use of certain drugs among cases (those with a defined adverse reaction) and noncases (all other reported adverse reactions). In our study, all ADRs coded by means of the WHO-ART as 'Heart rate and rhythm disorders' (System Organ Class 1030) were defined as cases. All other reports were defined as noncases.

Exposure definition

Cases and noncases were considered exposed, when one of the drugs used on the index date was a nonsedating antihistamine drug for systemic use (acrivastine, astemizole, cetirizine, ebastine, fexofenadine, loratadine, mizolastine or terfenadine). No distinction was made between 'suspected' and 'concomitant' medication.

Potential confounders

Possible risk factors for arrhythmias that could confound the association included advanced age [8], gender [16], history of cardiovascular disease, use of several groups of other drugs, including those known to be able to prolong the QTc-interval, those that may cause electrolyte disturbances, those that can inhibit the metabolism of the suspected drugs [17] and cardiotonic drugs [18].

Data analysis

ADR reporting odds ratios were calculated for the comparison of exposed and nonexposed patients with respect to the risk of developing cardiac arrhythmias. These ratios are defined as the ratio of exposure odds among reported arrhythmia cases to the exposure odds of all other ADRs. Multivariable logistic regression analysis was performed to adjust for the following potential confounders: type of health care professional who reported the ADR (pharmacist or physician), year of reporting, age and gender of the patient involved, drugs known to be able to cause QTc-prolongation (antiarrhythmics, antipsychotics, bepridil, chloroquine, cisapride, fluoroquinolone antibiotics, halofantrine, macrolide antibiotics, pentamidine, probucol, quinine, tricyclic antidepressants, trimethoprim), other cardiac therapies (ATC code C01A, C01C, C01D, C01E), antihypertensive drugs (ATC code C02), potassium-sparing diuretics (ATC code C03AB, C03BB, C03CB, C03D, C03E), non potassium-sparing diuretics (ATC code C03AA, C03AH, C03BA, C03BK, C03CA, C03CC), peripheral vasodilatating drugs (ATC code C04), β-blocking agents (ATC code C07), calcium channel blocking agents (ATC code C08), drugs acting on the RAAS system (ATC code C09), lipid-lowering drugs (ATC code C10), laxatives (ATC code A06), systemic corticosteroids (ATC code H02), systemic β-agonists (ATC code R03C) and inhibitors of cytochrome P450-3A4 (Appendix 3).

The overall ADR reporting odds ratio was calculated as well as the ratios before (<1998) and after the regulatory action (≥1998). Odds ratios were expressed as point estimates with 95% confidence intervals (95%CI). All statistical analyses were performed using SPSS 9.0.

RESULTS

Until July 1999, Lareb received 737 case reports of cardiac arrhythmias, categorised according to WHO-ART as system organ class 1030: 'heart rate and rhythm disorders' (3.0% of all included reports n=24,414). The most commonly reported arrhythmia was 'palpitation' (71.2%), followed by 'tachycardia' (8.4%) and 'arrhythmia not otherwise specified' (6.4%) (Table 1). On average, cases were a little older than the noncases (51.2 sd 17.4 *vs* 50.3 sd 19.7) and cases were more often female (67.3% *vs* 64.3%). Forty-three of the cases (5.8%) took a nonsedating antihistamine drug on the index date compared with only 2.9% of the noncases. In

most instances this nonsedating antihistamine was terfenadine (44.2%), followed by cetirizine (23.3%) and loratadine (16.3%).

Characteristics of the cases and noncases are presented in Table 2. The number of the various nonsedating antihistamine drugs used by the cases on the index date is listed in Table 3.

Table 1 *Number of adverse drug reactions reported to Lareb until July 1999 categorised as 'heart rate and rhythm disorders', sorted by type of arrhythmia*

Type of arrhythmia	Subcode	Number	%
Palpitation	221	525	71.2%
Tachycardia NOS*	224	62	8.4%
Arrhythmia NOS*	433	47	6.4%
Bradycardia	208	31	4.2%
Fibrillation atrial	439	19	2.6%
Extrasystoles	438	16	2.2%
Fibrillation ventricular	440	9	1.2%
Tachycardia supraventricular	229	8	1.1%
AV block	431	5	0.7%
Cardiac arrest	437	5	0.7%
QTc prolonged	1361	3	0.4%
Bundle branch block	436	2	0.3%
Torsades de Pointes	1431	2	0.3%
Arrhythmia ventricular	435	1	0.1%
Heart block	441	1	0.1%
Tachycardia ventricular	230	1	0.1%
Total		737	100%

* *NOS: Not otherwise specified*

Table 2 *Characteristics of cases and noncases*

	Cases n=737	Noncases n=23,677
Age		
< 20	3%	7%
20-39	24%	23%
40-59	38%	34%
60-79	33%	32%
≥ 80	3%	5%
Female gender	67%	64%
Reported by pharmacist	27%	29%
Year		
1986-1987	5%	8%
1988-1989	7%	9%
1990-1991	7%	8%
1992-1993	10%	11%
1994-1995	16%	18%
1996-1997	31%	27%
1998-1999	24%	20%
Nonsedating antihistamines	6%	3%
Comedication		
CYP3A4 inhibitors	12%	13%
CYP3A4 inhibitors and nonsedating antihistamines	1%	< 1%
QTc-prolonging drugs	14%	13%
Other cardiac drugs	7%	6%
Antihypertensive drugs	2%	2%
Potassium-sparing diuretics	4%	5%
Non potassium-sparing diuretics	9%	7%
Peripheral vasodilatating drugs	1%	1%
β-blocking agents	15%	12%
Calcium channel blocking agents	13%	8%
Drugs acting on the RAAS system	13%	11%
Lipid-lowering drugs	6%	7%
Laxatives	2%	3%
Systemic corticosteroids	4%	3%
Systemic β-agonists	2%	1%

Table 3 *Number of reports of arrhythmias associated with various nonsedating antihistamines*

Antihistamine	Number	%
Terfenadine	19	44.2%
Cetirizine	10	23.3%
Loratadine	7	16.3%
Fexofenadine	4	9.3%
Mizolastine	2	4.7%
Ebastine	1	2.3%
Total	43	100%

Nonsedating antihistamines were associated with reports of arrhythmia to a greater extent in comparison with other drugs (crude ADR reporting odds ratio 2.10, 95%CI 1.53 to 2.89). This did not essentially change after adjustment for potential confounding factors (OR 2.05, 95%CI 1.45 to 2.89). Concomitant use of CYP3A4 inhibitors did not modify the effect the nonsedating antihistamines significantly (adjusted OR nonsedating antihistamines plus CYP3A4 inhibitors 1.53, 95%CI 0.60 to 3.91). After stratification for time before or after regulatory action, the adjusted ADR reporting odds ratios considerably changed. There was no association between the use of nonsedating antihistamines before January 1, 1998 (adjusted OR 1.37, 95%CI 0.85 to 2.23). However, after the regulatory action, there was a clear association between the use of nonsedating antihistamines and reports of cardiac arrhythmias (adjusted OR 4.19, 95%CI 2.49 to 7.05). The results of the logistic regression analysis are presented in Table 4.

Table 4 *Results of logistic regression analysis, overall and before and after the regulatory action in 1998; ADR reporting odds ratios and 95% confidence intervals*

	Crude OR (95%CI)	Adjusted OR (95%CI)
Overall	2.10 (1.53 - 2.89)	2.05 (1.45 - 2.89)
Before January 1, 1998	1.36 (0.86 - 2.15)	1.37 (0.85 - 2.23)
After January 1, 1998	3.83 (2.41 - 6.09)	4.19 (2.49 - 7.05)

DISCUSSION

The overall reporting odds ratios we calculated from our data suggest that the systemic use of nonsedating antihistamines may be associated with an increased risk of cardiac arrhythmias, as also known from other sources. However, after stratification for the period before or after January 1, 1998 as a proxy for the absence and presence for major attention in the media for nonsedating antihistamine-induced cardiac arrhythmias, striking differences between the two stratum-specific risk estimates were observed. The association between cardiac arrhythmias and nonsedating antihistamines was statistically significant only for the period after January 1, 1998. Mass media attention appears to have biased the risk estimates after January 1, 1998.

The fact that ADRs are being reported on a voluntary basis remains the main problem, since whether an ADR will be reported depends on many factors. In general ADRs are underreported [19]. Therefore the number of reported adverse events per sold amount of drugs or per exposed number of patients in a certain area will always be an underestimation of the underlying problem. Selective under- and overreporting of certain ADRs within the overall underreporting can lead to misinterpretations when comparing drugs with respect to ADRs. ADRs more likely to be reported than others are ADRs of relatively new drugs [13, 20], severe ADRs [13, 21] and ADRs which are not listed in the summary of product characteristics [21]. In addition, selective reporting may occur as a result of attention in the media of a certain ADR [13], as was illustrated by the findings of our study. When more health care professionals are aware of a certain ADR, more will obviously have the tendency to notice this ADR and hence to report it.

Another factor strengthening this finding is supported by taking a closer look at ADRs of terfenadine only. The majority of publications in the medical literature on antihistamine-induced arrhythmias were published during our study period, with the number increasing over time. These publications may again have caused an increase in vigilance for such events among health care professionals, as was shown before [22]. We investigated whether there was a time trend in the arrhythmia ADR reports associated with the use of terfenadine and indeed found an increase of these reports over time in our database (Pearson χ^2-test for trend, p=0.001).

We were not able to gather further clinical information about the arrhythmia cases from reporting health care professionals, and therefore were not able to correct for misclassification regarding the outcome.

It may be argued that the broad definition of arrhythmias we used, including rather nonspecific rhythm disorders such as palpitation, tachycardia or non-specified arrhythmia, may have influenced our results. This broad definition may have diluted the association found, since not only specific validated QTc-interval related arrhythmias were included. In contrast, we think that this outcome definition enabled us to study the effect of media attention on specific reporting in more detail than if we had only included the specific cases. We now included reports from health care professionals who are not able to diagnose a specific type of arrhythmia (such as general practitioners or pharmacists), but may well be influenced by the media attention.

In conclusion, our data suggest that the systemic use of nonsedating antihistamines may be associated with an increased risk of developing cardiac arrhythmias. Our findings, however, strongly suggest that the increased risk identified may, at least partly, be explained by reporting bias as a result of publications on - and mass media attention paid to - antihistamine-induced arrhythmias.

We suggest that this method of reaction proportion signalling used to relate adverse reactions to certain drugs should be applied cautiously while taking into account the dynamics of risk communication, regulatory action, and other erratic features of the pharmaceutical marketplace over time.

BIBLIOGRAPHICAL REFERENCES

1. Moss AJ. The QT interval and torsade de pointes. *Drug Saf.* 1999; 21: 5-10.
2. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation.* 1991; 84: 1516-23.
3. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J.* 1999; 20: 278-84.
4. Good AP, Rockwood R, Schad P. Loratadine and ventricular tachycardia. *Am J Cardiol.* 1994; 74: 207.
5. Monahan BP, Ferguson CL, Killeavy ES, Lloyd BK, Troy J, Cantilena LR, Jr. Torsades de pointes occurring in association with terfenadine use. *JAMA.* 1990; 264: 2788-90.
6. Pinto YM, van Gelder IC, Heeringa M, Crijns HJ. QT lengthening and life-threatening arrhythmias associated with fexofenadine. *Lancet.* 1999; 353: 980.
7. Simons FE, Kesselman MS, Giddins NG, Pelech AN, Simons KJ. Astemizole-induced torsade de pointes. *Lancet.* 1988; 2: 624.
8. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999; 47: 307-13.
9. Finney DJ. Systemic signalling of adverse reactions to drugs. *Methods Inf Med.* 1974; 13: 1-10.
10. Stricker BH, Tijssen JG. Serum sickness-like reactions to cefaclor. *J Clin Epidemiol.* 1992; 45: 1177-84.
11. Egberts AC, Meyboom RH, De Koning FH, Bakker A, Leufkens HG. Non-puerperal lactation associated with antidepressant drug use. *Br J Clin Pharmacol.* 1997; 44: 277-81.
12. Van Puijenbroek EP, Egberts AC, Meyboom RH, Leufkens HG. Signalling possible drug-drug interactions in a spontaneous reporting system: delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazole. *Br J Clin Pharmacol.* 1999; 47: 689-93.
13. Milstien JB, Faich GA, Hsu JP, Knapp DE, Baum C, Dreis MW. Factors affecting physician reporting of adverse drug reactions. *Drug Inf J.* 1986; 20: 157-64.
14. de Koning GHP. *A regionalized spontaneous surveillance program for adverse drug reactions as a tool to improve pharmacotherapy [thesis]*. Utrecht: Utrecht University, 1993.
15. WHO. *International monitoring of adverse reactions to drugs: adverse reaction terminology*. Uppsala, Sweden: WHO Collaborating Centre for International Drug Monitoring, 1992.
16. Drici MD, Knollmann BC, Wang WX, Woosley RL. Cardiac actions of erythromycin: influence of female sex. *JAMA.* 1998; 280: 1774-6.

17. Woosley RL, Chen Y, Freiman JP, Gillis RA. Mechanism of the cardiotoxic actions of terfenadine. *JAMA.* 1993; 269: 1532-6.
18. Bouvy ML, Heerdink ER, De Bruin ML, Herings RM, Leufkens HG, Hoes AW. Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med.* 2000; 160: 2477-80.
19. Lumley CE, Walker SR, Hall GC, Staunton N, Grob PR. The under-reporting of adverse drug reactions seen in general practice. *Pharmaceut Med.* 1986; 1: 205-12.
20. Weber JCP. Epidemiology of adverse drug reactions to nonsteroidal antiinflammatory drugs. In: Rainsford KD, Velo GP, eds. *Adv Inflamm Res*. New York: Raven Press,1984:1-7.
21. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ('black triangle') drugs in general practice: observational study. *Br Med J.* 1998; 317: 119-20.
22. Lindquist M, Edwards IR. Risks of non-sedating antihistamines. Lancet. 1997; 349: 1322.

Chapter 2.2

QT_C-PROLONGING DRUGS AND HOSPITALISATIONS FOR CARDIAC ARRHYTHMIAS

Marie L De Bruin [1,2], Arno W Hoes [2], Hubert GM Leufkens [1]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaco-epidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands

The American Journal of Cardiology. 2003; 91: 69-73

SUMMARY

Objective: Cardiac arrhythmias as an adverse reaction of non-antiarrhythmic drugs has been an issue of growing importance during the past few years. In this population based study, we evaluated the risk of serious cardiac arrhythmias during the use of several non-antiarrhythmic QTc-prolonging drugs in day-to-day practice, and subsequently focused on several specific groups of patients who could be extremely vulnerable to drug-induced arrhythmias.

Methods: We performed a case-control study in which patients (cases), hospitalised for nonatrial cardiac arrhythmias from 1987 to 1998, were compared with their matched controls regarding current use of QTc-prolonging drugs. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariable conditional logistic regression, adjusting for potential confounding factors. Data were obtained from the PHARMO record linkage system.

Results: We identified 501 cases, 39 of whom used QTc-prolonging drugs. A statistically nonsignificant increased risk of arrhythmias (OR 1.2, 95%CI 0.8 to 1.9) was observed in patients who received QTc-prolonging drugs. A clearly increased risk of arrhythmias was, however, found in patients with a history of asthma (OR 9.9, 95%CI 1.0 to 100) and in patients concomitantly using potassium-lowering drugs (OR 5.3, 95%CI 1.1 to 25.9).

Conclusion: Our data do not suggest that there is a strong overall association between the use of QTc-prolonging drugs and hospitalisation for cardiac arrhythmias in the population at large. However, there appears to be clinically relevant association in patients with a history of asthma and patients taking potassium-lowering drugs. The use of QTc-prolonging drugs should therefore be either avoided or monitored closely in these specific patients.

INTRODUCTION

Cardiac arrhythmias as an adverse reaction of non-antiarrhythmic drugs has been an issue of growing importance in medical science during the past few years, resulting in regulatory action concerning several drugs [1]. Because of the seriousness of this adverse reaction, regulatory action has sometimes already been taken after a few case reports, before the actual risk has been quantified in large population-based studies. For only a few of all QTc-prolonging drugs, studies have unequivocally shown a causal relation between the use of the drugs and the occurrence of cardiac arrhythmias. The use of antihistamines has been associated with an increased risk of cardiac arrhythmias [2]. In contrast, no increased risk of serious rhythm disorders was observed in patients who took cisapride [3], although its use has been linked to the occurrence of cardiac arrhythmias in several case reports [4, 5]. In this population based study, we evaluated the risk of serious cardiac arrhythmias and the use of several non-antiarrhythmic QTc-prolonging drugs in day-to-day practice. Subsequently, we focused on several specific groups of patients who may be quite vulnerable to drug-induced arrhythmias.

METHODS

Setting

Data were obtained from the PHARMO record linkage system (Utrecht, the Netherlands), which contains drug-dispensing records from community pharmacies and linked hospital discharge records of a defined population of approximately 330,000 residents of 8 medium-sized cities in the Netherlands.

The computerised drug-dispensing histories contained data on the type and quantity of the dispensed drug, type of prescriber, dispensing date, and prescribed dose and daily regimens. Drugs were coded according to the Anatomical Therapeutic Chemical Classification. Hospital discharge records were coded according to the International Classification of Diseases, 9th revision, clinical modification.

Design

We conducted a case-control study in which patients were compared with their matched controls regarding current exposure to QTc-prolonging drugs. Cases were defined as patients hospitalised for nonatrial cardiac arrhythmias (ventricular or non-

specified) for the first time from 1987 to 1998. We only used primary hospital discharge records to exclude patients with noniatrogenic conditions, which may have been caused by myocardial infarction or heart failure, as much as possible. Controls were sampled from all noncases present in the PHARMO cohort on the hospitalisation date of the corresponding case (index date). Controls were matched according to age (5 year bands), gender and practice area in a 1:4 ratio. Cases as well as controls had to be in the PHARMO population at least 1 year before the index date.

Exposure definition

Current exposure to QTc-prolonging drugs was investigated. These included non-sedating antihistamines [2], classic as well as atypical antipsychotics [6], tricyclic and tetracyclic antidepressants [7], ketanserin [8], cisapride [3, 9], halofantrine [10], pentamidine [11], macrolide antibiotics (erythromycin and clarithromycin [12, 13]), fluoroquinolones [14], cotrimoxazole [15], glibenclamide [16] and probucol [17].

A patient was defined as a current user if the index date fell between the dispensing date and the theoretical end date of the prescription. The theoretical end date equals the dispensing date plus the legend duration of drug use, the latter being calculated by dividing the number of units dispensed by the prescribed daily dose. The legend of duration of drug use is extended with a 10% surplus in order to control for irregular drug use or early drug collection from the pharmacy.

High dosage (either caused by pharmacokinetic drug-drug interactions [9] or overdosing [18]) may be a risk factor for drug-induced arrhythmias. Furthermore, the duration of use may influence the risk of drug-induced arrhythmias. Dosage was calculated as standard doses (defined daily doses) per day. For patients using drugs which can inhibit metabolism (CYP3A4 for cisapride, some antihistamines and antidepressants, CYP2D6 for some antipsychotics) the doses of the QTc-prolonging drugs were multiplied by a factor 2, because concomitant use of these inhibitors increases blood plasma levels. The multiplication factor was an average of increases in maximum plasma concentrations found in pharmacokinetic studies [9, 19, 20]. Duration of use was only calculated for chronic therapies (excluding antihistamines and antibiotics) as days of use since first prescription. If more than one QTc-prolonging drug was taken at the index date, individual doses were added up and the shortest duration of use was taken.

Potential confounders

The association between the use of QTc-prolonging drugs and hospitalisation for cardiac arrhythmias in this population based study may be confounded by secondary factors which were associated with both the exposure and the outcome, such as confounding by indication [21]. We therefore adjusted the calculated associations for concomitant use of drugs which can lower blood potassium levels (non potassium-sparing diuretics [22], laxatives [23, 24], corticosteroids for systemic use [25] and systemic β-agonists [25, 26]). We also adjusted for current treatment for arrhythmias, number of hospitalisations in the year before the index date, history of cardiac disease, asthma [27], and diabetes mellitus [28]. To control for the last 3 factors, proxies obtained from our data were used (≥ 2 previous prescriptions for cardiac, antidiabetic, or asthma/chronic obstructive pulmonary disease drugs, and/or previous hospitalisation for ischaemic heart disease, heart failure, coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty, and diabetic causes, or asthma).

Effect modification

The risk of hospitalisation for drug-induced arrhythmias may differ among several subpopulations of our study population. We investigated whether the risk differed between gender, age groups (± 65 years) and patients with and without several diseases (asthma, diabetes mellitus, cardiac disease) or possible interfering medication (potassium-lowering drugs, antiarrhythmic drugs).

Data analysis

Odds ratios (OR) and 95% confidence intervals (CI) were calculated using conditional logistic regression. All statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, Illinois).

RESULTS

During the study period from 1987 to 1998, a total of 501 cases of ventricular or non-specified cardiac arrhythmia were identified in the study population. This corresponds to an incidence of approximately 16 new cases per 100,000 inhabitants per year. The most commonly reported arrhythmia was 'Other specified cardiac dysrhythmias', followed by 'Cardiac dysrhythmia, unspecified' and 'Paroxysmal ventricular tachycardia' (Table 1).

Table 1 *Number of various hospitalisations for ventricular and non-specified cardiac arrhythmias in PHARMO 1987 to 1998*

ICD-code	Arrhythmia	Number	%
427.1	Paroxysmal ventricular tachycardia	90	18.0%
427.2	Paroxysmal tachycardia, unspecified	6	1.2%
427.41	Ventricular fibrillation	46	9.2%
427.42	Ventricular flutter	1	0.2%
427.5	Cardiac arrest	22	4.4%
427.60	Premature beats, unspecified	2	0.4%
427.69	Other (ventricular) premature beats	19	3.8%
427.89	Other specified cardiac dysrhythmias	199	39.7%
427.9	Cardiac dysrhythmia, unspecified	116	23.2%
	Total	501	100.0%

ICD= International Classification of Diseases, 9th edition

Approximately 57% of the cases were male and the mean age was approximately 65 years. Thirty-nine patients (7.8%) were on a QTc-prolonging drug on the index date compared with 6.0% of the controls. Two patients and three controls were also receiving drugs which inhibited cytochrome P450 metabolism.

Characteristics of the cases and controls are presented in Tables 2 and 3. Compared with the controls, more patients had a history of cardiac disease, were hospitalised in the year before the index date, and took antiarrhythmic medication or drugs which could lower blood potassium levels at the index date.

Compared with non-users, patients who were using QTc-prolonging drugs more often had a history of diabetes (34% *vs* 10%) or cardiac disease (40% *vs* 31%), were hospitalised more often in the year before the index date (26% *vs* 16%), and took

potassium-lowering drugs more often (24% *vs* 17%). These patients were also significantly older than the non-users (69 *vs* 65 years, respectively).

Current use of any QTc-prolonging drug was not statistically significantly associated with an increased risk of hospitalisation for cardiac arrhythmias. This estimate did not change after adjustment for potential confounding factors (adjusted OR 1.2, 95%CI 0.8 to 1.9). Patients using higher dosages (> 1 defined daily dose) appeared to be slightly more at risk than patients taking lower dosages (≤1 defined daily dose) compared with non-users (adjusted OR 1.4, 95%CI 0.6 to 3.2 *vs* OR 1.2, 95%CI 0.7 to 1.9). Also, the risk of drug-induced arrhythmias appears to occur within the first 2 months of use (adjusted OR 3.4, 95%CI 1.1 to 10.3). The risk in patients using their long-term medication for > 2 months was 1.0 (95%CI 0.6 to 1.7). When looking at individual drug classes, the association between use and hospitalisation for cardiac arrhythmias was most pronounced for fluoroquinolones (adjusted OR 4.2, 95%CI 1.0 to 17.7). The 95% confidence limits of this estimate, however, are relatively wide.

Table 2 *Main characteristics of patients hospitalised for cardiac arrhythmias and their matched controls*

	Cases n=501		Controls n=2,004	
	Number	%	Number	%
Gender male	286	57.1%	1144	57.1%
Age (mean, sd)	64.9	15.0%	64.9	15.0%
Year of index date				
1987-1990	97	19.4%	388	19.4%
1991-1994	168	33.5%	672	33.5%
1995-1998	236	47.1%	944	47.1%
Comorbidity				
History of diabetes mellitus	66	13.2%	225	11.2%
History of asthma	81	16.2%	347	17.3%
History of cardiac disease*	298	59.5%	484	24.2%
Hospitalisation for any reason in year before*	152	30.3%	261	13.0%
Medication				
Current use of any QTc-prolonging drug	39	7.8%	120	6.0%
Current use of antiarrhythmics*	111	22.2%	104	5.2%
Current use of any potassium-lowering drug*†	125	25.0%	300	15.0%

* *Statistically significant difference at α=0.05*

† *Cases were taking significantly more non potassium-sparing diuretics*

Table 3 *Current use of specific QTc-prolonging drugs among cases and controls*

	Cases n=501		Controls n=2,004	
	Number	%	Number	%
Second generation antihistamines	3	0.6%	20	1.0%
Classic antipsychotics	6	1.2%	20	1.0%
Atypical antipsychotics	1	0.2%	1	< 0.1%
Tri- or tetracyclic antidepressives	8	1.6%	37	1.8%
Cisapride	3	0.6%	8	0.4%
Fluoroquinolones*	5	1.0%	4	0.2%
Cotrimoxazole	2	0.4%	8	0.4%
Glibenclamide	13	2.6%	29	1.4%
Any QTc-prolonging drug †	39	7.8%	120	6.0%

* *Statistically significant difference at α=0.05*

† *Some patients were taking more than one QTc-prolonging drug, numbers do not add up*

Table 4 *Adjusted odds ratios (OR) and 95% confidence intervals (CI) of cardiac arrhythmias in subgroups of users of QTc-prolonging drugs*

Subgroup	OR	(95%CI)
Overall	1.2	(0.8 - 1.9)
Men	1.1	(0.6 - 2.0)
Women	1.4	(0.8 - 2.7)
Age < 65	0.7	(0.3 - 1.8)
Age ≥ 65	1.6	(1.0 - 2.6)
History of diabetes mellitus	1.1	(0.1 - 9.5)
No history of diabetes mellitus	1.2	(0.7 - 2.1)
History of asthma	9.9	(1.0 - 100)
No history of asthma	1.0	(0.6 - 1.6)
History of cardiac disease	1.5	(0.8 - 2.9)
No history of cardiac disease	- *	
Current use of any potassium-lowering drug	5.3	(1.1 - 25.9)
No current use of potassium-lowering drugs	1.3	(0.8 - 2.1)
Current use of antiarrhythmic drugs	1.7	(0.2 - 13.6)
No current use of antiarrhythmic drugs	1.3	(0.8 - 2.3)

**Not possible to calculate because of lack of power*

Of the subgroups of patients studied, patients with a history of asthma (adjusted OR 9.9, 95%CI 1.0 to 100) and those taking potassium-lowering drugs (adjusted OR 5.3, 95%CI 1.1 to 25.9) were most prone to develop cardiac arrhythmias while on QTc-prolonging drugs. Results of the logistic regression are listed in Table 4.

DISCUSSION

Our findings do not support the hypothesis that the use of QTc-prolonging drugs results in increased hospitalisation rates for cardiac arrhythmias (OR 1.2, 95%CI 0.8 to 1.9). This may be because the clinical impact of the use of these drugs is not very high in the general population or that in day-to-day practice the drugs are avoided in high-risk groups.

Our findings indicate that patients with a history of asthma or those taking potassium-lowering drugs are most prone to develop cardiac arrhythmias.

Cardiac arrhythmias which require hospitalisation are not the only type of clinically relevant arrhythmia that can result from drug use. When drug-induced QTc-prolongation results in sudden death [6], patients will not be admitted to the hospital. Therefore, the cases we studied are not representative of all relevant arrhythmias that may have occurred. Because it is very difficult to identify fatal arrhythmia cases outside the hospital, we were unable to address this issue. We believe, however, that an increased risk of arrhythmias leading to hospital admissions will also manifest itself in an increased risk of sudden death.

Another factor which may have influenced our results is the fact that we were not able to verify whether all cases were real cases of ventricular arrhythmias. Until the present time, we were unable to review the electrocardiographic evidence for the different arrhythmias. However, we excluded all cases of atrial arrhythmias from our analyses, and when restricting the analysis to only the proved ventricular arrhythmias, comparable results were found despite loss of power.

In our study we used drug-dispensing records from community pharmacies. Patients who picked up their medication, however, may not have actually taken the prescribed drugs. This possible lack of compliance may have overestimated the actual exposure, and thus biased our results towards the null hypothesis.

The increased risk in patients using potassium-lowering drugs can be explained by the fact that low extracellular potassium reduces the delayed rectifier potassium current (I_{Kr}) [29], which is also blocked by the QTc-prolonging drugs. Drugs reducing blood potassium included non potassium-sparing diuretics, laxatives, corticosteroids

for systemic use and systemic β-agonists. Diuretics are prescribed for lowering blood pressure. Patients taking these drugs may have other cardiac diseases causing the higher risk of drug-induced arrhythmias. A similar bias may have occurred with the patients using systemic β-agonists for treating asthma. Asthma, and not the reduction in blood potassium, may have caused the increased risk we found [26, 30].

BIBLIOGRAPHICAL REFERENCES

1. Haverkamp W, Breithardt G, Camm AJ, et al. The potential for QT prolongation and pro-arrhythmia by non-anti-arrhythmic drugs: clinical and regulatory implications. Report on a Policy Conference of the European Society of Cardiology. *Cardiovasc Res.* 2000; 47: 219-33.
2. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999; 47: 307-13.
3. Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med.* 1999; 107: 356-62.
4. Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia. *N Engl J Med.* 1996; 335: 290-1.
5. Bran S, Murray WA, Hirsch IB, Palmer JP. Long QT syndrome during high-dose cisapride. *Arch Intern Med.* 1995; 155: 765-8.
6. Glassman AH, Bigger JT, Jr. Antipsychotic drugs: Prolonged QTc Interval, Torsade de Pointes, and sudden death. *Am J Psychiatry.* 2001; 158: 1774-82.
7. Burckhardt D, Raeder E, Muller V, Imhof P, Neubauer H. Cardiovascular effects of tricyclic and tetracyclic antidepressants. *JAMA.* 1978; 239: 213-6.
8. Zehender M, Meinertz T, Hohnloser S, et al. Incidence and clinical relevance of QT prolongation caused by the new selective serotonin antagonist ketanserin. Multicenter Ketanserin Research Group. *Clin Physiol Biochem.* 1990; 8: 90-100.
9. van Haarst AD, van 't Klooster GA, van Gerven JM, et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. *Clin Pharmacol Ther.* 1998; 64: 542-6.
10. Matson PA, Luby SP, Redd SC, Rolka HR, Meriwether RA. Cardiac effects of standard-dose halofantrine therapy. *Am J Trop Med Hyg.* 1996; 54: 229-31.
11. Eisenhauer MD, Eliasson AH, Taylor AJ, Coyne PE, Jr., Wortham DC. Incidence of cardiac arrhythmias during intravenous pentamidine therapy in HIV-infected patients. *Chest.* 1994; 105: 389-95.
12. Brandriss MW, Richardson WS, Barold SS. Erythromycin-induced QT prolongation and polymorphic ventricular tachycardia (torsades de pointes). *Clin Infect Dis.* 1994; 18: 995-8.
13. Lee KL, Jim MH, Tang SC, Tai YT. QT prolongation and Torsades de Pointes associated with clarithromycin. *Am J Med.* 1998; 104: 395-6.
14. Ball P. Quinolone-induced QT interval prolongation: a not-so-unexpected class effect. *J Antimicrob Chemother.* 2000; 45: 557-9.
15. Lopez JA, Harold JG, Rosenthal MC, Oseran DS, Schapira JN, Peter T. QT prolongation and torsades de pointes after administration of trimethoprim-sulfamethoxazole. *Am J Cardiol.* 1987; 59: 376-7.

16. Rosati B, Rocchetti M, Zaza A, Wanke E. Sulfonylureas blockade of neural and cardiac HERG channels. *FEBS Lett.* 1998; 440: 125-30.
17. Gohn DC, Simmons TW. Polymorphic ventricular tachycardia (Torsade de Pointes) associated with the use of probucol. *N Engl J Med.* 1992; 326: 1435-6.
18. Henderson RA, Lane S, Henry JA. Life-threatening ventricular arrhythmia (torsades de pointes) after haloperidol overdose. *Hum Exp Toxicol.* 1991; 10: 59-62.
19. Abernethy DR, Barbey JT, Franc J, et al. Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QTc prolongation. *Clin Pharmacol Ther.*2001;69:96-103.
20. Desta Z, Kerbusch T, Flockhart DA. Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolizers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther.* 1999; 65: 10-20.
21. Collet JP, Boivin JF. Bias and confounding in pharmacoepidemiology. In: Strom BL, ed. *Pharmacoepidemiology*. third ed. Chichester: John Wiley & Sons Ltd., 2000: 765-84.
22. Grobbee DE, Hoes AW. Non-potassium-sparing diuretics and risk of sudden cardiac death. *J Hypertens.* 1995; 13: 1539-45.
23. Chin RL. Laxative-induced hypokalemia. *Ann Emerg Med.* 1998; 32: 517-8.
24. Yelamanchi VP, Molnar J, Ranade V, Somberg JC. Influence of electrolyte abnormalities on interlead variability of ventricular repolarization times in 12-lead electrocardiography. *Am J Ther.* 2001; 8: 117-22.
25. Taylor DR, Wilkins GT, Herbison GP, Flannery EM. Interaction between corticosteroid and beta-agonist drugs. Biochemical and cardiovascular effects in normal subjects. *Chest.* 1992; 102: 519-24.
26. Bouvy ML, Heerdink ER, De Bruin ML, Herings RM, Leufkens HG, Hoes AW. Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med.* 2000; 160: 2477-80.
27. Rosero SZ, Zareba W, Moss AJ, et al. Asthma and the risk of cardiac events in the Long QT syndrome. Long QT Syndrome Investigative Group. *Am J Cardiol.* 1999; 84: 1406-11.
28. Arildsen H, May O, Christiansen EH, Damsgaard EM. Increased QT dispersion in patients with insulin-dependent diabetes mellitus. *Int J Cardiol.* 1999; 71: 235-42.
29. Yang T, Roden DM. Extracellular potassium modulation of drug block of IKr. Implications for torsade de pointes and reverse use-dependence. *Circulation.* 1996; 93: 407-11.
30. Williams C. Baseline rates of disease may account for some arrhythmia risk. *Arch Intern Med.* 2001; 161: 1235-6.

Chapter 2.3

PROARRHYTHMIC DRUGS AND CARDIAC ARREST, A HOSPITAL BASED CASE-CONTROL STUDY

Marie L De Bruin [1,2], Pim NJ Langendijk [3], Richard P Koopmans [4], Arthur AM Wilde [5], Hubert GM Leufkens [1], Arno W Hoes [2]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaco-epidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands
[3] Department Hospital Pharmacy, Academic Medical Center, Amsterdam, the Netherlands
[4] Department of Internal Medicine and Department of Pharmacology and Pharmacotherapy, Academic Medical Center, Amsterdam, the Netherlands
[5] Department of Clinical and Experimental Cardiology, Academic Medical Center, Amsterdam, the Netherlands

Submitted for publication

SUMMARY

Objective: QTc-interval prolonging drugs have been linked to cardiac arrhythmias, cardiac arrest and sudden death. In this study we aimed to quantify the risk of cardiac arrest associated with the use of non-antiarrhythmic proarrhythmic drugs in an academic hospital setting.

Methods: We performed a case-control study in which patients, for whom intervention of the advanced life support resuscitation team was requested for cardiac arrest between 1995 and 2003 in the Academic Medical Center, Amsterdam, were compared with controls regarding current use of non-antiarrhythmic proarrhythmic drugs. Odds ratios (OR) and 95% confidence intervals (CI) were calculated using unconditional logistic regression, adjusting for potential confounding factors.

Results: A statistically significant increased risk of cardiac arrest (OR 2.1, 95%CI 1.2 to 3.5) was observed in patients who received proarrhythmic drugs (42/140). The risk was more pronounced in patients receiving doses more than one defined daily dose (OR 2.5, 95%CI 1.1 to 5.9), patients taking more than one proarrhythmic drug simultaneously (OR 4.8, 95%CI 1.6 to 14), and patients taking pharmacokinetic interacting drugs concomitantly (OR 4.0, 95%CI 1.2 to 13)

Conclusion: Use of non-antiarrhythmic proarrhythmic drugs in hospitalised patients with several underlying diseases is associated with an increased risk of cardiac arrest. The effect is dose related and pharmacokinetic drug-drug interactions increase the risk substantially. Physicians caring for in-patients should be made aware of the fact these non-antiarrhythmic drugs may be hazardous, so that potential risks can be weighed against treatment benefits and additional cardiac surveillance can be requested, if necessary.

INTRODUCTION

A wide range of QTc-prolonging non-antiarrhythmic drugs have been linked to the occurrence of cardiac arrhythmias, especially Torsade de Pointes [1]. Torsade de Pointes is a polymorphic ventricular arrhythmia, which can be self-limiting or degenerate into ventricular fibrillation, cardiac arrest and sudden death [2]. Several population based epidemiological studies on drug-induced arrhythmias indicate that the proarrhythmic risk of non-antiarrhythmic drugs is not very high among the general population [3-6], but can be substantial among subgroups of patients with underlying diseases, such as schizophrenia [6] or asthma [3]. In daily practice, potential proarrhythmic drugs are advised not to be prescribed to patients with pre-existing risk factors [7]. In a hospital setting, however, and particularly a university hospital setting, this may be hard to achieve, since virtually all patients have some underlying disease, and treatment with potentially hazardous drugs may be necessary.
In this study we aimed to quantify the risk of cardiac arrest associated with the use of non-antiarrhythmic proarrhythmic drugs in a university hospital setting.

METHODS

Setting

This study was conducted in the Academic Medical Center, Amsterdam, a tertiary care and university teaching hospital (1,000 beds, 23,600 admissions per year, mean length of stay 9 days). All patients receiving in-hospital care between January 1, 1995 and December 25, 2003 with complete computerised medical records on drug exposure variables and potential confounders were initially eligible for the study.

Design

A case-control study was performed. Cases were defined as patients experiencing circulatory arrest for whom intervention of the advanced life support resuscitation team (including medical doctors in the field of anaesthesiology and cardiology, as well as a CCU-nurse) was requested. Patients in whom the arrest occurred either prior to hospital admission or in the emergency room were excluded. Per case four controls from all other patients receiving in-hospital care were selected at the date the case was resuscitated (index date).

Exposure definition

Current in-hospital exposure to non-antiarrhythmic drugs with a clinically relevant proarrhythmic risk (published clinical evidence for Torsade de Pointes or ventricular arrhythmias) was assessed for cases and controls (Appendix 2) [1]. A patient was defined as a current user if the index date fell between the prescription date and the end date of the prescription. Exposure was assessed through the automated pharmacy database in which all prescribed medication of patients receiving in-hospital care is collected. To ensure knowledge of all currently used drugs and exclude effects of previously used drugs, patients were eligible only if the medication records of the present hospitalisation started at least one day before the index date.

Among current users we evaluated the effect of dose, measured in defined daily dose equivalents, as defined by the World Health Organisation [8]. One defined daily dose equivalent represents the recommended daily dose for an adult (Appendix 2). In order to evaluate dose response effects, the daily dose of proarrhythmic drugs was categorised into less than or equal to 1 defined daily dose, and more than 1 defined daily dose. In addition, the effect of the number of different proarrhythmic drugs taken simultaneously was assessed. We also evaluated the effect of concomitant medication which can inhibit the metabolism of the study drugs, defined as clinically relevant cytochrome P450 interactions by Flockhart et al (Appendix 2 and 3) [1,9].

Potential confounders

The association between the use of proarrhythmic drugs and cardiac arrest in this hospital based study may be confounded by secondary factors which were associated with both the exposure and the outcome, such as confounding by indication [10]. We therefore evaluated the influence of age, gender, comorbidity (cardiac arrhythmias, other cardiac disease, diabetes mellitus, pulmonary disease, hepatic and renal impairment), concomitant use of class I and III antiarrhythmic drugs, total number of currently used drugs and electrolyte disturbances (calcium, magnesium, potassium) on the calculated association.

Data on potential confounders were retrieved from the medical records through computerised searches. Cardiac arrhythmias were defined by hospital discharge diagnosis for the disease (ICD-code 427). Antiarrhythmic proarrhythmic drug use was defined as current use of class I or III antiarrhythmic drugs. Other cardiac disease was defined as either a prescription for other cardiac drugs, and/or a hospital discharge diagnosis (ICD-code) for ischaemic heart disease (410-414), heart failure

(428), cardiomyopathy (425), valvulopathy (4240, 4241, 4242, 4243), artificial heart (valve) (V421, V422, V432, V433) and/or a hospital procedure for CABG (5361, 5362, 5363), or PTCA (88370, 88378, 88379). Diabetes mellitus was defined as either a prescription for antidiabetic drugs and/or a hospital discharge diagnosis for diabetes (ICD-code 250). Pulmonary disease was defined as either a prescription for antiasthmatic drugs and/or a hospital discharge diagnosis (ICD-code) for asthma (493), chronic bronchitis (491), emphysema (492). Normal serum electrolyte levels, based on the criteria used in the Academic Medical Center, were defined as calcium between 2.1 and 2.55 mmol/l, magnesium between 0.7 and 1 mmol/l, potassium between 3.5 and 5 mmol/l. Hepatic and renal impairment were defined by an expert panel consisting of an internist and a cardiologist as serum total bilirubine levels > 50 μmol/l and serum creatinine levels >110 μmol/l (males) or 100 μmol/l (females) respectively. Serum levels had to be measured during the 7 days previous to the index date. If multiple measurements were taken, the value closest to the index date was used.

Data-analysis

The relative risk, calculated as the odds ratio (OR), and 95% confidence interval (CI) of the association between exposure to proarrhythmic drugs and cardiac arrest was estimated using unconditional logistic regression analysis. All potential confounders were bivariately associated with cardiac arrest (at a $p < 0.1$ level) and included in the multivariate regression analyses. All statistical analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, Illinois).

RESULTS

During the study period, 140 patients were resuscitated for cardiac arrest in the Academic Medical Center and fulfilled the eligibility criteria. Mean age of cases was significantly higher (59.6) than of controls (47.5) and cases were more often male than controls (65.7% *vs* 48.9%). All known potential risk factors for cardiac arrest were associated with an increased risk, notably cardiac arrhythmias, other cardiac disease, diabetes mellitus, pulmonary disease, electrolyte disturbances and hepatic as well as renal impairment.

Table 1 *Characteristics of cases and controls*

	Cases (n=140)	%	Controls (n=560)	%	p-value
Gender female	48	34.3%	286	51.1%	<0.0001
Age (mean, sd)	59.6	± 21.7	47.5	± 26.8	<0.0001
Drug use					
Non-antiarrhythmic proarrhythmic drugs	42	30.0%	107	19.1%	0.005
Antiarrhythmic proarrhythmic drugs	13	9.3%	17	3.0%	0.001
Total number of current drugs (mean, sd)	9.4	± 4.4	7.5	± 4.6	<0.0001
Comorbidity					
Cardiac arrhythmias	50	35.7%	31	5.5%	<0.0001
Other cardiac disease	69	49.3%	110	19.6%	<0.0001
Diabetes mellitus	46	32.9%	68	12.1%	<0.0001
Pulmonary disease	41	29.3%	89	15.9%	<0.0001
Serum levels*					
K < 3.5 mmol/l	26	18.6%	67	12.0%	<0.0001
K 3.5 - 5	86	61.4%	304	54.3%	
K > 5	16	11.4%	15	2.7%	
K not measured during last week	12	8.6%	174	31.1%	
Ca < 2.1 mmol/l	30	21.4%	40	7.1%	<0.0001
Ca 2.1 - 2.55 mmol/l	51	36.4%	106	18.9%	
Ca > 2.55 mmol/l	2	1.4%	22	3.9%	
Ca not measured during last week	57	40.7%	392	70.0%	
Mg < 0.7 mmol/l	9	6.4%	18	3.2%	0.004
Mg 0.7 - 1 mmol/l	14	10.0%	35	6.3%	
Mg > 1 mmol/l	5	3.6%	4	0.7%	
Mg not measured during last week	112	80.0%	503	89.8%	
Bilirubine < 50 µmol/l	36	25.7%	97	17.3%	0.002
Bilirubine > 50 µmol/l	9	6.4%	13	2.3%	
Bilirubine not measured during last week	95	67.9%	450	80.4%	
Creatinine < 110µmol/l (m),100µmol/l (f)	82	58.6%	303	54.1%	<0.0001
Creatinine > 110µmol/l (m),100µmol/l (f)	50	35.7%	70	12.5%	
Creatinine not measured during last week	8	5.7%	187	33.4%	

* χ^2 *p-value for disproportionality in serum level categories*

Table 2 *Risk of cardiac arrest and non-antiarrhythmic proarrhythmic medication*

Use of proarrhythmic drugs	Cases (n=140)	Controls (n=560)	Crude odds ratio (95%CI)	Adjusted odds ratio* (95%CI)
Non-use	98	453	1 ref	1 ref
Current use	42	107	1.8 (1.2-2.8)	2.1 (1.2-3.5)
Daily dose				
Non-use	98	453	1 ref	1 ref
≤ 1 defined daily dose	28	78	1.7 (1.0-2.7)	1.9 (1.1-3.5)
>1 defined daily dose	14	29	2.2 (1.1-4.4)	2.5 (1.1-5.9)
Number of proarrhythmic drugs				
Non-use	98	453	1 ref	1 ref
1 drug	33	94	1.6 (1.0-2.6)	1.8 (1.0-3.1)
2 or more drugs simultaneously	9	13	3.2 (1.3-7.7)	4.8 (1.6-14)
Drug-drug interactions				
Non-use	98	453	1 ref	1 ref
Proarrhythmic drugs only	34	99	1.6 (1.0-2.5)	1.9 (1.1-3.2)
Proarrhythmic drugs + P450 inhibitors	8	8	4.6 (1.7-13)	4.0 (1.2-13)
Type of proarrhythmic drug used†				
Non-use	98	453	1 ref	1 ref
Amitriptyline	4	10	1.9 (0.6-6.0)	2.0 (0.5-8.1)
Cisapride	6	21	1.3 (0.5-3.4)	1.3 (0.4-4.0)
Clarithromycin	3	7	2.0 (0.5-7.8)	1.4 (0.2-8.6)
Cotrimoxazole	9	30	1.4 (0.6-3.0)	2.6 (1.1-6.4)
Domperidone	7	15	2.2 (0.9-5.4)	4.7 (1.4-16)
Haloperidole	15	18	3.9 (1.9-7.9)	3.8 (1.6-9.2)
Promethazine	3	13	1.1 (0.3-3.8)	1.2 (0.3-5.4)
Other proarrhythmic drug	4	9	2.1 (0.6-6.8)	1.3 (0.3-5.6)

* *Adjusted for age, gender, cardia arrhythmias, other cardiac disease, diabetes mellitus, pulmonary disease, total number of current drugs, concomitant use of antiarrhythmic drugs, serum potassium, calcium, magnesium, creatinine and bilirubine*

† *Some patients used more than 1 proarrhythmic drug, numbers do not add up*

As expected, the use of antiarrhythmic drugs and the total number of currently used drugs were associated with cardiac arrest as well (Table 1). The most pronounced were the associations between cardiac arrhythmias (adjusted OR 6.6, 95%CI 3.7 to 12) as well as hyperkalaemia (adjusted OR 4.1, 95%CI 1.6 to 10) and cardiac arrest. Current use of non-antiarrhythmic proarrhythmic drugs was associated with a two-fold increased risk of cardiac arrest (crude OR 1.8, 95%CI 1.2 to 2.8). This risk increased slightly after adjustment for confounders (adjusted OR 2.1, 95%CI 1.2 to 3.5). The risk of cardiac arrest increased with dose (adjusted OR >1 defined daily dose 2.5, 95%CI 1.1 to 5.9), number of proarrhythmic drugs taken simultaneously (adjusted OR > 1 drug 4.8 95%CI 1.6 to 14), and was twice as high when proarrhythmic drugs were taken concomitantly with other drugs which inhibit the metabolism (adjusted OR 4.0, 95%CI 1.2 to 13). Of the individual drugs, domperidone and haloperidol appeared to have the greatest risks (Table 2).

DISCUSSION

The results of our study indicate that current use of non-antiarrhythmic proarrhythmic drugs is associated with a doubled risk of cardiac arrest in a hospital setting. Although the study was not designed to study individual drugs risks, nor to study effects in subgroups, it is interesting to see that the risks were highest among patients taking two medications mainly used in palliative care: domperidone and haloperidol. Domperidone is used to treat gastrointestinal discomfort [11]. In a hospital, setting haloperidol is mainly used to treat delirium [12]. Both drugs are known for their potential proarrhythmic effects [12, 13], and warnings are implemented in the Summary of Product Characteristics. Apparently, the potential benefits of treatment outweigh the adverse effects in a clinical setting. Another interesting finding is the fact that the association between non-antiarrhythmic proarrhythmic drugs and cardiac arrest appears to be greater among the 93 patients with hypokalaemia (adjusted OR 3.3, 95%CI 0.7 to 15). Hypokalaemia is one of the main risk factors for drug-induced arrhythmias [14].

The number of cases included in our study may seem low for a university hospital, which is followed for almost 9 years [15]. The total number of cardiac arrests for whom intervention of the advanced life support resuscitation team was requested, in this study period, exceeded 1,200. However, almost 50% of the interventions took place in the emergency room. Other potential cases were not included because not

all requested information, especially concerning prescribed drugs, could be retrieved through computerised searches.

A finding consistent with other studies on the association between proarrhythmic drugs and cardiac arrhythmias is that there appears to be a positive dose response relationship [3, 6, 16-19]. In contrast with previous community based studies on drug-induced arrhythmias [3-5], we are the first to report that cytochrome P450 pharmacokinetic drug-drug interactions apparently play an important role.

The data we used were not recorded for research purposes, but to support medical and pharmaceutical care, to improve medication safety, and for administrative reasons. The main advantage of these data is the fact that they were collected prospectively and are unlikely to be subject to differential misclassification [20]. However, we cannot exclude the fact that some non-differential misclassification of outcome and exposure may have occurred or that some residual confounding may still be present. Firstly, some control patients with a do-not-attempt-resuscitation order may have actually experienced cardiac arrest, without intervention of the advanced life support resuscitation team. The fraction of patients with a do-not-attempt-resuscitation order was found to depend on age and comorbidity in the Academic Medical Center [21]. According to the age distribution we expect that 57 of the 560 control patients in our study may have had an do-not-attempt-resuscitation order. Assuming that 10% of these patients actually experienced a cardiac arrest implies that only 1% of our control patients were misclassified. This may have resulted in a minor underestimation of the true effect. Secondly, misclassification of exposure may have occurred, but was minimised, because only patients whose present medication started at least one day before the index date were included. In addition, it is likely that any such exposure misclassification will be random and will be evenly distributed between cases and controls. Thirdly, we may not have been able to fully control for disease severity. Patients appeared to be more severely ill than controls. This was reflected in the higher number of prescribed drugs, a higher prevalence of comorbidity as well as electrolyte disturbances and the fact that serum levels for electrolytes and renal and hepatic function were measured more often during the week before the index date. We took all these factors into account in our analyses, but we were not able to adjust for a standardised measure of disease severity such as the APACHE II score.

Another factor which may have influenced our results is the fact that doctors refrain from prescribing proarrhythmic drugs to high-risk patients, so called 'confounding

by contraindication' [10]. This may have resulted in an apparently absent association between use of cisapride and cardiac arrest on the one hand and a large association between use of domperidone and cardiac arrest on the other hand, when physicians prescribe domperidone instead of cisapride in high-risk patients. Cisapride-induced arrhythmias gained much more attention in recent years than domperidone-induced arrhythmias [13]. This hypothesis is strengthened by the fact that until 2001 cisapride was taken twice as often as domperidone, whereas after 2001 domperidone was taken twice as often as cisapride.

In conclusion, the results of our study indicate that current use of non-antiarrhythmic proarrhythmic drugs in hospitalised patients with several underlying diseases is associated with an increased risk of cardiac arrest. The effect is dose related and pharmacokinetic drug-drug interactions increase the risk substantially. Hospital specialists should be made aware of the fact that these non-antiarrhythmic drugs may be hazardous, so that potential risks can be weighed up against treatment benefits and additional cardiac surveillance can be requested, if necessary.

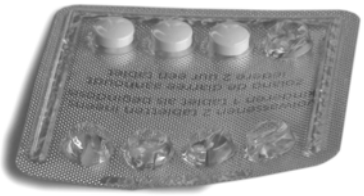
BIBLIOGRAPHICAL REFERENCES

1. De Ponti F, Poluzzi E, Vaccheri A, et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. *Br J Clin Pharmacol.* 2002; 54: 171-7.
2. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. *Prog Cardiovasc Dis.* 2001; 43: 1-45.
3. De Bruin ML, Hoes AW, Leufkens HGM. QTc-prolonging drugs and hospitalizations for cardiac arrhythmias. *Am J Cardiol.* 2003; 91: 59-62.
4. Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med.* 1999; 107: 356-62.
5. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999; 47: 307-13.
6. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *Br Med J.* 2002; 325: 1070.
7. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart.* 2003; 89: 1363-72.
8. WHO collaborating centre for drug statistics methodology. ATC/DDD index 2004. Available at: http://www.whocc.no/atcddd/; Accessed July 7, 2004.
9. Flockhart DA. Clinically relevant D-I table. Available at: http://medicine.iupui.edu/flockhart /clinlist.htm; Accessed June 28, 2004.
10. Collet JP, Boivin JF. Bias and confounding in pharmacoepidemiology. In: Strom BL, ed. *Pharmacoepidemiology*. third ed. Chichester: John Wiley & Sons Ltd., 2000: 765-84.
11. Soykan I, Sarosiek I, McCallum RW. The effect of chronic oral domperidone therapy on gastrointestinal symptoms, gastric emptying, and quality of life in patients with gastroparesis. *Am J Gastroenterol.* 1997; 92: 976-80.
12. Vella-Brincat J, Macleod AD. Haloperidol in palliative care. *Palliat Med.* 2004; 18: 195-201.
13. Drolet B, Rousseau G, Daleau P, Cardinal R, Turgeon J. Domperidone should not be considered a no-risk alternative to cisapride in the treatment of gastrointestinal motility disorders. *Circulation.* 2000; 102: 1883-5.
14. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med.* 2004; 350: 1013-22.
15. Jastremski MS. In-hospital cardiac arrest. *Ann Emerg Med.* 1993; 22: 113-7.
16. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry.* 2001; 58: 1161-7.
17. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther.* 2004; 75: 234-41.

18. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry.* 2002; 180: 515-22.
19. Straus SMJM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the risk of sudden cardiac death. *Arch Intern Med.* 2004; 164: 1293-7.
20. West SL, Strom BL. Validity of pharmacoepidemiology drug and diagnosis data. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester: John Wiley & Sons Ltd., 1994: 549-80.
21. de Vos R, Koster RW, de Haan RJ. Impact of survival probability, life expectancy, quality of life and patient preferences on do-not-attempt-resuscitation orders in a hospital. *Resuscitation.* 1998; 39: 15-21.

Chapter 3

SPECIAL FOCUS ON HIGH-RISK GROUPS



Chapter 3.1

USE OF CISAPRIDE WITH CONTRAINDICATED DRUGS IN THE NETHERLANDS

Marie L De Bruin[1,2], Martien JM Panneman[2], Hubert GM Leufkens[1], Arno W Hoes[3], Ron MC Herings[1,2]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] PHARMO Institute for Pharmacoepidemiology and Outcomes Research, Utrecht, the Netherlands
[3] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands

Supported by an unrestricted grant from Janssen Pharmaceutica NV

The Annals of Pharmacotherapy. 2002; 36: 338-343

SUMMARY

Objective: We investigated the prevalence of concomitant use and coprescribing of cisapride with potentially interacting drugs to evaluate the impact of drug warnings from 1994 to 1998.

Methods: Retrospective follow-up study of patients using cisapride. Data for this study are obtained from the pharmacy database of the Dutch PHARMO record linkage system (n= 834,000).

Results: From 1994 to 1998, the prevalence rate of the observed versus expected use of any potentially interacting drug decreased significantly over time ($p<0.01$). However, the number of days-at-risk and number of coprescriptions of potentially interacting drugs among patients taking cisapride increased on average 13% and 9% per year, respectively. This increase was almost exclusively explained by a large increase of concomitant prescribing of clarithromycin, the most commonly used potentially interacting drug. Decreases in prevalence rates were observed for all individual potentially interacting drugs, except for concomitant use of fluconazole and miconazole.

Conclusion: Over the last few years, health care professionals have refrained from dispensing potentially interacting drugs to patients who use cisapride, probably as a result of drug warnings implemented during this period. The limited absolute effects result from an increase of coprescription and concomitant use of clarithromycin and fluconazole among patients taking cisapride. Because therapeutically equivalent alternatives were available for both drugs, such combinations were avoidable. Communicating information on these drug-drug interactions to prescribers and pharmacist and inclusion of cardiovascular morbidity as a relative contraindication for prescribing cisapride with these drugs may substantially decrease the risk of adverse reactions to cisapride.

INTRODUCTION

The gastrointestinal prokinetic drug cisapride has been licensed for marketing in the Netherlands since September 1989 for symptomatic treatment of epigastric and abdominal complaints, gastroesophageal reflux disease and refluxoesophagitis [1]. Since the early 1990s, QTc-prolongation, syncope, and nonsustained ventricular tachycardia have been associated with high doses of cisapride [2, 3]. Gray [4] reported a case of QTc-prolongation and syncope resulting from concomitant use of cisapride and agents known to inhibit the metabolism of cisapride. Several other reports and clinical studies have associated use of cisapride with QTc-prolongation and Torsade de Pointes [5-8]. Cisapride has been taken off the market in the US, while its risks and benefits are now being re-evaluated by the European Agency for the evaluation of Medicinal Products.

Warnings for QTc-prolongation with respect to concomitant use of ketoconazole, miconazole or itraconazole were included in the Dutch Summary of Product Characteristics since May 10, 1995. This change in labelling was followed by a 'Dear Doctor' letter on October 20, 1995. A second modification in the labelling was issued on August 30, 1996, regarding concomitant use of three additional drugs: fluconazole, erythromycin and clarithromycin. The last label modification was issued on December 23, 1997, and included nefazodone, ritonavir and troleandomycin. No additional 'Dear Doctor' letters have been posted. These modifications were communicated to prescribers and pharmacists in medical and pharmaceutical journals as well as major textbooks.

Besides the 'Dear Doctor' letter, the warnings were included in package inserts and implemented in pharmacy medication surveillance systems. All Dutch pharmacies have medication surveillance systems that check for drug-drug and drug-disease interactions (including any contraindications) with each new prescription. Differences between surveillance systems exist with respect to the date these interactions were implemented.

The impact of warnings for drug-drug interactions may alter prescribing by minimising co-prescribing of contraindicated drugs altogether or by minimising the time (days-at-risk) patients use drugs which may interact. In this study, we investigated the prevalence of concomitant use and codispensing of cisapride and potentially interacting drugs as an evaluation of the impact of label changes in the period from 1994 to 1998.

We hypothesised that the prevalence of concomitant use and codispensing of cisapride and potentially interacting drugs declined after implementation of the warnings in current practice.

METHODS

Setting

Data for this study were obtained from the pharmacy database of the PHARMO record linkage system [9, 10]. This database prospectively collates the drug-dispensing records from 90 community pharmacies and hospital discharge records of all 834,000 community-dwelling inhabitants of 22 population defined areas in the Netherlands, and can be assumed to be a representative subset of the Dutch population. With exceptions, all inhabitants of the Netherlands are insured for health and pharmaceutical care and designate a single pharmacy to fill their prescriptions. Hence, drug-dispensing histories were virtually complete. The computerised drug-dispensing histories contained data concerning the type and quantity of the dispensed drug, type of prescriber, type of medication surveillance system, dispensing date, and prescribed dose and daily regimens. Prescription length was estimated from the total amount of dispensed drug and the prescribed units to be taken per day. In some pharmacies, the reason for prescribing was available, coded with an International Classification of Primary Care code.

Design

We conducted a retrospective follow-up study of patients using cisapride. Patients were followed from the first day of the first prescription of cisapride since September 1989 until the earliest of the following dates: 90th birthday, exit from the study population, death, or end of the follow-up (December 31, 1998). We excluded patients over 90 years old who largely reside in nursing homes and whose medication histories were rather incomplete. For each cohort member the use of cisapride and the use of potentially interacting drugs were assessed every day of the follow-up period. Potentially interacting drugs included ketoconazole, miconazole, fluconazole, itraconazole, erythromycin, clarithromycin, nefazodone, and ritonavir. Troleandomycin, mentioned in the drug labelling, was never marketed in the Netherlands.
Looking at this subject from a general health point of view, we wanted to know whether the drug warnings managed to decrease the number of days-at-risk of QTc-

prolongation during the study period. Assuming that patients were at risk every day they took cisapride and a potentially interacting drug concomitantly, we calculated the prevalence of combined use of both drugs to estimate the days-at-risk of cisapride users for effects attributable to the concomitant use of potentially interacting drugs in this study population.

Even if the prevalence of concomitant use of cisapride and potentially interacting drugs did not decline after the implementation of warnings, these warnings may still have been effective in preventing the prevalence of drug-drug interactions from increasing further. In other words, it is possible that even when the absolute number of days-at-risk rose over the years, compared to what the expected number could have been, this observed prevalence (P_o) was relatively low.

The main outcome measure was the rate of (P_o) of the use of potentially interacting drugs among patients taking cisapride divided by the expected prevalence (P_e) among these patients. These measures were the actual use of potentially interacting drugs among patients taking cisapride, compared with the expected use among these patients based on the prevalence of potentially interacting drugs among the source population, assuming that the prescribing pressures among both populations were comparable. A ratio of < 1 (observed *vs* expected) indicated that patients taking cisapride use fewer potentially interacting drugs than would be expected among this population and, hence, that the general health concerns these drug-drug interactions have caused were smaller than they might have been.

The codispensing rate, defined as the number of cisapride prescriptions with a least a 1-day overlap of a potentially interacting drug, was also calculated. This measure was based on the decision to codispense both cisapride and potentially interacting drugs concomitantly and clarifies whether the drug warnings were able to make health care professionals refrain from dispensing potentially interacting drugs to patients taking cisapride. Prevalence and codispensing rates were calculated per calendar year.

Statistical analyses

The P_o of concomitant use of cisapride and potentially interacting drugs was estimated as the summarised person-days concomitant use of those agents divided by the summarised person-days of use of all cisapride prescriptions: P_o= days-at-risk/ days cisapride use. The P_e represents the prevalence of concomitant use of cisapride and potentially interacting drugs that was expected based purely on the chance of combined prescribing of both drugs. It was estimated as $P_e = P_c \times P_P$, where P_c

represents the prevalence of use of cisapride and P_P the prevalence of use of potentially interacting drugs among the source population. The expected prevalence was adjusted for age, gender, and calendar year by direct standardisation with the study population. The prevalence rate, defined as the quotient of the observed and expected prevalence (P_o/ P_e), and 95% confidence intervals (CI) were calculated using EGRET statistical software [11].

Because of multiple dates of implementation of drug warnings in the healthcare system (drug labelling, 'Dear Doctor' letter, pharmacy software) we did not think a simple comparison of prevalence before and after a certain date was an appropriate measure to evaluate the effect of drug warnings. We therefore evaluated the prevalence per calendar year from 1994 until 1998. Trends in changes of the prevalence and prevalence rates were estimated using a χ^2-analysis.

RESULTS

Throughout the study period, a total of 30,051 patients were dispensed 95,578 prescriptions for cisapride. More than 60% of patients taking cisapride were women, and over 38% of patients were 40-64 years of age. Of these patients 944 (3.1%) used one or more potentially interacting drugs concomitantly with cisapride. Approximately 50% (n=448) of these 944 patients received clarithromycin. For all other individual potentially interacting drugs, the prevalence of concomitant users of cisapride was less than 0.6%. Nefazodone was used concomitantly with cisapride by only two patients, and ritonavir was never dispensed with cisapride in our study population. Both drugs were excluded from further analyses. General practitioners prescribed cisapride in most cases (83.2%), followed by internists (11.4%) and paediatricians (3.0%). The median prescription length was 30 days and the cumulative mean exposure time to cisapride varied from 60 days per patient in 1991 to 80 days per patient in 1998. Patients used cisapride and potentially interacting drugs concomitantly for a mean period of 14 days. Extrapolated to the Dutch population, approximately 800,000 patients were dispensed cisapride at least once in the Netherlands during the study period, of which 24,000 - 26,000 patients have been codispensed at least one potentially interacting drug. Characteristics of the study population are presented in Table 1.

Table 1 *Characteristics of patients taking cisapride and potentially interacting drugs (1991 to 1998)*

Characteristics	Number	%
Gender		
Male	11,848	39.4%
Female	18,203	60.6%
Age		
< 14	2,222	7.4%
15-39	8,972	29.9%
40-64	11,635	38.7%
≥ 65	7,222	24.0%
Concomitantly dispensed*		
Any†	944	3.1%
Ketoconazole	32	0.1%
Miconazole	120	0.4%
Itraconazole	83	0.3%
Fluconazole	131	0.4%
Erythromycin	187	0.6%
Clarithromycin	448	1.5%
Nefazodone‡	2	0.0%
Ritonavir‡	0	0.0%

* *Patients may be concomitantly exposed to several or single potentially interacting drugs more than once*

† *Patients may be dispensed several, or several different potentially interacting drugs alone or concomitantly with cisapride during the follow-up period; numbers do not add up*

‡ *Excluded from further analyses*

Table 2 presents the P_o and P_e, as well as the prevalence rates (observed/expected), of the selected potentially interacting drugs from 1994 to 1998. The prevalence of use of any potentially interacting drug among patients taking cisapride increased from 40.0 to 63.1 per 10,000 person-days exposure to cisapride during the study period. On average, the prevalence increased 13% per year, while the P_e increased on average 27% per year in the same period. The prevalence rate of the observed versus the expected use of any potentially interacting drug decreased significantly over time (χ^2 $p<0.01$) to 0.55 (95%CI 0.53 to 0.57) at the end of the study period. This means that cisapride users experienced only approximately one-half of the days at risk than would be expected based on the prevalence of the studied drugs in the source population (Figure 1).

Table 2 *Observed and expected prevalence of concomitant use of selected potentially interacting drugs per 10,000 person days exposure to cisapride from 1994 to 1998*

Drug	Year	Prevalence observed	Prevalence expected*	P_o/P_e	(95%CI)	Impact†
Overall	1994	40.0	47.0	0.85	(0.79-0.92)	
	1995	48.7	48.0	1.02	(0.95-1.09)	
	1996	54.6	51.7	1.06	(1.00-1.12)	
	1997	49.3	71.4	0.69	(0.66-0.73)	
	1998	63.1	115.2	0.55	(0.53-0.57)	--
Clarithromycin‡	1994	9.5	4.2	2.29	(1.84-2.84)	
	1995	13.9	8.5	1.64	(1.42-1.90)	
	1996	20.0	15.0	1.33	(1.20-1.48)	
	1997	18.3	22.4	0.82	(0.75-0.89)	
	1998	34.6	53.6	0.65	(0.61-0.68)	--
Erythromycin‡	1994	12.1	16.2	0.74	(0.65-0.86)	
	1995	10.5	13.0	0.81	(0.70-0.93)	
	1996	13.4	14.8	0.91	(0.81-1.02)	
	1997	7.8	15.0	0.52	(0.46-0.58)	
	1998	6.5	9.8	0.66	(0.58-0.75)	--
Fluconazole‡	1994	5.8	5.3	1.09	(0.88-1.36)	
	1995	5.1	6.1	0.84	(0.68-1.03)	
	1996	8.1	4.9	1.66	(1.39-0.98)	
	1997	12.1	6.6	1.85	(1.62-2.11)	
	1998	11.7	7.3	1.59	(1.41-1.80)	++
Itraconazole§	1994	5.2	7.2	0.72	(0.58-0.89)	
	1995	7.8	9.0	0.87	(0.73-1.02)	
	1996	6.5	9.1	0.72	(0.62-0.84)	
	1997	5.4	19.6	0.28	(0.24-0.32)	
	1998	4.3	21.7	0.20	(0.17-0.23)	--
Ketoconazole§	1994	4.1	6.2	0.66	(0.53-0.84)	
	1995	8.1	5.2	1.57	(1.30-1.90)	
	1996	1.8	4.9	0.36	(0.28-0.47)	
	1997	0.4	5.1	0.08	(0.05-0.13)	
	1998	0.9	4.9	0.18	(0.14-0.25)	--
Miconazole§	1994	4.6	4.0	1.16	(0.90-1.49)	
	1995	3.6	3.6	1.00	(0.78-1.28)	
	1996	5.1	3.6	1.40	(1.14-1.73)	
	1997	5.6	3.7	1.49	(1.24-1.80)	
	1998	4.3	4.4	0.97	(0.82-1.16)	0

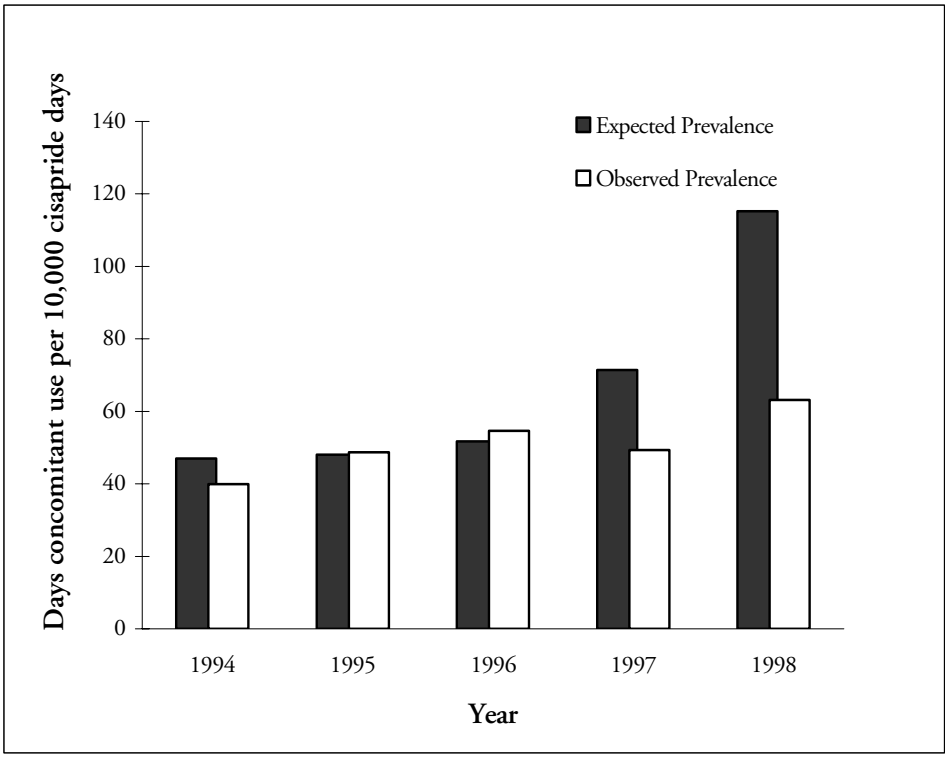
* *Expected prevalence estimated from the prevalence of cisapride (Pc) and individual potential interacting drug (Pp), adjusted for age (5 years bands), gender and calendar year; the expected prevalence (Pe) is estimated as Pe=Pc x Pp (see method section)*

† *-- Statistical significant decrease (p<0.01), 0 neither decrease nor increase, ++ significant increase (p<0.01); significant testing with* χ^2*-test*

‡ *SPC revision August 30, 1996*

§ *SPC revision May 10, 1995, Dear Doctor letter October 20, 1995*

Figure 1 *The prevalence of concomitant use of potentially interacting drugs (PID) among users of cisapride; the observed prevalence represents the true, measured prevalence in the PHARMO population from 1991 to 1998; the expected prevalence represents the prevalence of concomitant use of PID among cisapride users which is expected based on chance of concomitant use of both cisapride and PID; the difference between both prevalence is a measure of the effect of warnings*



Decreases in prevalence rates were observed for all individual potentially interacting drugs except for concomitant use of cisapride and fluconazole or miconazole. The prevalence of clarithromycin, fluconazole and ketoconazole increased among users of cisapride increased from 1994 to 1998 (on average 43%, 23%, and 15%, respectively). The use of erythromycin decreased (11% on average), and the use of itraconazole and miconazole stayed fairly stable. Large increases of the P_e were calculated for concomitant use of clarithromycin and itraconazole, indicating that in general both drugs were prescribed more frequently. The P_o was higher than the P_e only for fluconazole, suggesting a preference to coprescribe cisapride and fluconazole.

In Table 3, the prevalence of coprescriptions for the different potentially interacting drugs is presented. In 1998, approximately 2% of all prescriptions for cisapride had at least a 1-day overlap with prescriptions of potentially interacting drugs. Overall, the proportion co-prescriptions increased on average 9% a year from 1994 until 1998. This increase can largely be explained by the major increase of the codispensing of clarithromycin with cisapride (34% per year on average). Besides clarithromycin, the number of coprescriptions with itraconazole also shows an increasing trend (12% on average). The largest decreases of codispensing of potentially interacting drugs was observed for ketoconazole (26% per year on average), while coprescriptions of erythromycin, fluconazole and miconazole stayed fairly stable.

The results in Table 2 and 3 show differences that were explained by changes in average days of concomitant use of cisapride and the potentially interacting drugs. The average overlap of fluconazole and ketoconazole per cisapride prescription increased (from 4 to 11, and 9 to 17 days in the study period, respectively).

Table 3 *Co-prescription rate per 1,000 cisapride prescriptions of selected potentially interacting drugs from 1994 to 1998*

	1994	1995	1996	1997	1998	per year*
Any†	16.4	15.9	20.1	19.2	22.3	+9%
Clarithromycin‡	3.6	5.6	8.2	8.8	11.2	+34%
Erythromycin‡	4.0	3.2	3.7	2.6	3.5	+1%
Fluconazole‡	3.9	2.5	3.3	3.4	3.3	-1%
Itraconazole§	1.0	1.4	2.0	1.8	1.3	+12%
Ketoconazole§	1.3	1.3	0.3	0.1	0.2	-26%
Miconazole§	2.3	2.0	2.4	2.5	2.5	+2%

* *Average difference per year*

† *Patients may have been dispensed several, or several different potentially interacting drugs alone or concomitantly with cisapride during the follow-up period. Numbers do not add up*

‡ *Summary of Product Characteristics revision August 30, 1996*

§ *Summary of Product Characteristics revision May 10, 1995; 'Dear Doctor' letter October 20, 1995*

DISCUSSION

Since the introduction of cisapride on the Dutch market in 1989, more than 800,000 patients have been exposed to the drug. Of these, 24,000-26,000 received it with at least one potentially interacting drug for at least one day. During the study period, the prevalence rate of the observed versus the expected use of any potentially interacting drug decreased significantly over time indicating that cisapride users took fewer potentially interacting drugs concomitantly than would be expected. The number of days-at-risk and number of coprescriptions of potentially interacting drugs among cisapride users, however, increased on average by 13% and 9% per year, respectively. This increase could almost exclusively be explained by a large increase in concomitant prescribing of clarithromycin. Excluding clarithromycin, the number of days-at-risk and coprescriptions stayed fairly stable. The prevalence of contraindicated coprescriptions we found was somewhat lower than results from previous studies in the US [12] and Italy [13]. This could be explained by the fact that we limited the number of contraindications to the use of CYP3A4-inhibiting drugs mentioned in the drug labelling and not included other drugs or diseases that could possibly increase the risk of cardiac adverse reactions of cisapride. We limited the number of drugs in order to specifically study the effects of drug labelling changes.

These findings show that patients were dispensed relatively fewer potentially interacting drugs, either due to the fact that prescribers refrain from prescribing such

agents to patients taking cisapride since warnings were implemented or perhaps due to automated pharmacy dispensing management. The warnings, however, did not appear to be effective in decreasing the absolute number of days-at-risk or coprescriptions. Efforts in preventing codispensing of cisapride and potentially interacting drugs should focus on fluconazole (for which there appears to be a preference to prescribe concomitantly with cisapride) and clarithromycin (for which absolute use among cisapride users increased dramatically).

The increase in coprescribing cisapride and clarithromycin could be explained by an overlap in indication. Cisapride is mainly prescribed as prokineticum to patients with dyspepsia and refluxoesophagitis whereas clarithromycin is first choice antibiotic as part of *Helicobacter pylori* (*H. pylori*) eradication regimens [1]. Since 1995, the number of *H. pylori* eradication courses increased from 2,000 to 22,000 in 1998 in the Netherlands [9]. Subanalysis of the indication of prescribing, based on a sample of all prescriptions, showed that a substantial percentage (> 25%) of clarithromycin prescriptions were prescribed as part of *H. pylori* eradication regimens. The frequent concomitant use of clarithromycin and cisapride for overlapping indications may have introduced bias in our study. Because full compliance was assumed, it was possible that the moment an eradication regimen was started, cisapride was stopped. We, however, had no data that permitted further exploration of this bias which may result in an overestimation of the days-at-risk and an underestimation of the impact of warnings. Another implication of the sharp increase in concomitant use of cisapride and clarithromycin may be of importance in interpreting cardiovascular adverse events associated with cisapride use. Patients taking these drugs at the same time probably experience more serious acid-related diseases than patients using cisapride alone. Further research should focus on this group of patients because results from several studies [14, 15] indirectly suggest that cardiovascular morbidity was 3 to 5 times more prevalent in this group of patients. Subanalyses of our data showed that more than 50% of all patients taking cisapride had a history of cardiovascular diseases. The risk of QTc-prolongation is increased in these patients; therefore cisapride can be considered a relative contraindication. On the other hand, the elevated baseline risk increases the probability of inappropriate association of QTc-prolongation with cisapride. Reports of alleged adverse effects require careful evaluation because QTc-prolongation or arrhythmia may be the result of an underlying cardiovascular disease rather than a direct effect of cisapride. A study [7] describing the interaction of clarithromycin and cisapride in healthy

volunteers demonstrated a 3-fold increase in cisapride concentrations after combination of the recommended doses of the two drugs and an average increase in QTc-intervals of approximately 25ms, which could potentially be clinically signifycant in patients with risk factors for cardiac arrhythmias.

An unexplained finding in our study was the association between fluconazole and cisapride use. As shown in Table 2, the P_o doubled during the study period in contrast to expectations. This suggests that cisapride and fluconazole have an overlapping indication or that patients switched from other imidazoles for which warnings were issued earlier. In a sample of prescriptions used in this study, fluconazole was predominantly prescribed for treatment of candida vaginitis. The association of prescribing with patients using cisapride could be explained if fluconazole was prescribed for treatment of candida oesophagitis or other gastrointestinal fungal infections. We had, however, no data that permitted further elaboration of this hypothesis. A single dose of fluconazole was prescribed for treatment of candida vaginitis in the Netherlands. One may question whether a single dose of this potentially interacting drug is able to cause a clinically significant effect. Studies [16] have shown, however, that the cytochrome P450 inhibitory effects of azoles may be seen after only a single dose. We assumed, therefore, that patients are at risk every day during concomitant administration of cisapride and a potentially interacting drug.

A limitation of this type of study was that warnings for different drugs are implemented at different points in time. It was therefore difficult to define clear-cut periods before and after the implementation of warnings.

In this study we only investigated the concomitant use of cisapride and potentially interacting drugs mentioned in the Summary of Product Characteristics to learn whether these drug warnings are effective in preventing drug-drug interactions. One should, however, be aware that there can be potentially harmful pharmacokinetic as well as pharmacodynamic drug-drug interactions with drugs other than those investigated in this study.

In conclusion, our findings show that, over the last few years, healthcare professionals have refrained from dispensing potentially interacting drugs to patients who use cisapride, probably as a result of drug warnings implemented during this period. The limited absolute effect on days-at-risk and coprescriptions resulted from increased coprescription and concomitant use of these drugs among patients taking cisapride. Therapeutic equivalent alternatives are available for both drugs and

combinations with cisapride can be avoided. Furthermore, the risk of QTc-prolongation or arrhythmia may be further limited by inclusion of cardiovascular morbidity as a relative contraindication for prescribing cisapride. Despite these findings, one should realise that codispensing of potentially interacting drugs to patients taking cisapride was rare and affects less than 2% of cisapride users or approximately 5,000 patients per year, in the Netherlands. By limiting co-dispensing of clarithromycin and fluconazole alone, this number will decline to fewer than 1,500 patients per year and minimise a potential risk of unwanted adverse effects.

BIBLIOGRAPHICAL REFERENCES

1. Centrale Medisch Pharmaceutische Commissie. *Farmacotherapeutisch Kompas 1999*. Amstelveen, the Netherlands: Ziekenfondsraad, 1999.
2. Bran S, Murray WA, Hirsch IB, Palmer JP. Long QT syndrome during high-dose cisapride. *Arch Intern Med.* 1995; 155: 765-8.
3. Wysowski DK, Bacsanyi J. Cisapride and fatal arrhythmia. *N Engl J Med.* 1996; 335: 290-1.
4. Gray VS. Syncopal episodes associated with cisapride and concurrent drugs. *Ann Pharmacother.* 1998; 32: 648-51.
5. Heeringa M, Pulles-Heintzberger CF, van Puijenbroek EP, Verduijn MM. Lengthening of the QT-interval in a newborn treated with cisapride. *Ned Tijdschr Geneeskd.* 1999; 143: 2108-11.
6. Vitola J, Vukanovic J, Roden DM. Cisapride-induced torsades de pointes. *J Cardiovasc Electrophysiol.* 1998; 9: 1109-13.
7. van Haarst AD, van 't Klooster GA, van Gerven JM, et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. *Clin Pharmacol Ther.* 1998; 64: 542-6.
8. Olsson S, Edwards IR. Tachycardia during cisapride treatment. *Br Med J*. 1992; 305: 748-9.
9. Herings RMC, Panneman MJM, de Graag E. *Innovations in Pharmacotherapy*. Utrecht, the Netherlands: PHARMO Institute, 2000.
10. Herings RM, Klungel OH. An epidemiological approach to assess the economic burden of NSAID-induced gastrointestinal events in The Netherlands. *Pharmacoeconomics.* 2001;19:655-65.
11. EGRET for windows, software for the analysis of biomedical and epidemiological studies. Version 2.0.31. Cambridge, MA: Cytel Software Corporation, 1999.
12. Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of food and drug administration regulatory action. *JAMA.* 2000; 284: 3036-9.
13. Raschetti R, Maggini M, Da Cas R, Popoli P, Rossi A. Time Trends in the Coprescribing of Cisapride and Contraindicated Drugs in Umbria, Italy. *JAMA.* 2001; 285: 1840-1.
14. Chan TY, Critchley JA, Lau JT, Sung JJ, Chung SS, Anderson DC. The relationship between upper gastrointestinal hemorrhage and drug use: a case control study. *Int J Clin Pharmacol Ther.* 1996; 34: 304-8.
15. Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. *J Epidemiol Community Health.* 1992; 46: 136-40.
16. Michalets EL, Williams CR. Drug interactions with cisapride: clinical implications. *Clin Pharmacokinet.* 2000; 39: 49-75.

Chapter 3.2

PREDICTING CARDIAC ARRHYTHMIAS AND SUDDEN DEATH IN DIABETIC PATIENTS TAKING NON-ANTI-ARRHYTHMIC PROARRHYTHMIC DRUGS

Marie L De Bruin[1,3], Tjeerd P van Staa[1,2], Svetlana V Belitser[1], Hubert GM Leufkens[1], Arno W Hoes[3]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaco-epidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] Medical Research Council, Environmental Epidemiology Unit, Southampton University Hospital, Southampton, United Kingdom
[3] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands

Submitted for publication

SUMMARY

Objective: Diabetic patients have a relatively long QTc-interval, and a subsequent increase in QTc-interval by proarrhythmic drugs may lead to cardiac arrhythmias and sudden cardiac death. We developed a decision tool to predict the risk of serious ventricular arrhythmias and sudden death among diabetic patients taking non-antiarrhythmic proarrhythmic drugs, to be applied in daily practice.

Methods: A cohort study was performed among 142,175 diabetic patients using proarrhythmic medication in the General Practice Research Database (1987-2001). The study outcome was serious ventricular arrhythmia (notably ventricular tachycardia) or sudden death. Candidate predictors included: gender, age, diabetes duration, comorbidities and concomitant medication. Multivariate logistic regression in combination with bootstrapping techniques was used to derive a stable prediction model.

Results: In total, 61,280 diabetic patients were prescribed one or more proarrhythmic drugs on a total of 396,853 physician visits. Mean prescription length was 26 days, 94 events occurred during follow-up (incidence 24 per 100,000 prescriptions). Independent predictors of serious ventricular arrhythmias and sudden death were age, male gender, ischaemic heart disease and nonventricular arrhythmias. The scoring rule we derived identified patients with a 4 times higher risk of the study outcome.

Conclusion: The absolute risk of serious ventricular arrhythmias and sudden death among diabetic patients taking proarrhythmic drugs is low. The provided scoring rule can be used to identify patients with a considerable increased risk. Prescribing proarrhythmic drugs to these patients should be reconsidered or closely monitored.

INTRODUCTION

QTc-prolongation, which like QTc-dispersion, may be a marker for underlying cardiac disease [1], and has been identified as an independent predictor for cardiac and cardiovascular mortality in the population at large [2] as well as in both type 1 and type 2 diabetics [3, 4].

Diabetic patients have relatively long QTc-interval [5]. In accordance with the concept of 'reduced repolarisation reserve' [6], a subsequent increase in QTc-interval by proarrhythmic drugs may lead to cardiac arrhythmias and sudden cardiac death. Recently, it has been shown that patients with diabetes mellitus are at increased risk of drug-induced arrhythmias [7].

The number of QTc-prolonging drugs with a clinically relevant proarrhythmic risk exceeds thirty [8]. They belong to various therapeutic classes and are widely prescribed. In clinical practice, prescribing physicians have to weigh up the potential risks and benefits of drug treatment and decide whether a patient's risk of serious adverse reactions is acceptable. Since no quantitative decision tool for predicting the risk of serious ventricular arrhythmias and sudden death among patients taking proarrhythmic drugs is available, we developed such a tool to be applied in daily practice in diabetic patients.

METHODS

Setting

In order to facilitate implementation of the decision rule, we used potential predictors which are readily available for practising physicians providing daily care to diabetic patients.

This study was performed in the General Practice Research Database (GPRD) which contains the computerised medical records of approximately 650 general practices. Approximately 6.5% of the total population of England and Wales is represented on the database. The computer records contain patient demographics, characteristics (i.e. height, weight, and smoking status), symptoms and diagnosis (using Oxford Medical Information System (OXMIS) and READ codes, which are mapped onto International Classification of Diseases codes) referrals to specialist care, hospital admissions and their major outcomes, and all drug prescriptions in chronological order. The computerised recording of patient information was started by many general practitioners in the late 1980s, and replaced the handwritten records used previously [9]. Several independent validation studies have shown that the GPRD database has a high level of completeness and validity. The GPRD is owned by the UK Department of Health and managed by the Medicines Control Agency.

Data of all 142,175 patients with diabetes (both type 1 and type 2) recorded in the GPRD (1987 up to 2001) were used.

Study design and population

A cohort study among diabetic patients using potential proarrhythmic medication was performed between June 1, 1987 and January 21, 2001. Follow-up started on the first day of a prescription of any proarrhythmic drug after diagnosis of diabetes or prescription of antidiabetic drugs during study period. Follow-up was censored when the duration of (one of) the prescription(s) had elapsed, when the study outcome occurred, in case of death, exit from the study population or end of study period, whichever of these events came first. Patients contributed to the analysis every time they were prescribed a non-antiarrhythmic proarrhythmic drug.

Exposure definition

For each cohort member, exposure to any proarrhythmic drug was ascertained every day from the start of the follow-up until the end of the follow-up period. Only drugs, considered to have a clinically relevant proarrhythmic risk (published clinical evidence for Torsade de Pointes or ventricular arrhythmias) were included in our study [8]. These included prokinetics, cardiovascular drugs, antibacterials, antipsychotics, antidepressants, antimalarials, antihistamines, and others (Appendix 2). We excluded antiarrhythmic medications with proarrhythmic side effects.

GPs could prescribe more than one proarrhythmic drug at the same time. Therefore, two or more prescriptions for different drugs were regarded as one decision to expose a patient to a possible harmful drug-combination. In such cases, doses were added up and the shortest duration of use was taken as the 'exposure window'.

Outcome definition

The primary outcome of our study was severe ventricular arrhythmia (cardiac arrest, ventricular tachycardia, flutter and fibrillation) and sudden death. Ventricular arrhythmias occurring in the week following a myocardial infarction were excluded[10].

Candidate predictors

We selected 15 candidate pre-prescription predictors of serious ventricular arrhythmias and sudden death during proarrhythmic drug-use. These included:

- Patient factors: gender, age, duration of diabetes
- Diseases associated with QTc-prolongation or ventricular arrhythmias: other cardiac arrhythmias than the study outcome (mainly atrial fibrillation), ischaemic heart disease, heart failure, hypertension [11], pulmonary disease [12]
- Concomitant medication associated with potassium imbalance or ventricular arrhythmias: antiarrhythmic drugs [13], oral potassium, drugs which may lower blood potassium levels [14] (non potassium-sparing diuretics [15], laxatives, corticosteroids for systemic use and systemic β_2-agonists [16])
- Factors associated with prescribed drugs: dosage, previous prescriptions for the same drug in the past year
- Lifestyle factors associated with QTc-prolongation or ventricular arrhythmias: smoking [17], BMI [18, 19]

Concomitant drug-use was measured as a prescription in the same individual during the last 30 days. Continuous variables were initially analysed without categorisation, but cut off values were also evaluated.

Data analyses

We first estimated the association between each candidate predictor and the outcome (bivariate analysis). Incidence rates, crude odds ratios (OR), 95% confidence intervals (CI) and p-values were calculated. Because preselection of predictors based on p-values estimated from bivariate analyses may result in unstable prediction models [20], all candidate predictors were considered in the multivariable analysis using logistic regression modelling. Since in prediction research it is common to use a more liberal p-value than 0.05 for keeping variables in the model [20], the overall multivariable model was reduced deleting predictors with p-value > 0.15 based on the log likelihood ratio test.

Patients may have had more than one prescription for study drugs, contributing to the total follow-up, during the study period. To adjust for correlated data, weights (1 divided by the number of prescriptions per patient) were assigned to each follow-up period.

Bootstrapping techniques were used to validate the final prediction model (i.e. to adjust the estimated model for overoptimism or overfitting) [20]. Random bootstrap samples were drawn with replacement (100 replications) from the data consisting of all patients. The multivariable selection of variables was repeated within each bootstrap sample.

In order to obtain a straightforward applicable prediction rule based on the final bootstrapped model, the adjusted regression coefficients were multiplied by a factor 10 and rounded to the nearest integer. The model's performance (goodness-of-fit and discriminative ability) was tested by performing the Hosmer and Lemeshow test and calculating the area under the receiver operator characteristic (ROC) curve. The ROC area can range from 0.5 (useless model, like a coin flip) to 1.0 (perfect discrimination). A value over 0.7 can be interpreted as reasonable and over 0.8 as good [21]. Analyses were performed using SPSS 10.0 (SPSS Inc., Chicago, Illinois, USA) and S-Plus 6 (Insightful Corp., Seattle, WA, USA), with Harrell's Design library (http://hesweb1.med.virginia.edu/biostat/s/design.html, accessed November 2003).

Smoking status was not known for almost 40% of the study population. Unknown smoking status was analysed as a separate category. For the 28% of the patients with unknown BMI, we imputed missing data using the expectation maximisation method [20]. Such imputation is based on the correlation between each variable with missing values and all other variables, as estimated from the set of complete subjects.

RESULTS

Of the 142,175 diabetic patients, 61,280 were prescribed one or more pro-arrhythmic drugs on a total of 396,853 physician visits during the study period. The mean prescription length was 26 days. In 61% of the cases, these drugs were prescribed to women.

The overall mean age at start of follow-up was almost 65 years. During follow-up 94 cases of sudden death and serious ventricular arrhythmias occurred, including 49 sudden deaths, 34 cardiac arrests and 11 ventricular arrhythmias. The overall incidence rate of severe ventricular arrhythmias and sudden death among the study population was 24 per 100,000 'prescriptions' (94 / 396,853). Events were more frequent in males and increased with age. Other arrhythmias, ischaemic heart disease and heart failure as well as all studied concomitant medications were associated with the outcome (Table 1).

The majority (77%) of prescribed drugs were psychotropic (174,183 prescriptions) or antimicrobic (130,778 prescriptions) medications, with amitriptyline (82,745 prescriptions), trimethoprim (58,261 prescriptions) and erythromycin (47,262 prescriptions) as most frequently prescribed drugs. On 11,848 occasions, two or more proarrhythmic drugs were prescribed at the same time. Halofantrine, ketanserine, lidoflazine, pentamidine, sulfamethoxazol (without trimethoprim), sultopride and zimeldine were not prescribed at all to our study population.

Table 1 *Incidence of study outcome among diabetic patients taking proarrhythmic drugs according to candidate predictors and bivariate associations (OR, 95%CI, p-value)*

Candidate predictor	Events	Rx*	Incidence†	OR (95%CI)	p-value
Gender male	51	153,178	33	2.49 (1.12-5.53)	0.025
Age					
0-54	11	88,272	12	OR per year	
55-69	26	137,468	19	1.03 (1.00-1.06)	0.024
70-84	41	138,704	30		
≥ 85	16	32,409	49		
Duration of diabetes (years)					
< 2	34	175,350	19	OR per year	
2-4	38	145,366	26	0.99 (0.83-1.18)	0.889
≥ 5	22	76,043	29		
Comorbidity					
Other arrhythmia	17	30,596	56	4.18 (1.77-9.85)	0.001
Ischaemic heart disease	40	84,835	47	3.22 (1.51-6.85)	0.002
Heart failure	33	48,035	69	3.18 (1.40-7.21)	0.006
Elevated blood pressure	38	155,256	24	1.26 (0.59-2.72)	0.549
Pulmonary disease	14	63,012	22	1.11 (0.40-3.12)	0.842
Concomitant drugs					
Antiarrhythmics	4	2,213	181	8.02 (1.33-48.4)	0.023
Oral potassium	4	3,051	131	4.70 (0.47-47.4)	0.190
Potassium-lowering drugs ‡	51	145,130	35	2.10 (0.98-4.49)	0.056
Study drugs					
≥ 2 defined daily doses per day	6	28,475	21	0.77 (0.17-3.53)	0.732
Prescription for current drug last year	69	292,096	24	0.93 (0.42-2.08)	0.862
Smoking	19	86,994	22	0.68 (0.24-1.95)	0.475
BMI					
< 20	5	17,426	29	1.18 (0.17-8.49)	
20-25	17	90,799	19	Ref	0.959
25-30	37	145,965	25	1.17 (0.42-3.29)	
≥ 30	35	142,663	25	1.33 (0.48-3.70)	
Total	94	396,853	24		

* *Rx: prescription(s)*

† *Incidence per 100,000 prescriptions*

‡ *Non potassium-sparing diuretics, laxatives, systemic corticosteroids or systemic β_2-agonists*

Table 2 *Reduced and final model to predict serious ventricular arrhythmias and sudden death among diabetic patients taking proarrhythmic drugs*

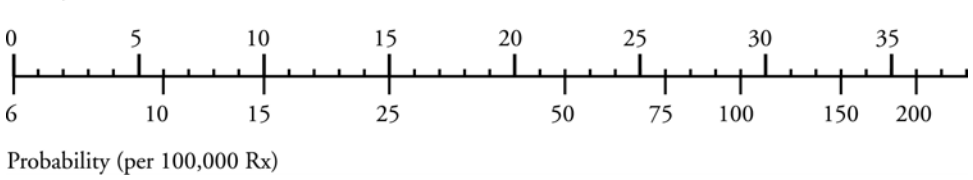
Predictor	Reduced model		Final model				
	Regression coefficient	(SE)	Regression coefficient	(SE)	Score*	OR	p-value
Age (per year)	0.026	(0.015)	0.021	(0.015)	0.2	1.02	0.17
Male gender	0.94	(0.41)	0.75	(0.42)	7	2.11	0.07
Other cardiac arrhythmia	1.04	(0.46)	0.83	(0.48)	8	2.29	0.11
Ischaemic heart disease	0.79	(0.40)	0.63	(0.40)	6	1.88	0.17
Intercept	-10.4	(1.1)	-9.8	(1.1)		0.00	<0.0001

* *The score predictor is obtained by multiplying the regression coefficient by 10, and then rounded off to the nearest integer*

The initial multivariable model with all 15 predictors yielded an ROC area of 0.71 (95%CI 0.66 to 0.77). Only 4 of these 15 predictors, i.e. age, gender, ischaemic heart disease and cardiac arrhythmia other than the study outcome, independently contributed to the prediction of the outcome defined as a p-value ≤ 0.15. Other predictors, which were significant in crude analysis (Table 1) such as heart failure, and concomitant use of blood-potassium-influencing drugs, were not independent predictors in the multivariable analysis. Apparently, their predictive information was already provided for by the four retained predictors. The reduced model including the four predictors yielded a ROC area of 0.69 (95%CI 0.63 to 0.74), and after bootstrapping, the ROC area of the final model remained 0.69 (95%CI 0.63 to 0.74) (Table 2). The goodness-of-fit of this final model was excellent (p-value Hosmer and Lemeshow test: 0.91).

The risk score for predicting serious ventricular arrhythmias and sudden death among diabetic patients taking proarrhythmic drugs derived from the final model was: Age(years)*0.2 + male gender*7 + arrhythmias other than the study outcome*8 + ischaemic heart disease*6 points. The corresponding probability for the study outcome can be seen in Figure 1. As an example of using this nomogram, a male (7 points) of 60 years old (60*0.2=12 points) with ischaemic heart disease (6 points) without a history of any cardiac arrhythmias (0 points) receives a total risk score of 7+12+6=25. Using Figure 1, this corresponds to a probability of serious ventricular arrhythmias and sudden death of approximately 70 per 100,000 prescriptions.

Figure 1 *Nomogram for estimating the probability for serious ventricular arrhythmias and sudden death*



† *Score= Age(years)*0.2+ Male gender*7+ Other cardiac arrhythmia*8+ Ischaemic heart disease*6*

Table 3 *Distribution of patients according to the risk score derived from final model*

Score	Events	%	Rx*	%	Incidence rate†	Sensitivity‡	Specificity‡
< 15	14	(15%)	146,481	(37%)	10		
15-22	34	(36%)	163,790	(41%)	21	0.85	0.37
22-26	21	(22%)	49,456	(12%)	42	0.49	0.78
26-29	11	(12%)	21,017	(5%)	52	0.27	0.91
≥ 29	15	(15%)	16,109	(4%)	87	0.15	0.96
Total	94	(100%)	396,853	(100%)	24		

* *Rx: prescription(s)*

† *Per 100,000 prescriptions*

‡ *Lower limit of score category is used as cut-off value*

Table 3 shows the observed incidence rates of events per predefined risk stratum, which increased from 10 to 87 per 100,000 prescriptions. It also provides the estimates of the sensitivity and specificity of the scoring rule at different cut-off points.

DISCUSSION

Although the incidence of severe ventricular arrhythmias and sudden death among diabetic patients taking non-antiarrhythmic proarrhythmic drugs is very low (24/100,000 prescriptions), prescribing physicians can identify groups of patients with a high risk using a scoring rule with only 4 predictors (i.e. age, gender and the presence of ischaemic heart disease and cardiac arrhythmias other than the study outcome) readily available in clinical practice. The highest risk group, with a score ≥ 29, has an almost 4 times higher risk of the study outcome compared with the study population as a whole.

Even though we had a very large population of more than 61,000 patients with almost 400,000 prescriptions for proarrhythmic drugs, only 94 events were observed. Because the study outcome is so rare, no assertions on individual drug risks could be made. In addition, development of a highly discriminative prediction rule is very difficult. We were, however, able to develop a rule with reasonable discriminative properties (ROC = 0.7).

We adjusted our predictive model for overoptimism. External validation on a new study population can, however, be necessary in prediction research, as internal validation by bootstrap techniques may not be sufficient and indicative for the model's performance in future patients [22].

In our study we used data from general practices. Unfortunately we were not able to validate our study outcomes. The validity and completeness of the used database have been proved before [9]. Moreover, we selected very well-defined study outcomes for which misclassification in a previous study was found to be not very likely (chapter 5.1).

Exposure was measured using prescription information from the same database. However, patients who were prescribed proarrhythmic drugs may not have picked up their medication from the pharmacy, or actually taken the drugs at the time they were prescribed. This possible lack of compliance may have overestimated the actual exposure, which may have biased our results towards the null-hypothesis.

All selected predictors in our rule had been reported as predictors for the study outcome among users of the proarrhythmic drug cisapride [10]. Age and heart disease or high-risk cardiovascular status were associated with an increased risk of study outcomes similar to those studied here in patients taking various potential

proarrhythmic antihistamine drugs [23-26], whereas male gender does not appear to be a risk factor in these studies.

Although prognostic value of various risk factors for cardiac and cardiovascular death in both type 1 [3] and type 2 [4, 27] diabetics have been studied repeatedly, studies on risk factors for sudden death and serious ventricular arrhythmias in diabetics are scarce. Comparable to the prognostic factor 'arrhythmias other than the study outcome' in the present study, in diabetic patients 'atrial fibrillation' has been identified before as a risk factor for sudden cardiac death [28]. Diabetes duration, diabetic complications and elevated blood pressure were described as risk factors for sudden death in type 2 diabetes [29]. However, they were not significant predictors in our study, probably because their predictive information was already provided by the other predictors.

To prevent adverse effects of proarrhythmic drugs in high-risk patients, which can be identified with this decision rule, it may be wise not to prescribe the drugs. Therapeutic alternatives are available for most drugs. When use of potentially hazardous drugs is necessary, however, it is advised not to exceed the recommended dose or to prescribe other drugs which may inhibit the proarrhythmic drugs' metabolism, have proarrhythmic effects themselves, or which may cause electrolyte disturbance concomitantly. Furthermore, it may be sound clinical practice to perform electrocardiographic screening routinely and check serum potassium concentrations regularly before and after initiation of a proarrhythmic drug [30].

To estimate the consequences of using this decision rule in clinical practice, it is interesting to take a closer look at Table 3. For example, introducing a threshold at 22, a score < 22 will be considered as 'test negative' and ≥ 22 as 'test positive'. When taking additional security measures (e.g. pretherapy electrocardiographic measurements or prescribing therapeutic alternatives) for patients with a score ≥ 22, 49% of the 94 prescriptions during which an event actually happened would be treated correctly (sensitivity or true positive rate), whereas in those with a score < 22, in 78% additional security measures are correctly withheld (specificity, true negative rate). Table 3 also shows that a treatment-threshold at a score of 22 needs additional security measures for 21% (12% + 5% + 4%) of all prescriptions. Increasing the threshold for example to 30 results in a lower sensitivity of only 15%, but the amount of extra work decreases substantially, since additional security measures are needed in just 4% of all prescriptions.

We conclude that although the absolute risk of serious ventricular arrhythmias and sudden death among diabetic patients taking non-antiarrhythmic proarrhythmic drugs is low (24/100,000 prescriptions), the scoring rule provided can be used to identify patients with a considerably increased risk. Prescribing proarrhythmic drugs to these patients should be reconsidered or closely monitored.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Dr Carl Moons for his statistical advice and valuable critical comments.

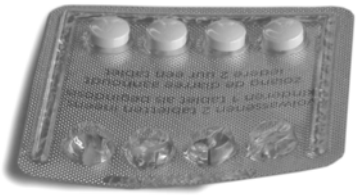
BIBLIOGRAPHICAL REFERENCES

1. Rana B, Band M, Ogston S, Morris A, Pringle S, Struthers A. Relation of QT interval dispersion to the number of different cardiac abnormalities in diabetes mellitus. *Am J Cardiol.* 2002; 90: 483.
2. de Bruyne MC, Hoes AW, Kors JA, Hofman A, van Bemmel JH, Grobbee DE. Prolonged QT interval predicts cardiac and all-cause mortality in the elderly. The Rotterdam Study. *Eur Heart J.* 1999; 20: 278-84.
3. Rossing P, Breum L, Major-Pedersen A, et al. Prolonged QTc interval predicts mortality in patients with Type 1 diabetes mellitus. *Diabet Med.* 2001; 18: 199-205.
4. Cardoso CR, Salles GF, Deccache W. Prognostic value of QT interval parameters in type 2 diabetes mellitus: results of a long-term follow-up prospective study. *J Diabetes Complications.* 2003; 17: 169-78.
5. Bednar MM, Harrigan EP, Anziano RJ, Camm AJ, Ruskin JN. The QT interval. *Prog Cardiovasc Dis.* 2001; 43: 1-45.
6. Roden DM. Taking the 'idio' out of 'idiosyncratic': predicting torsades de pointes. *Pacing Clin Electrophysiol.* 1998; 21: 1029-34.
7. Pathak A, Tournamille JF, Senard JM, Montastruc JL, Lapeyre-Mestre M. Diabetes increases the risk of drug-induced Torsade de Pointes: analysis of data from the French pharmacovigilance database. *Pharmacoepidemiol Drug Saf.* 2004; 13 (Suppl 1): S204.
8. De Ponti F, Poluzzi E, Vaccheri A, et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. *Br J Clin Pharmacol.* 2002; 54: 171-7.
9. Walley T, Mantgani A. The UK General Practice Research Database. *Lancet.* 1997; 350: 1097-9.
10. Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med.* 1999; 107: 356-62.
11. Elming H, Brendorp B, Kober L, Sahebzadah N, Torp-Petersen C. QTc Interval in the Assessment of Cardiac Risk. *Card Electrophysiol Rev.* 2002; 6: 289-94.
12. De Bruin ML, Hoes AW, Leufkens HGM. QTc-prolonging drugs and hospitalizations for cardiac arrhythmias. *Am J Cardiol.* 2003; 91: 59-62.
13. Thibault B, Nattel S. Optimal management with Class I and Class III antiarrhythmic drugs should be done in the outpatient setting: protagonist. *J Cardiovasc Electrophysiol.* 1999;10:472-81.
14. Yelamanchi VP, Molnar J, Ranade V, Somberg JC. Influence of electrolyte abnormalities on interlead variability of ventricular repolarization times in 12-lead electrocardiography. *Am J Ther.* 2001; 8: 117-22.
15. Grobbee DE, Hoes AW. Non-potassium-sparing diuretics and risk of sudden cardiac death. *J Hypertens.* 1995; 13: 1539-45.

16. Bouvy ML, Heerdink ER, De Bruin ML, Herings RM, Leufkens HG, Hoes AW. Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med.* 2000; 160: 2477-80.
17. Andrassy G, Szabo A, Dunai A, et al. Acute effects of cigarette smoking on the QT interval in healthy smokers. *Am J Cardiol.* 2003; 92: 489-92.
18. Esposito K, Marfella R, Gualdiero P, et al. Sympathovagal Balance, Nighttime Blood Pressure, and QT Intervals in Normotensive Obese Women. *Obes Res.* 2003; 11: 653-9.
19. Cooke RA, Chambers JB, Singh R, et al. QT interval in anorexia nervosa. *Br Heart J.* 1994; 72: 69-73.
20. Harrell FE, Jr., Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 1996; 15: 361-87.
21. Weinstein MC, Fineberg HV. *Clinical Dicision Analysis*. Philadelphia: WB Saunders, 1980.
22. Bleeker SE, Moll HA, Steyerberg EW, et al. External validation is necessary in prediction research: A clinical example. *J Clin Epidemiol.* 2003; 56: 826-32.
23. Hanrahan JP, Choo PW, Carlson W, Greineder D, Faich GA, Platt R. Terfenadine-associated ventricular arrhythmias and QTc interval prolongation. A retrospective cohort comparison with other antihistamines among members of a health maintenance organization. *Ann Epidemiol.* 1995; 5: 201-9.
24. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999; 47: 307-13.
25. Pratt CM, Hertz RP, Ellis BE, Crowell SP, Louv W, Moye L. Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the-counter antihistamines, ibuprofen and clemastine. *Am J Cardiol.* 1994; 73: 346-52.
26. Straus SMJM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the Risk of Sudden Cardiac Death. *Arch Intern Med.* 2004; 164: 1293-7.
27. Linnemann B, Janka HU. Prolonged QTc interval and elevated heart rate identify the type 2 diabetic patient at high risk for cardiovascular death. The Bremen Diabetes Study. *Exp Clin Endocrinol Diabetes.* 2003; 111: 215-22.
28. Lindholm LH, Dahlof B, Edelman JM, et al. Effect of losartan on sudden cardiac death in people with diabetes: data from the LIFE study. *Lancet.* 2003; 362: 619-20.
29. Tong N, Chen J, Huang H, Liang J. A clinical study of sudden death in patients with type 2 diabetes mellitus. *Hua Xi Yi Ke Da Xue Xue Bao.* 1999; 30: 331-3.
30. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart.* 2003; 89: 1363-72.

Chapter 4

MOLECULAR STRATEGIES



Chapter 4.1

PHARMACOGENETICS OF DRUG-INDUCED ARRHYTHMIAS, A FEASIBILITY STUDY USING SPONTANEOUS ADVERSE DRUG REACTIONS REPORTING DATA

Marie L De Bruin [1,3], Eugene P van Puijenbroek [2], Madelon Bracke [1], Arno W Hoes [3], Hubert GM Leufkens [1]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, the Netherlands
[3] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands

Submitted for publication

SUMMARY

Objective: The bottleneck in pharmacogenetic research on rare adverse drug reactions is retrieval of patients. Spontaneous reports of adverse drug reactions may form a useful source of patients. We investigated the feasibility of a pharmacogenetic study, in which cases were selected from the database of a spontaneous reporting system for adverse drug reactions, using drug-induced arrhythmias as an example.

Methods: Reports of drug-induced arrhythmias to proarrhythmic drugs were selected from the database of the Netherlands Pharmacovigilance Centre (1996-2003). Information on the patient's general practitioner (GP) was obtained from the original report, or from another health care provider who reported the event. GPs were contacted and asked to recruit the patient as well as two age, gender and drug matched controls. Patients were asked to fill in a questionnaire and provide a buccal swab DNA sample through the mail. DNA samples were screened for 10 missense mutations in 5 genes associated with the congenital long-QT syndrome (KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2).

Results: We identified 45 eligible cases, 29 GPs could be contacted of which 7 were willing to participate. Four cases and 5 matched controls could be included in the study, giving an overall participation rate of 9% (4/45). The main reason for GPs not being willing to participate was lack of time. Variants were identified in KCNH2, SCN5A and KCNE1.

Conclusion: Spontaneous reporting systems for adverse drug reactions may be used for pharmacogenetic research. The methods described, however, need to be improved to increase participation and international collaboration may be required.

INTRODUCTION

Implementation of pharmacogenetic and pharmacogenomic research is thought to be likely to result in a clinically important reduction in adverse drug reactions in the near future [1]. During the last decade the single most common cause of the withdrawal or restriction of the use of drugs on the market has been drug-induced arrhythmias [2, 3]. This adverse drug reaction (ADR) is very rare (less than one in 100,000 [4]), but it may be fatal. It has been hypothesised that there may be some genetic predisposition for drug-induced arrhythmias [3, 5, 6]. Genes which are involved in congenital long-QT (LQT) syndromes may also be involved in acquired LQT syndrome. Sporadic studies of genetic risk factors of congenital LQT syndrome among patients with acquired LQT syndrome have been performed in the United States [7-11], Japan [12] and Western-Europe [13]. The results from these studies suggest that genetic polymorphisms in congenital LQT genes are equally to more common among patients experiencing drug-induced arrhythmias compared with control patients. The number of patients included in these studies, however, is quite low and no significant relationships were found.

In order to study such a rare disease, it would be helpful to make use of databases in which events that happen in a very large population are filed. In the Netherlands, as in many other countries, health care professionals submit reports of adverse drug reactions to the national pharmacovigilance centre named 'Lareb' on a voluntary basis, through a so called 'yellow card' system [14].

In this study we aimed to investigate whether it was feasible to conduct a pharmacogenetic study involving collection of genetic material from a population of patients in whom specific adverse drug reactions to selected drugs have been reported anonymously to a national pharmacovigilance institute.

METHODS

Setting

The Netherlands Pharmacovigilance Centre Lareb maintains the spontaneous ADR reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Its objective is to collect and analyse reports of the adverse reactions of medicines and hence signal new ADRs as soon as possible [14].

ADRs are provided by health care professionals on a voluntary basis and provide relevant clinical information about the patient (age, gender), the suspected ADR, medication used at time of the event ('suspected' and 'concomitant'), source (physician or pharmacist) and year of reporting. Each report is reviewed by a qualified assessor (physician or pharmacist) and is coded according to the medical dictionary for regulatory activities (MedDRA) [15]. For this study all ADRs reported between January 1, 1996 and June 1, 2003 to the Netherlands Pharmacovigilance Centre were used.

Case and control definition

From the database of the Netherlands Pharmacovigilance Centre Lareb all reports of ventricular and non-specified cardiac arrhythmias, QTc-prolongation and cardiac arrest were selected. These reports were included as eligible cases, only if one of the drugs, marked as suspected by the reporting health care provider, was known to have a potential clinically relevant proarrhythmic risk according to De Ponti et al (published clinical evidence for Torsade de Pointes or ventricular arrhythmias) [16] (Appendix 2), the patient had not died as a result of the ADR, and the patient was at least 18 years old at time of the inquiry. Original reports were checked for completeness of ADR information and the reporters were approached for additional information (e.g. available electrocardiogram, hospital discharge letter) using a mailed questionnaire.

The objective was to select two gender and age matched controls per case from the same general practice, who used the same proarrhythmic drug in the same year and did not experience heart rhythm disorders. Matching on general practice, drug and year was desired to correct for selective (refrain from) prescribing of certain drugs to patients with certain diseases, which is likely to vary between physicians and over time [17-19].

Inclusion

Patient inclusion, through their general practitioner (GP), consisted of three phases:

1. Retrieval of information on case patient's GP
2. Participation of GP
3. Participation of case and controls

Information on the GP of the case patients was obtained from the original report received by the Netherlands Pharmacovigilance Centre, if the ADR was reported by

the GP itself. If the ADR was reported by another health care provider (e.g. pharmacist or hospital specialist), the latter was asked to provide information on the GP of the patient. Subsequently, the GPs were contacted to participate in the study. They were asked to identify the patient who experienced the ADR, through the provided birth date, gender, prescribed drug(s) (name and prescription date) and ADR. In addition, they were asked to select two control patients from their practice (same gender and decade of birth), who were prescribed the same proarrhythmic drug in the same year as the case patient. Participating GPs were sent three envelopes with study material for the case and the two controls which were to be forwarded to the concerned patients. Cases and controls of participating GPs received the envelope with information about the study, informed consent, a questionnaire and buccal swab. Patients could return forms and buccal swabs by mail, and remained anonymous to the researchers until the moment they decided to participate.

DNA-extraction and genotyping

DNA was extracted from buccal cells collected by the patients themselves using supplied cotton bud sticks [20]. DNA was screened for 10 missense mutations in genes which have been associated with the congenital long-QT syndrome and are present in > 1% of the Caucasian population (obtained from the long-QT syndrome database [21]): KCNQ1 (1178 G>T [22]), KCNH2 (2690 A>C, 2750 C>T, 3140 G>T [22]), SCN5A (100 C>T, 1673 A>G [7], 4500 G>T [23]), KCNE1 (112 A>G, 253 G>A [22]), and KCNE2 (22 A>G [22]). Analyses were performed by a laboratory experienced in LQT genotyping, using previously described techniques [13].

Data analyses

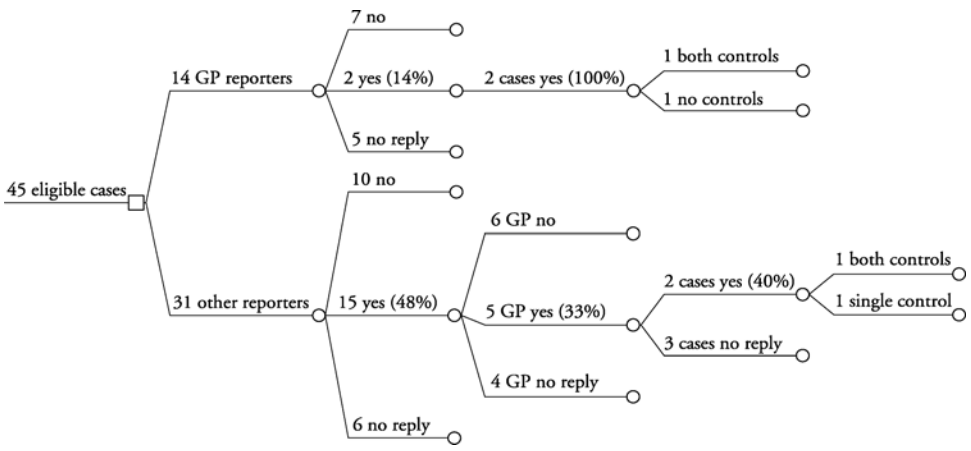
The feasibility of the study was evaluated by calculating participation rates at the three different phases of inclusion. First, the fraction of GPs that could be found was determined, hence the participation among contacted GPs, eligible cases and controls respectively was calculated. The overall participation rate was calculated as the fraction of all eligible cases providing buccal swabs which were usable for DNA analyses. Differences between characteristics of participating and non-participating patients were evaluated. Reporters and GPs, who were not willing to participate or gave no reply, were asked about their participation in a phoned questionnaire.

RESULTS

During the study period (January 1, 1996 to June 1, 2003) Lareb received a total of 23,236 ADR reports including 694 reports of cardiac arrhythmias of interest. Of these reports 51 concerned proarrhythmic drugs which were marked as suspected by the reporter. Five patients taking proarrhythmic drugs were younger than 18 years at the time of the study inquiry (2003). One report was excluded because the description of the ADR on the original report did not quite correspond with the coded ADR in the database. As a result 45 reports were eligible for inclusion in our study and reporters were contacted (Figure 1).

Patient inclusion, phase 1: fourteen cases were reported by GPs and name and address could be retrieved from the original reports. Of the 31 other reporters, 15 (48%) provided information on the patient's GP. As a result, 29 of the 45 GPs could be contacted (64%). Of the 16 reporters who could not provide information on the patients GP, we were able to find out the main reasons for non-participation, either by means of the reaction form or the phone interview in 15 of the cases (Table 1).

Figure 1 *Cases eligible for study participation*



In most instances, the contacted reporters were not able to identify the patients GP, because he or she did not have the patient's medical or pharmaceutical record at his or her disposal anymore. Phase 2: of the 29 contacted GPs, 7 (24%) were willing to participate in the study, select two control patients from their practice and send both cases and controls study material. The most common reason for not participating, provided by the 17 out of the 22 non-participating GPs, was lack of time (Table 1). Of the seven non-participating GPs who were willing to answer the phoned questionnaire, two GPs, who reported the ADR themselves, could recall the event. Of the five GPs that could not recall the event, the ADR was reported by another health care provider in four cases. Three out of seven said that they were interested in pharmacogenetic research in general. Two others thought our research was a burden to the case patients. Three out of seven thought our research was a burden to the control patients.

Table 1 *Reasons for not participating in the study*

Reason	Other reporters (15/16)	Contacted GPs (17/22)
Lack of time	2	10
High patient burden	-	1
Patient died	3	1
Patient lost to follow-up	5	3
Event happened too long ago	3	-
Quitted job	3	1
Other	2	6
Total*	18	22

**Health care providers could give more than one reason for non-participation, numbers do not add up*

Phase 3: of the seven cases and 14 controls that were contacted, four (57%) and five (36%) respectively were willing to participate in the study. All buccal swabs received were usable for DNA-analyses, giving an overall participation rate of 9% (4/45) among eligible case patients. Participating cases included a 43 year old female who developed palpitations within a few hours after starting terfenadine (2dd 60mg). She was not taking any comedication (case 1). Case 2 was a 62 year old female who developed palpitations within the first day of cisapride use (2dd 20mg). She took ranitidine (1dd 150mg), acetyl salicylic acid (1dd 80mg), simvastatin (1dd 20mg), carvedilol (2dd 6.25mg), as well as flecainide (1dd 100mg) concomitantly. Case 3 was a 45 year old male, who developed an arrhythmia (electrocardiogram showed circle tachycardia and AV-block) on the third day after starting terfenadine (2dd 60mg), he took flucloxacilline (4dd 500mg) as well as intranasal beclometason (2dd 50μg) concomitantly and had no history of cardiac disease. Case 4 was a 48 year old female who developed palpitations after the second dose of erythromycin (3dd 500mg). She was taking cetirizine (1dd 10mg) as well as an ethinylestradiol and levonorgestrel containing oral contraceptive concomitantly.

Characteristics of eligible cases, according to participation are presented in Table 2. Patients of participating GPs included more women and a relatively large proportion of terfenadine-cases compared with other eligible cases. Contacted case patients were more likely to participate when the ADR happened more recently. Due to small numbers, no significant differences were found.

All participating cases (n=4) and their matched controls (n=5) were genotyped for the 10 predefined single nucleotide polymorphisms (SNPs). Variants were identified in KCNH2, SCN5A and KCNE1 (Table 3). Numbers were too small to draw any significant conclusions.

Table 2 *Characteristics of eligible cases according to participation*

Variable	GP did not participate (n=38)		GP participated (n=7)			
			Patient did not participate (n=3)		Patient participated (n=4)	
Gender female	25	66%	3	100%	3	75%
Age (mean, sd)	48	± 16	45	± 20	50	± 9
Reporter	23	61%	3	100%	2	50%
Pharmacist						
GP	11	29%	2	67%	2	50%
Hospital specialist	3	8%				
Hospital pharmacist	1	3%				
Drug	3	8%				
Amitriptyline						
Cisparide	7	18%			1	25%
Clarithromycin	8	21%				
Clomipramine	1	3%				
Cotrimoxazole	5	13%				
Domperidone	1	3%				
Erythromycin	4	11%			1	25%
Terfenadine	7	18%	2	67%	2	50%
Trimethoprim	1	3%	1	33%		
Ketanserin+cisapride	1	3%				
Adverse drug reaction	9	24%			1	25%
Arrhythmia NOS						
Palpitations	21	55%	3	100%	3	75%
Tachycardia NOS	3	8%				
Torsade de Pointes	3	8%				
Ventricular Fibrillation	2	5%				
Year (mean, sd)	1998.8	±2	1996.7	±1	1999.8	±2

Table 3 *Results from genotyping*

Gene	*KCNH2*	*SNC5A*	*KCNE1*
Mutation	2690 A>C	1673 A>G	112 A>G
Case 1	A/C	A/A	A/G
Case 2	A/C	A/A	A/G
Control 2A	C/C	A/A	G/G
Control 2C	A/C	A/A	A/G
Case 3	A/C	A/A	G/G
Control 3A	A/A	A/G	G/G
Case 4	A/A	A/A	G/G
Control 4A	A/A	A/A	A/G
Control 4B	A/C	A/A	A/G

DISCUSSION

The bottleneck in pharmacogenetic research on rare adverse drug reactions is retrieval of phenotypes. Spontaneous reports of adverse drug reactions, collected by national pharmacovigilance institutions, may form a useful source of case patients. Our findings show that retrospective use of spontaneous reporting systems for adverse drug reactions to include patients in a cross-sectional pharmacogenetic study is feasible, although it results in an overall participation rate of approximately 10%.

We chose to approach the patients of interest through their general practitioner (GP), because GPs were able to select control patients from their practice who in theory had a comparable risk of developing cardiac arrhythmias. Although controls were not matched to the case on underlying diseases, they had the same gender, were about the same age, and were in need of the same potential proarrhythmic drug, for which the same GP decided treatment benefits outweighed treatment risks at about the same moment in time. We think this matching on prescriber is very important, since attitudes towards ADRs, perception of drug related risk, and ADR reporting behavior vary among physicians [19]. Control selection, however, may have increased the threshold for GPs to participate in the study. Three out of seven GPs interviewed thought our research was a burden to the control patients. One of these as well as two other out of the seven GPs had experienced problems when selecting controls. In addition, 10 out of 17 non-participating GPs mentioned lack of time to be a reason for not participating in the study, and control sampling is the most time-

consuming part of study participation. An optional method of improving participation may be by including patients and controls through their pharmacists instead of through their GPs. Dutch pharmacists are able to select gender, age, drug, time and GP matched controls from their computerised pharmacy databases. More than 80% of the pharmacists approached participated in another pharmacogenetic study from our group, in which patients were included through their pharmacies [data on file]. In other countries, however, this approach may not be feasible.

Of the seven cases and 14 controls which were contacted, four (57%) and five (36%) respectively were willing to participate in the study. Patient participation appeared to be at least as high as in the above-mentioned pharmacogenetic study from our group using mailed buccal swabs to collect genetic material, in which 38% of approximately 2,000 hypertensive patients participated [data on file]. The non-invasive buccal swab procedure appears to result in higher participation rates, compared with a study using blood samples [24]. This pharmacogenetic pilot study using previously collected postmarketing data found a participation rate of 21% among 150 patients with adverse reactions to selected drugs.

Although reports of patients which could be tracked back were not received more recently than reports of patients which could not be tracked back (Table 2), the majority of the reasons for health care providers not participating in the study were time related (Table 1). In contrast, contacted patients who participated in the study experienced the adverse drug reaction more recently than those who did not take part (Table 2). We therefore believe that prospective inclusion of patients immediately after reporting of adverse drug reactions of interest may improve overall participation rates.

For pharmacogenetic research on drug-induced arrhythmias, very well-defined phenotypes criteria are often used to identify cases [7]. Unfortunately, a spontaneous reporting system for adverse drug reactions as used by us does not provide such detailed information. In most cases, electrocardiograms are lacking, and often the events can only be coded as 'arrhythmia NOS' or 'palpitation'. One may argue that these cases are not suitable for genetic research. We think, however, that patients who experienced drug-induced arrhythmias, severe enough for their health care provider to report it to the national pharmacovigilance centre, fulfill criteria sufficiently to function as a phenotype. In addition, we only included selected case reports if they concerned drugs which are known to be able to cause drug-induced arrhythmias [16], to narrow the phenotype definition.

The strength of this study method is that it uses nation-wide screening for adverse drug reactions. Spontaneous reporting systems like the Dutch 'yellow card' system are known to represent only a fraction (< 10%) of the actual drug-related adverse events [25, 26], depending on the type of adverse drug reaction. Nevertheless rarer events can be studied than for instance in a hospital-setting. The total number of patients included in this pilot study, however, was still very small and no striking genetic differences between cases and controls were observed (Table 3). We therefore advise national pharmacovigilance centers from several countries to collaborate in order to increase sample sizes, and propagate international initiatives such as 'Eudragene', a European collaboration to establish a case-control DNA collection for studying the genetic basis of adverse drug reactions (www.eudragene.com).

In conclusion, spontaneous reporting systems for adverse drug reactions are a potential source for case finding in pharmacogenetic research on adverse drug reactions. The described method, using patient inclusion and control selection through general practitioners, however, leads to an overall participation rate of approximately 10%. Participation may be increased by patient inclusion immediately after the adverse event has been reported, or by including the pharmacists in the patient recruitment phase.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge J van der Meijden and H L Vos of the Department of Haematology of the Leiden University Medical Center, for the isolation of DNA from buccal swab samples. In addition, we gratefully thank the practitioners, pharmacists and patients who participated in this project.

BIBLIOGRAPHICAL REFERENCES

1. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W. Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions: A Systematic Review. *JAMA.* 2001; 286: 2270-9.
2. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med.* 2004; 350: 1013-22.
3. Shah RR. Pharmacogenetic aspects of drug-induced torsade de pointes : potential tool for improving clinical drug development and prescribing. *Drug Saf.* 2004; 27: 145-72.
4. Darpo B. Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. *Eur Heart J Supplements.* 2001; 3 (suppl K): K70-K80.
5. Vos MA, Paulussen ADC. Genetic basis of drug-induced arrhythmias. *Ann Med.* 2004; 36 (suppl 1): 1-7.
6. Roden DM. Pharmacogenetics and drug-induced arrhythmias. *Cardiovasc Res.* 2001; 50: 224-31.
7. Yang P, Kanki H, Crolet B, et al. Allelic variants in long-QT disease genes in patients with drug associated torsades de pointes. *Circulation.* 2002; 105: 1943-8.
8. Wei J, Yang IC, Tapper AR, et al. KCNE1 polymorphism confers risk of drug-induced long QT syndrome by altering kinetic properties of IKs potassium channels.*Circulation.*1999;Suppl I:I-495.
9. Kanki H, Yang P, Xie HG, Kim RB, George AL, Jr., Roden DM. Polymorphisms in beta-adrenergic receptor genes in the acquired long QT syndrome. *J Cardiovasc Electrophysiol.* 2002; 13: 252-6.
10. Sesti F, Abbott GW, Wei J, et al. A common polymorphism associated with antibiotic-induced cardiac arrhythmia. *Proc Natl Acad Sci U S A.* 2000; 97: 10613-8.
11. Abbott GW, Sesti F, Splawski I, et al. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell.* 1999; 97: 175-87.
12. Iwasa H, Kurabayashi M, Nagai R, Nakamura Y, Tanaka T. Genetic variations in five genes involved in the excitement of cardiomyocytes. *J Hum Genet.* 2001; 46: 549-52.
13. Paulussen AD, Gilissen RA, Armstrong M, et al. Genetic variations of KCNQ1, KCNH2, SCN5A, KCNE1, and KCNE2 in drug-induced long QT syndrome patients. *J Mol Med.* 2004; 82: 182-8.
14. van Puijenbroek E, Diemont W, van Grootheest K. Application of quantitative signal detection in the Dutch spontaneous reporting system for adverse drug reactions. *Drug Saf.* 2003; 26: 293-301.
15. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf.* 1999; 20: 109-17.
16. De Ponti F, Poluzzi E, Vaccheri A, et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. *Br J Clin Pharmacol.* 2002; 54: 171-7.

17. Tamblyn R, McLeod P, Hanley JA, Girard N, Hurley J. Physician and practice characteristics associated with the early utilization of new prescription drugs. *Med Care.* 2003; 41: 895-908.
18. Egberts AC, Veenstra M, de Jong-van den Berg LT. Antidepressant drug choice for first users in two regions in The Netherlands. *Pharm World Sci.* 1999; 21: 132-6.
19. Cosentino M, Leoni O, Oria C, et al. Hospital-based survey of doctors' attitudes to adverse drug reactions and perception of drug-related risk for adverse reaction occurrence. *Pharmacoepidemiol Drug Saf.* 1999; 8 Suppl 1: S27-35.
20. Meulenbelt I, Droog S, Trommelen GJ, Boomsma DI, Slagboom PE. High-yield noninvasive human genomic DNA isolation method for genetic studies in geographically dispersed families and populations. *Am J Hum Genet.* 1995; 57: 1252-4.
21. The long QT syndrome database. Available at: http://pc4.fsm.it:81/cardmoc; Accessed April 28, 2004.
22. Ackerman MJ, Tester DJ, Jones GS, Will ML, Burrow CR, Curran ME. Ethnic differences in cardiac potassium channel variants: implications for genetic susceptibility to sudden cardiac death and genetic testing for congenital long QT syndrome. *Mayo Clin Proc.* 2003; 78: 1479-87.
23. Wattanasirichaigoon D, Vesely MR, Duggal P, et al. Sodium channel abnormalities are infrequent in patients with long QT syndrome: identification of two novel SCN5A mutations. *Am J Med Genet.* 1999; 86: 470-6.
24. Clark D, Morgan A, Hananeia L, Coulter D, Olds R. Drug metabolism genotypes and their association with adverse drug reactions in selected populations: a pilot study of methodology. *Pharmacoepidemiology Drug Saf.* 2000; 9: 393-400.
25. Lumley CE, Walker SR, Hall GC, Staunton N, Grob PR. The under-reporting of adverse drug reactions seen in general practice. *Pharmaceut Med.* 1986; 1: 205-12.
26. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ('black triangle') drugs in general practice: observational study. *Br Med J.* 1998; 317: 119-20.

Chapter 4.2

ANTI-HERG ACTIVITY AND THE RISK OF DRUG-INDUCED ARRHYTHMIAS AND SUDDEN DEATH

Marie L De Bruin [1,2], Monica Pettersson [3], Ronald HB Meyboom [1,3], Arno W Hoes [2], Hubert GM Leufkens [1]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaco-epidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands
[3] The Uppsala Monitoring Centre, Uppsala, Sweden

Submitted for publication

SUMMARY

Objective: Drug-induced QTc-prolongation, resulting from inhibition of HERG potassium channels, may lead to serious ventricular arrhythmias and sudden death. We studied the quantitative anti-HERG activity of proarrhythmic drugs as a risk factor for this outcome in day-to-day practice.

Methods: Data were extracted from the International Drug Monitoring Program of the World Health Organisation (WHO-UMC), which consists of more than 3 million case reports of suspected adverse drug reactions. For this study all reports up to the first quarter of 2003 of drugs with known anti-HERG activity were used. As a measure of association, the reporting odds ratios were calculated. Cases were defined as reports of cardiac arrest, sudden death, Torsade de Pointes, ventricular fibrillation, and ventricular tachycardia. Cases were compared with all other reports regarding the anti-HERG activity, defined as the effective therapeutic plasma concentrations ($ETCP_{unbound}$) divided by the HERG IC_{50} value, of suspected drugs.

Results: During the study period, the WHO-UMC received 284,426 reports of ADRs of study drugs, of which 5,591 concerned ADRs of interest. We identified a significant association of 1.93 (95%CI 1.89 to 1.98) between the anti-HERG activity of drugs, measured as $\log^{10}$ ($ETCP_{unbound}/IC_{50}$), and reporting of serious ventricular arrhythmias and sudden death to the WHO-UMC database.

Conclusion: Drugs which bind to HERG potassium channels in concentrations close to or lower than therapeutic plasma concentrations have a high risk of reports of serious ventricular arrhythmias and sudden death in the WHO-UMC database, indicating a higher proarrhythmic risk. These findings support the value of preclinical HERG testing to predict proarrhythmic effects of medicines.

INTRODUCTION

Drug-induced prolongation of the QTc-interval usually results from concentration-dependent blocking of cardiac HERG potassium channels. An excessively prolonged QTc-interval can, under the right circumstances, lead to a polymorphic ventricular arrhythmia known as Torsade de Pointes. When Torsade de Pointes is sustained, symptoms arising from impaired cerebral circulation such as dizziness, syncope and/or seizures, may become manifest. Torsade de Pointes subsequently degenerates into ventricular fibrillation in approximately 20% of the cases and, not uncommonly, cardiac arrest or sudden death may occur. Over the last decade, this adverse reaction has attracted considerable clinical and regulatory interest and has been the most common cause of withdrawal or restriction of the use of drugs on the market [1, 2].

In 1997, the Committee for Proprietary Medicinal Products (CPMP) of the European Union adopted a 'Points to Consider' document which made recommendations for nonclinical and clinical approaches to assess the risk of QTc-interval prolongation and Torsade de Pointes for noncardiovascular drugs [3]. The strategies described are now being harmonised by the International Conference of Harmonisation (ICH), and a draft version of the 'Note for Guidance' document is currently available [4]. Based on these regulatory recommendations, most new drugs are tested nowadays for their ability to block HERG potassium channels and I_{Kr} currents. However, there is still much debate going on within the pharmaceutical industry as well as regulatory authorities on the predictive value of HERG channel binding and the risk of cardiac arrhythmias in man. For example, collaborating researchers from several pharmaceutical industries recently published an extensive overview of 100 QTc-prolonging drugs and their ability to bind to HERG-channels in relation to free-plasma concentrations [5]. These authors related this anti-HERG activity to the torsadogenic propensities of the drugs. Drugs were assigned to one of the following 5 categories of decreasing torsadogenicity: 1: antiarrhythmic drugs, 2: drugs withdrawn or suspended due to Torsade de Pointes-risk, 3: drugs with measurable Torsade de Pointes risk in humans or many Torsade de Pointes case reports in published literature, 4: isolated Torsade de Pointes case reports, 5: no published reports of Torsade de Pointes in humans, but with a certain degree of suspicion because, for example, therapeutic class, drug interactions, etc. The clinical relevance of this type of categorisation, however, remains to be confirmed.

We therefore studied the magnitude of anti-HERG activity in relation to pro-arrhythmic risk, defined as the occurrence of serious ventricular arrhythmias and sudden death, in day-to-day practice, using drug safety data obtained from the World Health Organisation (WHO) adverse drug reactions database.

METHODS

Setting

Data from the International Drug Monitoring Program of the WHO were used [6]. The database of this program is maintained by the Uppsala Monitoring Centre (WHO-UMC) and contains summaries of case reports originally submitted by health care professionals to national pharmacovigilance centres in more than 70 countries all over the world. At the end of 2003, this database contained more than 3 million individual case reports of suspected adverse drug reactions (ADRs) regarding specific, but anonymous, patients. The reports contain administrative data, patient data, ADR data, medication data and other information. The information in these reports is not homogenous, at least with regard to origin, completeness of documentation or the likelihood that the suspected drugs caused the adverse events.

The domain of this study were all reports up to the first quarter of 2003 of a previously published list of 52 proarrhythmic drugs, for which information on both effective free therapeutic plasma concentrations ($ETCP_{unbound}$) as well as inhibition of HERG/I_{Kr} currents were available [5].

Design

A wide-spread method for quantitative signal detection in spontaneous reporting systems is the calculation of Reporting Odds Ratios (ROR) as a measure of disproportionality. This method compares the exposure odds with certain drugs among case reports of interest with the exposure odds among all other reports, as a measure of background risk, and is calculated like a normal odds ratio (Table 1). The advantage of this method is that it is easily applicable and adjustment for covariates is possible in logistic regression analysis [7]. A ROR significantly higher than 1 indicates a disproportionate share of a certain drug in a certain ADR and hence an increased risk of this ADR of interest.

Table 1 *Calculation of the reporting odds ratios (ROR.*

	Reports with the suspected ADR	Reports without the suspected ADR
Reports with the suspected drug (exposed)	A	B
All other reports (nonexposed)	C	D

ROR= (a/c)/(b/d) = ad/bc

In the WHO-UMC database the case reports of interest were identified by means of the WHO-ART adverse reaction terms: 'cardiac arrest', 'sudden death', 'Torsade de Pointes', 'ventricular fibrillation' and 'ventricular tachycardia' [8]. The anti-HERG activity of the study drugs was regarded as the exposure. Anti-HERG activity was defined as the free plasma concentrations attained during clinical use (effective therapeutic plasma concentrations; $ETCP_{unbound}$) divided by the concentration which inhibits 50% of the potassium channels (IC_{50}). When multiple HERG-binding properties or free plasma concentrations have been described in the literature, the lowest IC_{50} and the maximum $ETCP_{unbound}$ were used [5]. Per ADR-report, anti-HERG activities of all study drugs which were assigned as 'suspect' were assessed. If multiple study drugs were reported, anti-HERG activities were added up using the following formula: $Sum_{anti\text{-}HERG\ activity} = (IC_{50} / ETCP_{unbound})A + (IC_{50} / ETCP_{unbound})B + \ldots\ldots + (IC_{50} / ETCP_{unbound})Z$. The $ETCP_{unbound}/IC_{50}$ ratio of the study drugs varied from less than 0.0003 to 40, and a $\log^{10}$ transformation was used. This exposure measure can be regarded as the therapeutic/toxic ratio of a drug or drug combination. It was expected that with increasing $ETCP_{unbound}/IC_{50}$ ratio, the risk of an adverse event of interest increases.

Potential confounders

The association between anti-HERG activity and the study outcome may be confounded by secondary factors including age, sex, several concomitant diseases (heart disease, pulmonary disease, diabetes mellitus), pharmacokinetic drug-drug interactions, concomitant use of drugs which may lower blood potassium levels, year of reporting and time since first marketing. When multiple study drugs were reported, in the analyses, the shortest latency period between marketing and reporting was used.

For the assessment of concomitant diseases proxies derived from the available information provided by the reporters were used (Table 2). Time since marketing was calculated as the year of reporting minus the year of first marketing.

Table 2 *Definition of cardiac disease, diabetes mellitus and pulmonary disease*

Disease	Definition
Cardiac disease	Concomitant medication of cardiac drugs (ATC-code C01, verapamil or diltiazem) or, predisposing or contributing conditions marked as ischaemic heart disease, heart failure, cardiac dysrhythmias, conduction disorders, hart valve replacement or cardiac pacemaker
Diabetes mellitus	Concomitant medication of antidiabetic drugs (ATC-code A10) or, predisposing or contributing conditions marked as diabetes mellitus
Pulmonary disease	Concomitant medication of antiasthmatic drugs (ATC-code R03) or, predisposing or contributing conditions marked as chronic bronchitis, emphysema, asthma or COPD

Data analysis

To estimate the association between anti-HERG activity and serious ventricular arrhythmias and sudden death, RORs were calculated using unconditional logistic regression. The analyses were adjusted for the potential confounding factors mentioned above using multivariate logistic regression. All statistical analyses were performed using SPSS 10.0 statistical software (SPSS Inc., Chicago, Illinois, USA).

Subgroup analyses

In order to study whether the association differed among several sub-populations of the study population, separate RORs were calculated for subgroups based on gender, age, type of drugs used, part of the world where reports originated from, time since marketing (to study the Weber effect [9]), and reporting date (to study the influence of mass media attention [10]).

Different case definitions

Since we used a composite study outcome, we also looked at the five different endpoints separately. Cardiac arrest, sudden death, Torsade de Pointes, ventricular fibrillation and ventricular tachycardia are the most precisely defined serious outcomes which may result from drug-induced QTc-prolongation in the WHO-

ART terminology. Other, less well-defined terms, such as cardiac fibrillation and ventricular arrhythmias, however, may also include study outcomes of interest. We therefore also calculated RORs using these two latter case definitions. The association of anti-HERG activity with QTc-prolongation, a precursor for drug-induced arrhythmias, and syncope, one of the clinical symptoms, were assessed as well. As a negative control, we studied the association between anti-HERG activity and two randomly picked study outcomes, without proven association with HERG: hepatitis and skin ulcer.

Missing values

The WHO-UMC data are summaries of case reports of suspected adverse drug reactions, originally submitted to national pharmacovigilance centres. However, reports such as these often do not contain a full medical history, and data on confounders may be incomplete or lacking. To assess the presence of concomitant diseases, use was made of the information in the field 'predisposing or contributing conditions' (shown in 2% of the reports), as well as known comedication (shown in 50% of the reports).

Age and gender of the patient were unknown in 20% and 9% ADR-reports respectively. Unknown gender was analysed as a separate category. Missing ages were imputed based on the mean age of patients of the same gender, using the same drugs.

RESULTS

During the study period, the WHO received 284,426 reports of ADRs of 49 of the 52 study drugs. The greatest number of reports concerned fluoxetine, followed by nifedipine and ciprofloxacin. An overview of anti-HERG activities and ADR-reports is presented in Table 3.

Table 3 *Study drugs and anti-HERG activities*

Drug name	1st year marketed[11]	$ETCP_{unbound}$ (nM)	IC_{50} (μM)	Ratio*	log^{10} (ratio)	Cases	Noncases
Nifedipine	1975	7.7	275	0.00003	-4.6	94	20,437
Nitrendipine	1985	3.02	10	0.00030	-3.5	3	610
Amiodarone	1962	0.5	1	0.00050	-3.3	271	10,467
Cetirizine	1987	56	108	0.00052	-3.3	18	5,217
Diphenhydramine	1946	34	30	0.00113	-2.9	37	3,296
Erythromycin	1952	170	72.2	0.00235	-2.6	54	12,173
Loratadine	1988	0.45	0.173	0.00260	-2.6	58	4,265
Ciprofloxacin	1987	5281	966	0.00547	-2.3	72	14,936
Chlorpheniramine	1968	11	1.6	0.00688	-2.2	13	3,915
Amitriptyline	1961	41	4.66	0.00880	-2.1	92	7,301
Fluoxetine	1986	29	3.1	0.00935	-2.0	203	45,834
Risperidone	1993	1.81	0.15	0.0121	-1.9	143	12,254
Diltiazem	1973	122	10	0.0122	-1.9	145	11,282
Terfenadine	1982	0.29	0.02	0.0145	-1.8	200	5,162
Ebastine	1990	5.1	0.3	0.0170	-1.8	2	112
Mefloquine	1986	95.2	5.6	0.0170	-1.8	12	8,399
Tamoxifen	1973	21	1	0.0210	-1.7	69	8,504
Olanzapine	1996	5.2	0.231	0.0225	-1.6	136	8,994
Mizolastine	1998	8.7	0.35	0.0249	-1.6	6	222
Pimozide	1969	0.43	0.015	0.0287	-1.5	22	482
Imipramine	1958	106	3.4	0.0312	-1.5	21	3,576
Tedisamil	-	80	2.5	0.0320	-1.5	0	1
Mibefradil	1997	12	0.35	0.0343	-1.5	95	2,370
Clarithromycin	1990	1206	32.9	0.0367	-1.4	115	11,473
Cibenzoline	1985	976	23	0.0424	-1.4	13	214
Phenytoin	1938	4360	100	0.0436	-1.4	118	14,578
Bepridil	1981	33	0.6	0.0550	-1.3	59	125
Fexofenadine	1996	345	5	0.0690	-1.2	24	2,224
Grepafloxacin	1997	2087	27	0.0773	-1.1	6	287
Desipramine	1962	108	1.39	0.0777	-1.1	41	2,111
Ketoconazole	1981	177	1.9	0.0932	-1.0	9	4,734

* $ETCP_{unbound}/IC_{50}$

Table 3 *Study drugs and anti-HERG activities, continued*

Drug name	1st year marketed[11]	$ETCP_{unbound}$ (nM)	IC_{50} (μM)	Ratio*	log^{10} (ratio)	Cases	Noncases
Sertindole	1996	1.59	0.014	0.114	-0.9	20	266
Erythromycin i.v.	1952	8516	72.2	0.118	-0.9	75	1,671
Domperidone	1978	19	0.16	0.119	-0.9	12	1,216
Haloperidol	1959	3.6	0.027	0.133	-0.9	247	7,864
Procainamide	1950	54186	310	0.175	-0.8	101	2,652
Sematilide	-	4449	25	0.178	-0.7	0	0
Flecainide	1982	753	3.91	0.193	-0.7	332	1,894
Sotalol	1974	14733	74	0.199	-0.7	337	1,477
Astemizole	1983	0.26	0.0009	0.289	-0.5	68	1,974
Dofetilide	1999	2	0.005	0.400	-0.4	68	676
Disopyramide	1969	742	1.8	0.412	-0.4	110	1,843
Terfenadine +3A4inhibitor	1982	9	0.02	0.450	-0.3	60	264
Propafenone	1979	241	0.44	0.548	-0.3	97	1,146
Verapamil	1963	81	0.14	0.579	-0.2	332	10,788
Azimilide	1999	70	0.1	0.700	-0.2	0	0
Aprindine	1973	239	0.23	1.04	0.0	1	164
Cisapride	1988	4.9	0.002	2.45	0.4	596	6,278
Almokalant	-	150	0.05	3.00	0.5	0	0
Terodiline	1986	12	0.004	3.00	0.5	66	1,160
Sparfloxacin	1993	1766	0.23	7.68	0.9	10	420
Quinidine	1918	3237	0.3	10.8	1.0	181	3,399
Ibutilide	1996	140	0.01	14.0	1.1	154	27
Thioridazine	1958	979	0.033	29.7	1.5	152	3,520
> 1 drug						421	4,581
Total						5,591	278,835

* $ETCP_{unbound}/IC_{50}$

5,591 of these reports concerned serious ventricular arrhythmias and/or sudden death (2,533 cardiac arrests, 1,085 ventricular fibrillations, 1,675 ventricular tachycardias, 1,031 Torsade de Pointess and 468 sudden deaths). Reports could include more than one ADR term of interest, consequently the numbers do not add up. Table 4 summarises the characteristics of the case reports of serious ventricular arrhythmias and sudden death (cases), plus all other reports. Cases had a significantly higher $ETCP_{unbound}/IC_{50}$ ratio, patients were older and ADRs were reported more recently than other reports. In significantly more cases, heart disease was marked as a predisposing factor. Both cases and other reports concerned a slight preponderance of females.

Table 4 *Characteristics of reports of cardiac arrest, sudden death, Torsade de Pointes, ventricular tachycardia, or ventricular fibrillation (cases) and other reports (noncases)*

	Cases (n=5,591)		Noncases (n=278,835)		p-value
$ETCP_{unbound}/IC_{50}$ (mean, sd)	2.24	± 5.9	0.69	± 3.6	<0.001
Age (mean, sd)	57.3	± 18.7	49.6	± 19.5	<0.001
Gender					
Male	2,314	41.4%	105,902	38.0%	<0.001
Female	2,976	53.2%	147,699	53.0%	
Unknown	301	5.4%	25,234	9.0%	
Comorbidity					
Pulmonary disease	154	2.8%	6,037	2.2%	0.003
Heart disease	2,540	45.4%	58,269	20.9%	<0.001
Diabetes mellitus	225	4.0%	6,029	2.2%	<0.001
Comedication					
Drug-drug interaction	332	5.9%	6,132	2.2%	<0.001
Use of potassium-lowering drugs*	670	12.0%	16,170	5.8%	<0.001
Time					
Reporting year (mean, sd)	1996	± 6.0	1994	± 6.4	<0.001
Years since marketing (mean, sd)	20.8	± 16.7	19.0	± 15.6	<0.001

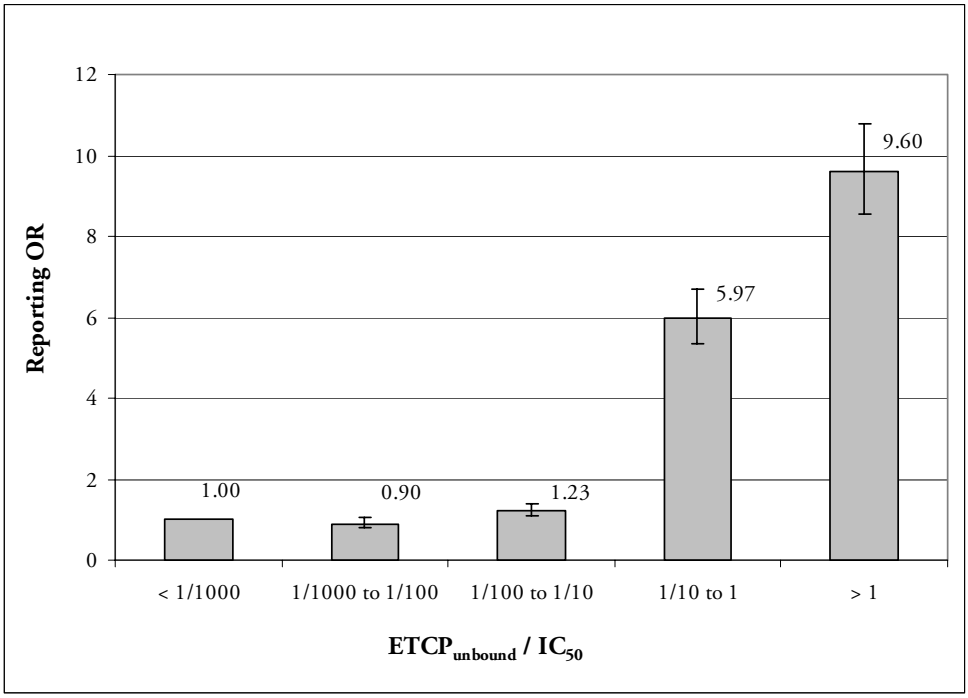
* *Non potassium-sparing diuretics, laxatives, systemic β-agonists, systemic corticosteroids*

The crude logistic regression analysis revealed a positive association between anti-HERG activity and the risk of serious ventricular arrhythmias and sudden death. The ROR for the $\log^{10}$ $ETCP_{unbound}/IC_{50}$ ratio was 1.93 (95%CI 1.89 to 1.97). After adjustment for age, gender, year of reporting, heart disease, diabetes mellitus, pulmonary disease, pharmacokinetic drug-drug interactions, concomitant use of potentially potassium-lowering drugs and years between marketing and report, the ROR changed marginally 1.93 (95%CI 1.89 to 1.98).

When taking a $IC_{50}/ETCP_{unbound}$ ratio of 30, corresponding to a $ETCP_{unbound}/IC_{50}$ ratio of 0.033, as a cut-off point, as suggested by Redfern et al [5], the adjusted ROR for a ratio over 0.033 *vs* a ratio below 0.033 was 3.68 (95%CI 3.47 to 3.91). This indicates that drugs which bind to HERG K^+ channels at levels less than 30 times the therapeutic levels, have a three to four times stronger association with serious ventricular arrhythmias and sudden death as an adverse reaction, compared with drugs which bind to HERG K^+ channels at concentrations more than 30 times the therapeutic levels.

In Figure 1 anti-HERG activities of the study drugs were grouped into five categories. Adjusted RORs were calculated for these categories using an $ETCP_{unbound}/IC_{50}$ ratio of < 1/1,000 as the reference category. The ROR of 5.97 indicates that for drugs for which the IC_{50} is 1 to 10 times higher than the $ETCP_{unbound}$ the risk of reporting serious ventricular arrhythmias and sudden death is six times higher compared with drugs for which the IC_{50} is more than 1,000 times higher than the $ETCP_{unbound}$ (reference category).

Figure 1 *The association between $ETCP_{unbound}/IC_{50}$ ratio and the composite endpoint (cardiac arrest, sudden death, Torsade de Pointes, ventricular tachycardia, or ventricular fibrillation)*



Subgroup analysis and different study outcomes

Adjusted RORs in studied subgroups varied between 1.6 and 3.5 and were all significantly higher than 1 (Table 5). The association is stronger in females, patients aged < 65, reports of non-antiarrhythmic drugs and reports from North-American countries. The association decreases when a drug has been longer on the market, and is more pronounced after January 1, 1998 than before that date.

Table 5 *Association between log[10] ($ETCP_{unbound}/IC_{50}$) and serious ventricular arrhythmias or sudden death for several subgroups and between log[10] ($ETCP_{unbound}/IC_{50}$) and several study endpoints*

$\log^{10}$ ($ETCP_{unbound}/IC_{50}$)	OR_{crude}	(95%CI)	$OR_{adjusted}$*	(95%CI)
Overall†	1.93	(1.89-1.97)	1.93	(1.89-1.98)
Gender†				
Males	1.74	(1.68-1.80)	1.76	(1.70-1.83)
Females	2.08	(2.02-2.14)	2.08	(2.01-2.15)
Age†				
< 65	2.08	(2.02-2.14)	2.06	(1.99-2.12)
≥ 65	1.66	(1.60-1.71)	1.78	(1.71-1.84)
Suspected drug†				
Antiarrhythmic drugs	1.39	(1.34-1.44)	1.73	(1.66-1.80)
Other medication	2.02	(1.97-2.08)	2.01	(1.96-2.07)
Reporting country†				
Europe	1.85	(1.78-1.93)	1.79	(1.72-1.87)
North-America	2.05	(1.99-2.10)	2.03	(1.97-2.09)
Rest of the world	1.60	(1.46-1.76)	1.58	(1.42-1.77)
Time†				
1st year after marketing	3.56	(2.91-4.34)	3.50	(2.48-4.94)
≤ 5 years after marketing	2.91	(2.72-3.11)	2.06	(1.882.26)
> 10 years after marketing	1.71	(1.67-1.75)	1.83	(1.78-1.88)
> 20 years after marketing	1.46	(1.41-1.50)	1.59	(1.54-1.65)
Reported before January 1, 1998	1.79	(1.74-1.84)	1.74	(1.67-1.80)
Reported after January 1, 1998	2.29	(2.21-2.37)	2.20	(2.12-2.28)
Different case-definitions				
Cardiac arrest	1.80	(1.74-1.86)	1.80	(1.74-1.86)
Sudden death	1.62	(1.50-1.75)	1.74	(1.60-1.89)
Torsade de pointes	2.21	(2.10-2.32)	2.34	(2.22-2.49)
Ventricular tachycardia	2.04	(1.96-2.12)	2.01	(1.92-2.10)
Ventricular fibrillation	2.34	(2.23-2.45)	2.61	(2.47-2.76)
QTc-prolongation	2.27	(2.18-2.37)	2.73	(2.61-2.86)
Cardiac fibrillation	1.63	(1.20-2.21)	1.57	(1.14-2.17)
Ventricular arrhythmia	1.54	(1.44-1.65)	1.48	(1.38-1.59)
Syncope	1.24	(1.21-1.28)	1.23	(1.19-1.26)
Hepatitis	1.02	(0.99-1.05)	0.97	(0.94-1.00)
Skin ulcer	1.06	(0.91-1.24)	1.06	(0.92-1.24)

* *Adjusted for age, gender, year of reporting, heart disease, diabetes mellitus, pulmonary disease, pharmacokinetic drug-drug interactions, concomitant use of potassium-lowering drugs and years since first marketing*

† *Composite endpoint: cardiac arrest, sudden death, TdP, ventricular tachycardia, ventricular fibrillation*

When the five study outcomes are regarded separately adjusted RORs varied between 1.7 and 2.6. QTc-prolongation, a precursor for drug-induced arrhythmias was also strongly associated with anti-HERG activity (ROR 2.7). When less well-defined endpoints were used, the association weakened. Anti-HERG activity showed no association with either of the negative control end-points: hepatitis and skin ulcer (Table 5).

DISCUSSION

We identified a significant association of 1.93 (95%CI 1.89 to 1.98) between the anti-HERG activity of drugs, measured as $\log^{10}$ ($ETCP_{unbound}/IC_{50}$), and reporting of serious ventricular arrhythmias and sudden death to the WHO-UMC database.

Our findings support the hypothesis that anti-HERG activity is associated with risk of serious ventricular arrhythmias and sudden death in daily clinical practice. As expected, drugs which bind to HERG potassium channels in concentrations close to therapeutic plasma concentrations, have a high risk of reporting serious ventricular arrhythmias and sudden death, probably indicating a proarrhythmic effect. The smaller the margin between IC_{50} (toxic drug level) and $ETCP_{unbound}$ value (therapeutic drug level), the higher the risk (Figure 1). The ORs in this study represent a relative risk, but do not estimate the actual proarrhythmic risk in day-to-day practice. They reflect the disproportionality of serious ventricular arrhythmias and sudden death as an ADR among all possible ADRs of a certain drug. The overall OR of 1.93 indicates that for every single unit increase in the $\log^{10}$ (e.g. from 1/1,000 to 1/100, from 1/100 to 1/10, from 1/10 to 1 etc) of the therapeutic/toxic ratio of a drug, the risk of reporting serious ventricular arrhythmias and sudden death doubles.

General limitations of the dataset should be discussed. Firstly, the study was restricted to drugs for which HERG-binding properties as well as therapeutic free plasma concentrations have been studied and published. The number of drugs being tested for HERG activities is still increasing and these analyses should be repeated when more data are available. Secondly, the $ETCP_{unbound}/IC_{50}$ ratios were based on therapeutic plasma levels at recommended doses. The case reports in the WHO-UMC database, however, do not disclose in sufficient detail the doses used by these patients. Plasma levels may increase when pharmacokinetic drug-drug interactions occur or alternative routes of administration are used. Specific anti-HERG activities were only known for terfenadine plus CYP3A4 inhibitors and i.v. erythromycin, and as can be seen in Table 3, major differences were observed. Of all reports concerning

terfenadine co-administered with CYP3A4-inhibitors, in 19% of the cases the ADR was a serious ventricular arrhythmia or sudden death, while this fraction in terfenadine reports without co-administration of CYP3A4 inhibitors was only 3.5%. Similar differences were observed for erythromycin i.v. (4%) versus other routes of administration (0.4%). Uncertainty of actual plasma levels may have influenced our results.

The method of reaction proportion signalling has several drawbacks. ADRs were reported on a voluntary basis, and therefore represent only a fraction (< 10%) of the actual adverse events that occurred [12, 13]. Selective under- and overreporting of particular ADRs within the overall underreporting can lead to misinterpretations when comparing drugs with respect to ADRs. ADRs which are more likely than others to be reported are ADRs of relatively new drugs [9, 14], severe ADRs [12, 14] and ADRs which are not listed in the summary of product characteristics [12]. All these aspects can be seen in the subgroup analyses we performed. The association was stronger shortly after marketing, it was less well pronounced among patients taking antiarrhythmic drugs, for which the proarrhythmic side effects have been already described (Table 4). The association weakens when the study event is less severe (syncope *vs* ventricular arrhythmia). Another factor which may have influenced our results is selective reporting as a result of media attention. This factor has been described previously for the association between cardiac arrhythmias and the use of antihistamine drugs [10], and similarly in our study the association between exposure and outcome is stronger after January 1, 1998, than before.

We did not of course study the effects of individual drugs, but the *in vitro* anti-HERG activities of drugs and combinations of drugs. These molecular properties of drugs are unlikely to be known by health care providers in daily practice. We therefore think that we have used a more objective exposure measure, which is less susceptible to recognised bias. Moreover, all subgroup analyses point in a similar direction and negative control outcomes which should not be related to anti-HERG activity (hepatitis, skin ulcer) are indeed unrelated to the exposure. We therefore believe that our findings represent a true connection.

Some drugs appear not to follow the predicted association, as seen when we plotted anti-HERG activities against the fraction of ADRs which concern serious ventricular arrhythmias and sudden death of all study drugs with at least 500 reports in the WHO-UMC database. For amiodaron, sotalol and flecainide, the fraction is higher than expected. These three drugs are prescribed to patients with cardiac arrhythmias

and therefore 'confounding by indication' may have caused this relatively high fraction of 'case-events'. For ketoconazole and mefloquine, the fraction of 'case-events' in the WHO-UMC database is much lower than expected, based on anti-HERG activity. Ketoconazole and mefloquine, could be regarded as drugs with 'false positive' anti-HERG activities. For ketoconazole this effect was described before [5].
Drugs that bind to HERG potassium channels in concentrations close to or lower than therapeutic plasma concentrations (i.e. have a high $\log^{10}$ $ETCP_{unbound}/IC_{50}$ ratio) have a high risk of reports of serious ventricular arrhythmias and sudden death in the WHO-UMC database, indicating a higher proarrhythmic risk. The higher the IC_{50} (toxic drug level) compared with the $ETCP_{unbound}$ value (therapeutic drug level), the higher this risk. These findings support the value of preclinical HERG testing to predict proarrhythmic effects of medicines.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge Professor John Urquhart for his valuable critical comments.

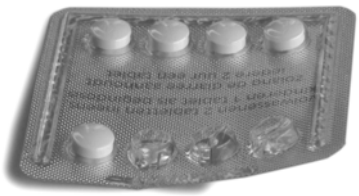
BIBLIOGRAPHICAL REFERENCES

1. Viskin S. Long QT syndromes and torsade de pointes. *Lancet.* 1999; 354: 1625-33.
2. Shah RR. Pharmacogenetic aspects of drug-induced torsade de pointes : potential tool for improving clinical drug development and prescribing. *Drug Saf.* 2004; 27: 145-72.
3. Committee for Proprietary Medicinal Products (CPMP). *Points to Consider: the assessment for the potential for QT interval prolongation by non-cardiovascular medicinal products (CPMP/986/96).* London: European Agency for the Evaluation of Medicinal Products, 1997.
4. Committee for Proprietary Medicinal Products (CPMP). *Note for guidance on safety pharmacology studies for assessing the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticls (CPMP/ICH/423/02).* London: European Agency for the Evaluation of Medicinal Products, 2002.
5. Redfern WS, Carlsson L, Davis AS, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovascular Research.* 2003; 58: 32-45.
6. Edwards IR, Olsson S. The WHO International Drug Monitoring Program. In: Aronson JK, ed. *Side Effects of Drugs, Annual 26*. Amsterdam: Elsevier Science, 2003: 548-57.
7. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* 2002; 11: 3-10.
8. WHO. *International monitoring of adverse reactions to drugs: adverse reaction terminology*. Uppsala, Sweden: WHO Collaborating Centre for International Drug Monitoring, 2003.
9. Weber JCP. Epidemiology of adverse drug reactions to nonsteroidal antiinflammatory drugs. In: Rainsford KD, Velo GP, eds. *Adv Inflamm Res*. New York: Raven Press,1984:1-7.
10. De Bruin ML, van Puijenbroek EP, Egberts AC, Hoes AW, Leufkens HGM. Non-sedating antihistamine drugs and cardiac arrhythmias - biased risk estimates from spontaneous reporting systems? *Br J Clin Pharmacol.* 2002; 53: 370-4.
11. Wetenschappelijk Instituut Nederlandse Apothekers (WinAP). *Informatorium Medicamentorum*. 's Gravenhage, the Netherlands: Koninklijke Nederlandse Maatschappij ter bevoordering der Pharmacie, 2004.
12. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ('black triangle') drugs in general practice: observational study. *Br Med J.* 1998; 317: 119-20.

13. Lumley CE, Walker SR, Hall GC, Staunton N, Grob PR. The under-reporting of adverse drug reactions seen in general practice. *Pharmaceut Med.* 1986; 1: 205-12.
14. Milstien JB, Faich GA, Hsu JP, Knapp DE, Baum C, Dreis MW. Factors affecting physician reporting of adverse drug reactions. *Drug Inf J.* 1986; 20: 157-64

Chapter 5

METHODOLOGICAL ISSUES



Chapter 5.1

VALIDATION OF HOSPITAL DISCHARGE DIAGNOSES OF CARDIAC ARRHYTHMIAS

Marie L De Bruin[1,2], Norbert M van Hemel [3], Hubert GM Leufkens[1], ArnoW Hoes[2]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmaco-epidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands
[3] Heart Lung Center Utrecht, Department of Cardiology, St Antonius Hospital Nieuwegein and University Medical Center Utrecht, the Netherlands

Submitted for publication

SUMMARY

Objective: We investigated the positive predictive value of hospital discharge diagnosis of cardiac arrhythmias as a marker for ventricular arrhythmias or cardiac arrest.
Methods: We identified patients whose record in the PHARMO record linkage system database showed a code for ventricular or non-specified cardiac arrhythmias according to codes of the International Classification of Diseases 9th revision Clinical Modification (ICD-9-CM). The validity of well-defined diagnoses (427.1, 427.4, 427.41, 427.42, 427.5, 427.69) and other diagnoses (427.2, 427.60, 427.8, 427.89, 427.9) of ventricular or non-specified cardiac arrhythmias was ascertained through manual review of hospital clinical records. Positive predictive values (PPV) were calculated and differences between characteristics of true and false positives were evaluated.
Results: The PPV of well-defined diagnoses was 82% (95%CI 72% to 92%), whereas the PPV of other diagnoses was as low as 10% (95%CI 2% to 18%), giving an overall PPV of 50% (95%CI 40% to 59%). Among well-defined diagnoses, true positive results were associated with male gender (p=0.09) and younger age (p=0.05).
Conclusion: Well-defined hospital discharge diagnosis of ventricular cardiac arrhythmias and sudden death have a high PPV and are useful to identify cases in a case-control study, whereas other diagnoses do not.

INTRODUCTION

Adverse drug reactions which require in-patient hospitalisation fulfil the criteria for 'serious' according to the ICH Harmonised Tripartite Guideline [1]. Hospitalisations are widely used to define outcomes in pharmacoepidemiological database studies on adverse reactions of drugs [2-6]. The most commonly applied coding system to categorise hospital discharge diagnosis is the International Classification of Diseases (ICD) [7]. Classification in a computerised medical database, however, can be subject to errors, ranging from incomplete reporting by a physician to typing errors by the coding clerk [8]. Several researchers have assessed the validity of hospital discharge records of various diseases, comparing the data with either original medical records [9-12] or computerised information from the clinical chemical laboratory [13].

Drugs which prolong cardiac repolarisation, manifested as a prolonged QTc-interval on the surface electrocardiogram, may induce Torsade de Pointes arrhythmias, which are generally preceded by ventricular premature beats [14]. This specific type of ventricular tachycardia may develop into ventricular fibrillation, which leads to cardiac arrest and requires electrocardioversion to restore normal rhythm [15]. Hospitalisations for cardiac arrhythmias may function as an epidemiological study endpoint of interest, when assessing the risk of drug-induced arrhythmias among patients taking QTc-prolonging drugs.

We investigated the positive predictive value of hospital discharge diagnosis of cardiac arrhythmias, classified according to ICD-codes, as a marker for ventricular arrhythmias or cardiac arrest.

METHODS

Setting

Data were obtained from the PHARMO record linkage system, containing drug-dispensing records from community pharmacies and linked hospital discharge records of a defined population of 330,000 residents of 8 medium-sized Dutch cities. In the Netherlands, as in many other countries, every hospital is obliged to collect diagnostic data on all admissions. Discharge diagnoses, coded according to the International Classification of Diseases, 9th revision, clinical modification (ICD-9-CM), were obtained from the discharge abstract form (retrieved from the medical record). At discharge, treating physicians are asked to fill in the principal diagnosis (primary hospital discharge diagnosis) which precipitated the hospital admission on these forms. The source population of the present study consisted of all hospital diagnosis records from four of the main hospitals in the PHARMO area between 1999 and 2000.

Case definition

Cases were defined as incident primary hospital discharge diagnoses of ventricular or non-specified cardiac arrhythmias. Cases were divided into two subgroups, well-defined diagnoses and other diagnoses. ICD-codes which match closest to the study endpoint of interest when studying drug-induced arrhythmias are defined as well-defined diagnoses, and included paroxysmal ventricular tachycardia (427.1), ventricular fibrillation and/or flutter (427.4, 427.41, 427.42), cardiac arrest (427.5) and ventricular premature beats (427.69). Other cardiac arrhythmias which may also include ventricular arrhythmias were paroxysmal tachycardia, unspecified (427.2), premature beats, unspecified (427.60), other cardiac dysrhythmias (427.8, 427.89), and cardiac dysrhythmias, unspecified (427.9).

Validation

Medical records of the cases were retrieved from the four hospitals and were reviewed by an independent cardiologist, blinded for the coded discharge diagnosis. Hospital discharge letters, electrocardiograms at hospital admission as well as discharge date, and serum electrolyte levels were scrutinised. When no discharge letter was available, copies from the original medical chart were provided. The cardiologist was asked to give a diagnosis based on the available data and categorise

this new diagnosis according to the ICD-9-CM. The researchers assigned the cardiologist's diagnosis to one of the following four categories:

1. Ventricular arrhythmia or cardiac arrest (ICD-9-CM 427.1, 427.4, 427.41, 427.42, 427.5, 427.69)
2. Other cardiac arrhythmia (ICD-9-CM 427.0, 427.2, 427.3, 427.31, 427.32, 427.6, 427.60, 427.61, 427.8, 427.81, 427.89, 427.9)
3. Other cardiac diagnosis, no arrhythmia (ICD-9-CM 390-426, 428-459)
4. No cardiac diagnosis

Data analysis

Taking the independent cardiologist's diagnosis as the 'gold standard', cases assigned to category 1 were regarded as true positives, and cases assigned to categories 2, 3 and 4 were regarded as false positives. Positive predictive values were calculated as the true positive percentage of all cases in a certain category. Ninety-five percent confidence intervals (CI) were calculated according to Altman [16]. Differences between characteristics of true and false positives were evaluated. Continuous variables and proportions were compared using the Students' T-test and χ^2-test respectively. Fisher's Exact test was used if not all expected numbers in a two-by-two table were 5 or higher.

Analyses were performed at three levels. First, overall, secondly, for well-defined diagnoses and other diagnoses separately, and thirdly for all individual ICD-codes.

RESULTS

During the study period, a total of 111 patients were admitted to one of the four hospitals for ventricular or non-specified cardiac arrhythmias for the first time. All medical records could be retrieved and included 61 records of well-defined diagnoses and 50 records of other diagnoses (Table 1).

Table 1 *Validated diagnoses of hospital discharge diagnosis of ventricular or non-specified cardiac arrhythmia*

Observed ICD-9-CM code	True positives	False positives			Total	PPV
	*	†	‡	§		
Well-defined diagnosis	50	4	4	3	61	82%
427.1 Paroxysmal ventricular tachycardia	24				24	100%
427.41 Ventricular fibrillation	10	1	2		13	77%
427.5 Cardiac arrest	13	2	2	3	20	65%
427.69 Ventricular premature beats	3	1			4	75%
Other diagnosis	5	36	4	5	50	10%
427.2 Paroxysmal tachycardia, unspecified		1			1	0%
427.60 Premature beats, unspecified				1	1	0%
427.89 Other cardiac dysrhythmias	2	27	2	1	32	6%
427.9 Cardiac dysrhythmias, unspecified	3	8	2	3	16	19%
Total	55	40	8	8	111	50%

PPV: positive predictive value

* *Ventricular arrhythmia or cardiac arrest (ICD-9-CM 427.1, 427.4, 427.41, 427.42, 427.5, 427.69)*

† *Other cardiac arrhythmia (ICD-9-CM 427.0, 427.2, 427.3, 427.31, 427.32, 427.6, 427.60, 427.61, 427.8, 427.81, 427.89, 427.9)*

‡ *Other cardiac diagnosis, no arrhythmia (ICD-9-CM 390-426, 428-459)*

§ No cardiac diagnosis

Overall, 55 of the 111 selected discharge diagnoses were validated as being either ventricular cardiac arrhythmia or cardiac arrest, giving a PPV of 50% (95%CI 40% to 59%). Of the 61 hospitalisations with well-defined diagnoses, 50 were validated as being either ventricular cardiac arrhythmia or cardiac arrest, giving a PPV of 82% (95%CI 72% to 92%). All individual ICD-codes within this group had a PPV of at least 65%, and true positive results were associated with male gender (p=0.09) and younger age (p=0.05), no differences were found between hospitals and years of hospitalisation (Table 2). The PPV among other diagnoses was as low as 10% (95%CI 2% to 18%), ranging from 0% to 19% according to the individual ICD-codes (Table 1). True positive results in this group were associated with hospital (p=0.04) and year of hospitalisation (p=0.05).

Forty patients (36%) were diagnosed as having a cardiac arrhythmia outside the case-definition, being a well-defined nonventricular arrhythmia (e.g. supraventricular tachycardia) in 34 of the cases. The ventricular origin of two of the well-

defined diagnoses could not be verified, whereas in four cases no ventricular or other specific type of arrhythmia could be identified for the other diagnoses (Table 1). Sixteen patients (14%) were not admitted to the hospital for cardiac arrhythmias at all. Most of these patients, however, experienced cardiac arrhythmias at some time during their hospitalisation, or were observed for electrocardiographic abnormalities, with the exception of three patients. In two cases a vasovagal collapse was misinterpreted as a cardiac arrest (427.5), in another case a cardiac conduction disorder (AV-block) was coded as a cardiac dysrhythmia (427.89).

Table 2 *Determinants of misclassification of hospitalisations coded as ventricular arrhythmias or cardiac arrest*

Variable	False positives (n=11)		True positives (n=50)		p-value
Gender					0.08
Male	4	11%	34	89%	
Female	7	30%	16	70%	
Hospital					0.94
A	5	19%	22	81%	
B	2	18%	9	82%	
C	1	11%	8	89%	
D	3	21%	11	79%	
Year					0.50
1999	5	14%	30	86%	
2000	6	23%	20	77%	
Age (mean, sd)	71	± 10	64	± 16	0.05

DISCUSSION

In this study we found a positive predictive value of 82% for ventricular arrhythmias and cardiac arrest of hospitalisations specifically coded as such according to the ICD-9-CM classification. The PPV did not depend on the hospital nor on the year of hospitalisation, and therefore extrapolation of the results to other hospitals and other years may be justified. Widening the outcome definition by including other hospital discharge diagnoses of non-specified cardiac arrhythmias considerably decreases the PPV to only 50%, and is therefore not recommended.

Correct classification according to ICD-codes appeared to be more difficult for females and older patients. Female gender is related to age within these 61 patients (mean age females 70 *vs* males 62), and age may be correlated with disease

complexity, making it difficult to assign primary ICD-codes. This hypothesis is supported by the fact that most of the patients who, according to our 'gold standard', did not meet the criteria of primary hospital discharge diagnosis of cardiac arrhythmias, did experience cardiac arrhythmia at some time during their hospitalisation. Other mistakes that were made during the coding process included assigning electrocardiographic observations to ICD-codes of suspected diseases which could not be verified, misinterpretation of other diseases with similar symptoms (such as vasovagal collapse) as being cardiac arrhythmias, and coding specific cardiac arrhythmias into unspecified categories, either due to misinterpretation by the coding clerk or lack of clearly described information by the treating physician.

As far as known, no previous studies on validation of the study outcome in research on drug-induced arrhythmias have been performed. Most epidemiological studies on this adverse reaction used quite broad outcome definitions, followed by case verification through screening of all original medical records. As expected, much lower PPVs were calculated from these studies, compared with our study. The PPV varied from 4 to 73% in studies using claims data [17-19] and from 12 to 27% in studies using data from general practices [20, 21]. In a study using hospital discharge codes, cardiac outpatient encounters and sudden deaths as a combined outcome, the positive predictive value of the study outcome was 14% [20].

A factor which may have influenced our results is the fact that we were not able to use a more comprehensive medical history for diagnosis by the independent cardiologist. Although we believe that we have used the most relevant information needed to make a diagnosis, more detailed information or contact with the physician who treated the specific patient could have improved the accuracy of the 'gold standard' diagnosis. It is therefore possible that some residual misclassification is still present in our validated outcomes, and true PPVs are lower than presented. Another limitation is that, although the results may be applicable to other hospitals, extrapolation outside the Netherlands may not be allowed due to potential differences between countries in coding of hospital discharge diagnoses.

Misclassification of outcome may occur in both case-control and cohort studies. In case-control studies, outcome misclassification influences the selection of cases and controls in the study. In cohort studies, it is related to the way the information on study variables is measured during the study, after index and control groups have been defined, and may cause information bias [22].

In general, selection bias in case-control studies, as a result of disease misclassification, occurs when not all observed cases (or controls) are true cases (or controls). It is therefore important to study how many of the cases (and controls) are true cases (and controls), which can be measured through positive (and negative) predictive values. In case of a rare disease, misclassification from diseased to nondiseased patients will cause a negligible decrease in the negative predictive value of the controls, making the PPV of disease the most important measure in overall validity assessment.

As an example of the impact of the validity of the outcome measure on selection of cases in a case-control study, we applied the results from this study to the data from a previously performed case-control study on drug-induced arrhythmias [23] (chapter 2.2). Multiplying the number of cases per ICD-category by the PPV of that category, results in a true number of cases of 189 instead of the observed 501 (overall PPV 38%). It could well be that the risk is diluted and the observed OR of 1.2 (95%CI 0.8 to 1.9) is an underestimation of the true effect.

Information bias in cohort studies, as a result of disease misclassification, occurs when not all true diseased (or nondiseased) patients are identified as such by the outcome measure used. It may lead to underestimation of the absolute incidences. The fraction of all true diseased (or nondiseased) patients, identified through the outcome measure, is expressed as the sensitivity (or specificity) of the outcome measure.

In conclusion, because drug-induced cardiac arrhythmias are rare, a case-control design is often applied to quantify the problem. In this design, a high positive predictive value is important. Well-defined hospital discharge diagnoses (a combination of paroxysmal ventricular tachycardia, ventricular fibrillation, ventricular flutter, ventricular premature beats and cardiac arrest) have a PPV of 82% and therefore may be used in studies on relative risks for drug-induced arrhythmias, even without further validation.

ACKNOWLEDGEMENTS

We gratefully thank the PHARMO Institute and the hospitals which participated in this project.

BIBLIOGRAPHICAL REFERENCES

1. Committee for Proprietary Medicinal Products (CPMP). *Note for guidance on definitions and standards for expedited reporting (CPMP/ICH/3945/03).* London: European Agency for the Evaluation of Medicinal Products, 2003.
2. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA.* 1997; 277: 887-91.
3. Erkens JA, Klungel OH, Stolk RP, Spoelstra JA, Grobbee DE, Leufkens HG. Cardiovascular drug use and hospitalizations attributable to type 2 diabetes. *Diabetes Care.* 2001; 24: 1428-32.
4. Lapane KL, Spooner JJ, Mucha L, Straus WL. Effect of nonsteroidal anti-inflammatory drug use on the rate of gastrointestinal hospitalizations among people living in long-term care. *J Am Geriatr Soc.* 2001; 49: 577-84.
5. Rawson NS, Harding SR, Malcolm E, Lueck L. Hospitalizations for aplastic anemia and agranulocytosis in Saskatchewan: incidence and associations with antecedent prescription drug use. *J Clin Epidemiol.* 1998; 51: 1343-55.
6. Myers MW, Jick H. Hospitalization for serious blood and skin disorders following co-trimoxazole. *Br J Clin Pharmacol.* 1997; 43: 649-51.
7. World Health Organisation. *International Classification of Diseases, ninth revision (ICD9)*. Geneva, Switzerland: World Health Organisation, 1977.
8. West SL, Strom BL. Validity of pharmacoepidemiology drug and diagnosis data. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester: John Wiley & Sons Ltd., 1994: 549-80.
9. Cattaruzzi C, Troncon MG, Agostinis L, Garcia Rodriguez LA. Positive predictive value of ICD-9th codes for upper gastrointestinal bleeding and perforation in the Sistema Informativo Sanitario Regionale database. *J Clin Epidemiol.* 1999; 52: 499-502.
10. Bogliun G, Beghi E. Validity of hospital discharge diagnoses for public health surveillance of the Guillain-Barre syndrome. *Neurol Sci.* 2002; 23: 113-7.
11. Chio A, Ciccone G, Calvo A, et al. Validity of hospital morbidity records for amyotrophic lateral sclerosis. A population-based study. *J Clin Epidemiol.* 2002; 55: 723-7.
12. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. *Am Heart J.* 2004; 148: 99-104.
13. Movig KL, Leufkens HG, Lenderink AW, Egberts AC. Validity of hospital discharge International Classification of Diseases (ICD) codes for identifying patients with hyponatremia. *J Clin Epidemiol.* 2003; 56: 530-5.

14. Locati EH, Maison-Blanche P, Dejode P, Cauchemez B, Coumel P. Spontaneous sequences of onset of torsade de pointes in patients with acquired prolonged repolarization: quantitative analysis of Holter recordings. *J Am Coll Cardiol.* 1995; 25: 1564-75.
15. Shah RR. Pharmacogenetic aspects of drug-induced torsade de pointes : potential tool for improving clinical drug development and prescribing. *Drug Saf.* 2004; 27: 145-72.
16. Altman DG. Comparing groups, categorical data. In: Altman DG, ed. *Practical Statistics for Medical Research*. 1st edition ed. London: Chapman & Hall, 1991: 229-76.
17. Hanrahan JP, Choo PW, Carlson W, Greineder D, Faich GA, Platt R. Terfenadine-associated ventricular arrhythmias and QTc interval prolongation. A retrospective cohort comparison with other antihistamines among members of a health maintenance organization. *Ann Epidemiol.* 1995; 5: 201-9.
18. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *Br Med J.* 2002; 325: 1070.
19. Staffa JA, Jones JK, Gable CB, Verspeelt JP, Amery WK. Risk of selected serious cardiac events among new users of antihistamines. *Clin Ther.* 1995; 17: 1062-77.
20. Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med.* 1999; 107: 356-62.
21. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999; 47: 307-13.
22. Copeland K, Checkoway H, McMichael A, Holbrook R. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol.* 1977; 105: 488-95.
23. De Bruin ML, Hoes AW, Leufkens HGM. QTc-prolonging drugs and hospitalizations for cardiac arrhythmias. *Am J Cardiol.* 2003; 91: 59-62.

Chapter 5.2

NON-DIFFERENTIAL MISCLASSIFICATION OF EXPOSURE IN PHARMACOEPIDEMIOLOGICAL STUDIES, THE EXAMPLE OF DRUG-INDUCED ARRHYTHMIAS

Marie L De Bruin [1,2], Arno W Hoes [2], Hubert GM Leufkens [1]

[1] Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, Utrecht, the Netherlands
[2] Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, the Netherlands

Submitted for publication

SUMMARY

Objective: Pharmacoepidemiological studies in large pre-existing databases are a powerful tool to study drug-induced disease. However, non-differential misclassification of exposure, leading to bias towards the null, is not always adequately addressed in these studies. We aimed to identify, evaluate and quantify the bias which may occur as a result of non-differential misclassification in drug-exposure and to estimate the impact on the results of studies quantifying the risk of drug-induced arrhythmias.

Methods: Basic algebraic methods were applied to calculate observed versus true relative risk according to varying sensitivity and specificity of exposure assessment. Four cohort scenarios, with different exposed to nonexposed person time ratios, and four case-control scenarios with different background exposures were performed. For three previously published studies, the potential impact of non-differential misclassification of exposure on study results were estimated.

Results: In cohorts studies, observed relative risks decreased with decreasing sensitivity, whereas specificity was less important. With increasing exposed to nonexposed person time ratio, the influence of sensitivity decreases, whereas the influence of specificity increases. In case-control studies specificity is the most important factor in the association between observed and true odds ratio. When the background exposure increases, the influence of the specificity decreases, whereas the influence of sensitivity increases. The three examples are in concordance with this theory.

Conclusion: Non-differential misclassification of exposure may result in considerable underestimation of true effects. In drug safety issues, such as drug-induced arrhythmias, conservative estimates of harmful effects may be misleading when estimating the public health impact of a drug-induced disease.

INTRODUCTION

In the past decade, the single most common cause of the withdrawal or restriction of the use of drugs has been the prolongation of the QTc-interval associated with polymorphic ventricular tachycardia, or Torsade de Pointes, which can be fatal [1, 2]. In many cases regulatory action has been taken based on case reports, but epidemiological studies are nowadays being performed more often to quantify the risk in day-to-day practice. Epidemiological studies are regularly performed in pre-existing large databases, because they can be used to study rare diseases promptly. Different databases have their specific potentials and drawbacks, when studying this specific adverse reaction.

In pharmacoepidemiological studies on drug-induced adverse reactions, emphasis is usually on validation of the study-outcome, whereas misclassification of exposure is not always addressed in a systematic fashion. It has been generally accepted that databases in which drug-exposure is measured through pharmacy records, physicians prescriptions, or claims data are unlikely to be subject to differential misclassification of exposure. This contrasts with questionnaire information, which may be susceptible to recall bias for example [3]. Since non-differential misclassification of exposure generally leads to underestimation of the true association between exposure and outcome, this validity issue is often not even discussed in (pharmaco)epidemiological studies. Since this bias towards the null leads to conservative results in positive drug-efficacy studies, it is not regarded as a major problem. In drug safety issues, however, conservative estimates of harmful effects may be misleading when estimating the public health impact of a drug-induced disease. Not only the presence of an association, but also the true magnitude of the association is crucial. It is therefore important to quantify the potential influence of misclassification on the point estimate.

The purpose of this paper is bipartite. The first aim was to identify, evaluate and quantify the bias which may occur as a result of non-differential misclassification of drug-exposure in pre-existing databases used for pharmacoepidemiological research. Secondly, we estimated the impact it may have had on the results of several available studies quantifying the risk of adverse reactions, taking drug-induced arrhythmias as a case example.

Table 1 *Characteristics of databases which have been used to study drug-induced arrhythmias*

Database	Type	Size	Country	Drug-use measure	Drug classification codes
HCHP [4]	Health Maintenance Organisation	900,000 (1993)	USA	Pharmacy dispensings and prescriptions in encounter records	National Drug Codes American Hospital Pharmacy Service codes
GPRD [5]	General practice	3,000,000 (1998)	UK	GP prescriptions	Multilex-codes
IPCI [6]	General practice	500,000 (2003)	Netherlands	GP prescriptions	ATC-codes
Medicaid [7, 8]	Health insurance for the disadvantaged	5 900,000 (1996)	USA	Outpatient drug billing records	National Drug Codes
Saskatchewan [9]	Governmental health organisation	1,000,000 (1994)	Canada	Pharmacy dispensings	Drug Identification Numbers
PHARMO [10]	Record linkage system	1,000,000 (2004)	Netherlands	Pharmacy dispensings	ATC-codes

THEORY

To understand the context in which non-differential misclassification of exposure may occur, the characteristics of various databases which have been used to study drug-induced arrhythmias will first be discussed. Consequently, both database related and drug class related factors causing this type of misclassification in these databases are discussed. In order to enable a realistic simulation of the impact of non-differential misclassification of exposure on the point-estimate in cohort and case-control studies, assumptions are made on sensitivity (probability of administrative data revealing exposure, given actual use of the drug) and specificity (probability of administrative data revealing nonexposure, given actual nonexposure) of exposure measures.

Data sources

In total, six administrative databases were used by various researchers to quantify the risk of drug-induced arrhythmias: the Harvard Community Health Plan (HCHP) [11], the General Practice Research Database (GPRD) [12, 13], the database of the Integrated Primary Care Information (IPCI) project [14], Medicaid [15-20], and the PHARMO record linkage system [21]. General characteristics of the databases are presented in Table 1.

Factors contributing to non-differential misclassification of exposure

For a patient to be exposed to a certain drug, this drug must be prescribed by a physician, dispensed by a pharmacist and actually taken by the patient. Over-the-counter (OTC) drugs can also be bought directly at drugstores and pharmacies without a prescription. In order to measure drug exposure in patients, proxy measures available in physicians', pharmacists' and health insurance databases are often used. Misclassification of exposure may occur at several levels and can be classified as either database related (a and b) or drug-class related (c and d).

a. From physician to pharmacist

Overestimation of drug exposure measured at physicians' offices is estimated to be as high as 7-20%, because prescribed medication is not necessarily filled [22]. Underestimation of exposure may also occur, notably in general practice-based studies, because drugs prescribed by other physicians are usually not included in these databases. For example, a study on drug-induced arrhythmias, performed in the

PHARMO database, showed that only 81% of the medication dispensed to the cases was prescribed by their general practitioner [21].

b. From pharmacist to patient

When using prescription billing records to measure drug exposure, misclassification may occur depending on the source from which the data are obtained. The HCHP includes drug-dispensing records from all affiliated outpatient pharmacies. Over 90% of the HCHP members receive prescription drugs for a nominal payment when they fill prescriptions at an HMO pharmacy. Drug data may be missing for the 10% of the members without drug benefits, for drugs which cost less than the co-payment, or for those who do not submit their drug claim for reimbursement [4]. When drug exposure is defined on the basis of either dispensing or prescribing, the underestimation will be much lower [23], while at the same time overestimation of 7-20% may be introduced because prescribed medication may not be filled [22].

Medicaid includes all information on drugs which have been dispensed at affiliated pharmacies. Since Medicaid covers an indigent population, it is less likely that drugs will be purchased outside the insurance plan [23], and the underestimation of the true drug exposure will be lower.

The Saskatchewan prescription drug plan is estimated to contain 90% of all outpatient prescription drugs. The 10% missing in the database are drugs for which payment is not claimed, either because the drugs are not listed in the Saskatchewan formulary or the prescriptions were not filled [9, 23].

The PHARMO record linkage system contains information of all drugs dispensed by community pharmacies (prescribed by general practitioners or other physicians, including hospital specialists) in several medium-sized Dutch cities. Data are collected for both reimbursement and patient surveillance purposes. Within the participating cities, all community pharmacies are included. In daily practice, patients almost never fill their prescriptions outside the PHARMO area, resulting in a low underestimation of drug-exposure. Overestimation in this database may occur when prescriptions received and administrated by pharmacists, are not picked up by the patients. This is estimated to concern only 0.5% of filled prescriptions and is unlikely to hit any drug group disproportionally [24].

c. OTC-drugs and in-hospital drug-use

Underestimation of drug-exposure regarding all databases described above occurs when study drugs are available without prescription. QTc-prolonging drugs which

have been studied for their ability to cause cardiac arrhythmias include antihistamine drugs [11, 12, 15, 16, 21], some of which can be bought over the counter in most countries. Medication which is taken when a patient is admitted to the hospital is generally also not registered systematically in databases. Underestimation of drug-use may therefore be differentially correlated to hospitalisation and, hence, disease severity [23].

d. Patient's compliance and drugs prescribed to be used 'as needed'

The fact that a patient picked up his or her medication does not necessarily imply that the drugs are actually taken by the patient. Compliance rates, measured by electronic monitoring devices, vary from 50 to 80%, according to the medication prescribed and dosing regimen. In practice this means that on 20 to 50% of the days, drugs are not used as prescribed. Patients could either not take the prescribed daily amount of drugs, not take the doses within the appropriate time interval, or not take the drugs at all [25]. Drugs which have been studied for their ability to induce cardiac arrhythmias can be grouped under respiratory drugs [11, 12, 15, 16, 21] (estimated compliance 54%), psychiatric drugs [17-19, 21] (estimated compliance 78%), diabetes medication [21] (estimated compliance 73%), cardiovascular drugs [21] (estimated compliance 71%), infectious disease drugs [20, 21] (estimated compliance 74%) and other [13, 21] (estimated compliance 74%).

Antihistamine drugs are prescribed to alleviate allergic symptoms, are often used 'as needed', and exposure varies over the year depending on season. It is likely that a new prescription is filled when symptoms arise. The drug may be stopped, however, before the theoretical end date of the prescription, e.g. when allergy triggering factors have disappeared. Remaining pills may be taken when a new allergy attack emerges, before a new prescription is filled.

Estimation of sensitivity and specificity

Measurement errors at all different levels mentioned above (compliance, co-prescribing by other physicians, etc) are combined in the sensitivity (the probability of the administrative data revealing exposure, given actual use of the drug) and specificity (probability of the administrative data revealing nonexposure, given actual non-exposure) of the use of administrative data as a metric for actual drug exposure.

For pharmacy records, several researchers calculated sensitivity and specificity using either home inventories [26] or detailed questionnaires [27] as the gold standard. Drug

exposure based on Medicaid pharmacy claims was compared with information in medical charts by McKenzie et al [28], using the medical charts as the gold standard. The sensitivity and specificity for drugs of interest were estimated as 0.71 and 1.0 for antidiabetic drugs, 0.89 and 0.93 for antihypertensive drugs, 0.85 and 0.99 for lipid-lowering drugs [27], 0.67 and 1.0 for antibiotics, 0.71 and 0.99 for the anti-asthmatic drug salbutamol [26], 0.93 and 0.97 for antipsychotic drugs and 0.98 and 0.98 for antidepressants respectively [28].

METHODS

We simulated the theoretical impact of non-differential misclassification of exposure when studying the association between exposure to QTc-prolonging drugs and the occurrence of cardiac arrhythmias. We simulated the effect in cohort studies, where misclassification of exposure may cause selection bias, as well as in case-control studies, where it may cause information bias. In addition, simulations of the potential impact of non-differential misclassification of exposure on point-estimates in three available studies on drug-induced arrhythmias are presented.

Theoretical impact

Because the absolute impact of non-differential misclassification of exposure depends on study design and amount of exposure, we plotted true versus observed relative risk, according to various values of sensitivity and specificity for 8 different scenarios. Four scenarios of cohort studies varied in exposed to nonexposed person time ratios and 4 case-control scenarios (with a 1:4 case to control ratio) varied in exposure rates among controls.

Calculation of observed relative risk

The observed relative risk was calculated using basic algebraic methods [29, 30]. The number of observed cell frequencies in the two-by-two tables were calculated using the formulas in Table 2. The asterisk symbol * is used for observed numbers. For person-time follow-up data B1, B0, B1* and B0* were substituted for T1, T0, T1* and T0* [30]. According to the results presented in the first part of this paper (theory), we simulated the impact of sensitivity ranging from 0.80 to 1.00 and specificity ranging from 0.98 to 1.00.

Table 2 *Calculation of observed exposure among diseased and nondiseased patients*

	Diseased	Disease-free †	Total
Exposed	A1*=(Se x A1)+((1-Sp) x A0)	B1*=(Se x B1)+((1-Sp) x B0)	A1*+B1*
Nonexposed	A0*=(Sp x A0)+((1-Se) x A1)	B0*=(Sp x B0)+((1-Se) x B1)	A0*+B0*
Total	A	B	

A1: exposed cases, A0: nonexposed cases

B1: exposed controls, B0: nonexposed controls

* *observed numbers*

† *For person-time follow-up data B1, B0, B1* and B0* were substituted for T1, T0, T1* and T0**

Exposure to QTc-prolonging drugs in the background population

In Europe, the exposure to QTc-prolonging non-antiarrhythmic drugs is estimated at 13.9 defined daily doses (DDD)/1000 inhabitants per day. Overall use of a group of 37 drugs with clinically relevant proarrhythmic risk ranged from 12.9 to 29.1 DDD /1000 per day in these countries [31]. In the US the most commonly used QTc-prolonging drug is fluoxetine (30 users per 1000 inhabitants, using a total of 170 prescriptions per year) [32]. This corresponds to 13 DDD /1000 inhabitants per day when each prescription equals 28 DDD.

We used exposed to nonexposed person time ratios in the 4 cohort scenarios of 1:2, 1:6, 1:10 and 1:20. An exposed to nonexposed person time ratio of 1:2 is realistic for comparison of a cohort of users of the index-drug, compared with a twice as large cohort of users of a comparison drug. A ratio of 1:20 is realistic for comparison of exposed and nonexposed days among a cohort which uses the study drug for an average of 5% of the year. In the 4 case-control scenarios we used background exposures of 5/1000, 13/1000, 30/1000 and 75/1000. A background exposure of 5/1000 is realistic for studying exposure to a single drug, 75/1000 is realistic for exposure to a group of drugs.

Incidence of outcome events in the background population

The incidence of outcomes of interest among control groups in the various cohort studies on drug-induced arrhythmias varied between 3 to 15 events per 10,000 prescriptions[11,15,16] and between 0.5 and 30 events per 10,000 person years[12,13,17-19]. The incidence of sudden cardiac death among the general population is estimated to be 2 to 20 per 10,000 per year and varies with age, gender and comorbidity [33,34]. The incidence of Torsade de Pointes (TdP) arrhythmias and other ventricular

arrhythmias is estimated to be 0.4 and 1.7 per 10000 per year respectively [35]. Consequently, annual incidences of outcomes of interest vary from 0.5 to 30 events per 10,000 in the background population. In the 4 cohort scenarios we used an incidence of 10 events per 10,000 patients per year. In the 4 case-control scenarios, this resulted in 1000 cases in a theoretical database population of 1,000,000 patients.

Three examples

Simulations of the potential impact of non-differential misclassification of exposure on point-estimates in studies on drug-induced arrhythmias are presented. Three published examples from daily epidemiological practice were used [12, 18, 21]. We chose these three studies because they differed in study design as well as exposure measurement and they were conducted in three different, internationally well-recognised databases. De Abajo et al compared the incidence of ventricular arrhythmias in days of current use of antihistamines with the incidence in days of non-use among the same patients in the GPRD [12]. Ray et al compared the incidence of sudden death in days of use of antipsychotic drugs with the incidence in days of non-use among a cohort of Medicaid enrolees [18]. De Bruin et al compared the exposure to a number of different QTc-prolonging drugs among cardiac arrhythmia cases with the exposure among controls selected from the PHARMO database [21]. Data necessary to calculate crude point estimates for these examples were obtained from the original publications. These included number of events in exposed and nonexposed patients, and total exposed and unexposed follow-up time in cohort studies. In case-control studies, data were collected on total number of cases and controls as well as exposure rate among those patients. When multiple comparison groups were used, the groups were combined to a single large control-group. Past users were excluded as a reference category, when information on both past and non-users was available.

Per study, the true relative risk was calculated for a sensitivity of 1.00, 0.90 and 0.80 as well as a specificity of 1.00, 0.99 and 0.98.

Calculation of true relative risk

True crude relative risks were calculated using basic algebraic methods [29, 30]. The number of true cell frequencies in the two-by-two tables were calculated using the formulas in Table 3. The asterisk symbol * is used for observed numbers. For person-time follow-up data B1, B0, B1* and B0* were substituted for T1, T0, T1* and T0* [30].

Table 3 *Calculation of true exposure among diseased and nondiseased patients*

	Diseased	Disease-free †	Total
Exposed	A1=(A1*-((1-Sp)xA))/(Se+Sp-1)	B1=(B1*-((1-Sp)xB))/(Se+Sp-1)	A1+B1
Nonexposed	A0 = A - A1	B0 = B - B1	A0+B0
Total	A	B	

A1: exposed cases, A0: nonexposed cases

B1: exposed controls, B0: nonexposed controls

* *observed numbers*

† *For person-time follow-up data B1, B0, B1* and B0* were substituted for T1, T0, T1* and T0**

RESULTS

In cohort studies with a background incidence of 10 events per 10,000 person years and a exposed to nonexposed person days ratio of 1:2, the observed relative risk dramatically decreases with decreasing sensitivity, whereas the influence of decreasing specificity appears to play a less important role. When the exposed to nonexposed person time ratio increases, the influence of sensitivity decreases, whereas the influence of specificity increases (Figure 1a and b). Observed relative risks are up to 33% lower than the true relative risk, in the different cohort scenarios.

In case-control studies with a case to control ratio of 1:4 specificity appears to have the largest impact on the relationship between observed and true odds ratio. When the background exposure increases, the influence of the specificity decreases, whereas the influence of sensitivity increases. The influence of sensitivity, however, remains minimal throughout all 4 scenarios. At equal specificity, the observed relative risks at a sensitivity of 0.80 are up to 10% lower than the observed relative risks at a sensitivity of 1.00. (Figure 2a and b). Overall, observed relative risks are up to 65% lower than the true relative risk, in the different case-control scenarios.

Figure 1a *Effect of sensitivity and specificity on true relative risk compared with observed relative risk of cohort studies with an exposed to nonexposed person time rate of 1:2 and 1:6 and a background incidence rate of 10/10000*

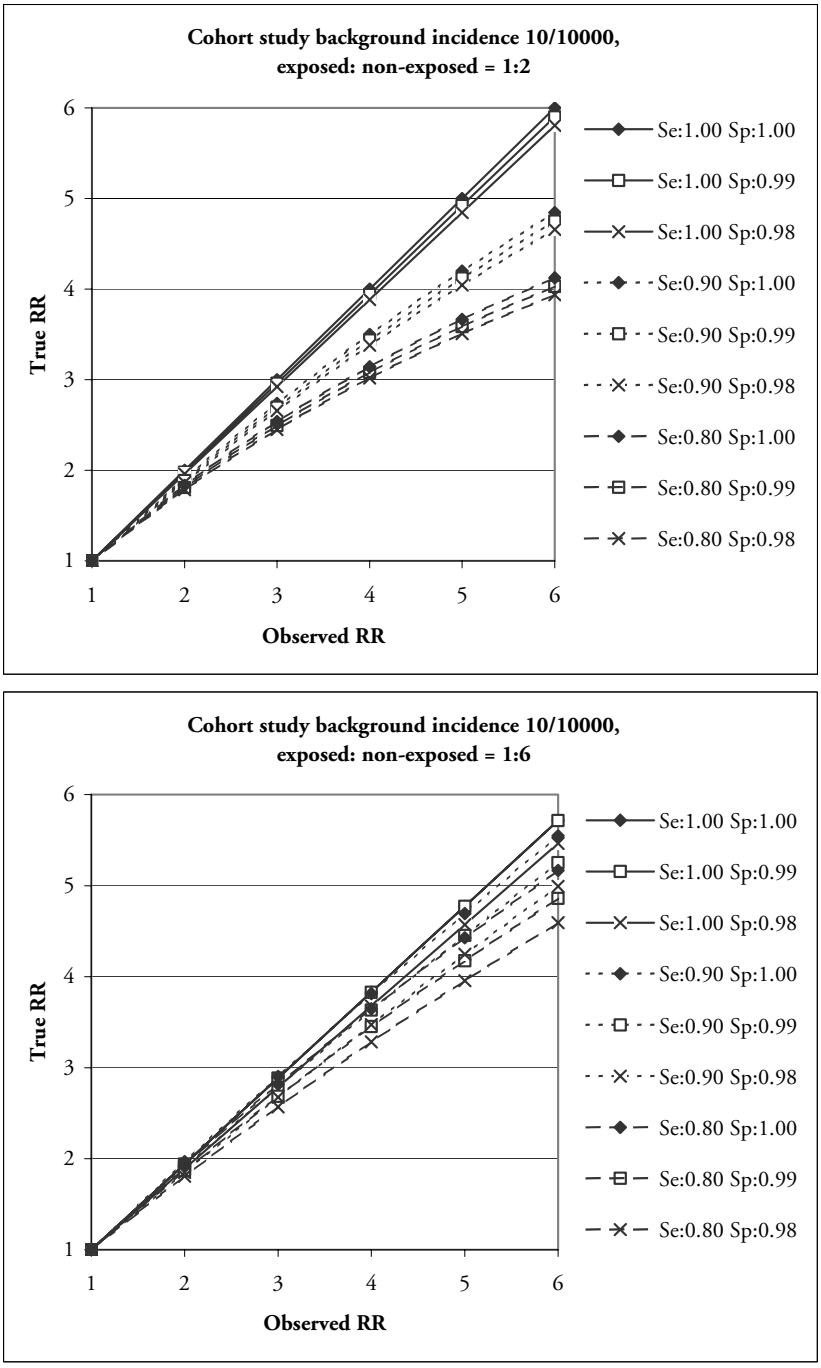
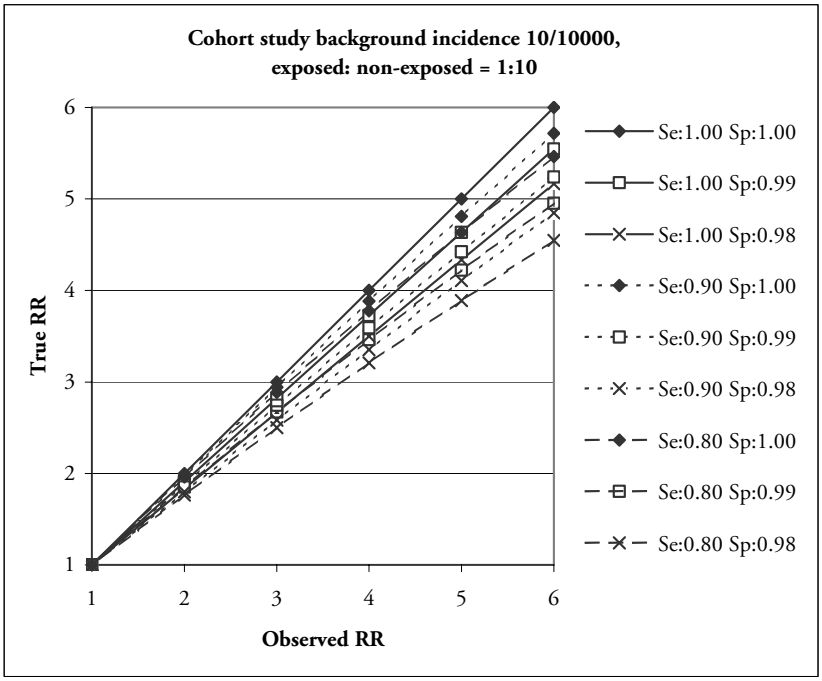


Figure 1b *Effect of sensitivity and specificity on true relative risk compared with observed relative risk of cohort studies with an exposed to nonexposed person time rate of 1:10 and 1:20 and a background incidence rate of 10/10000*



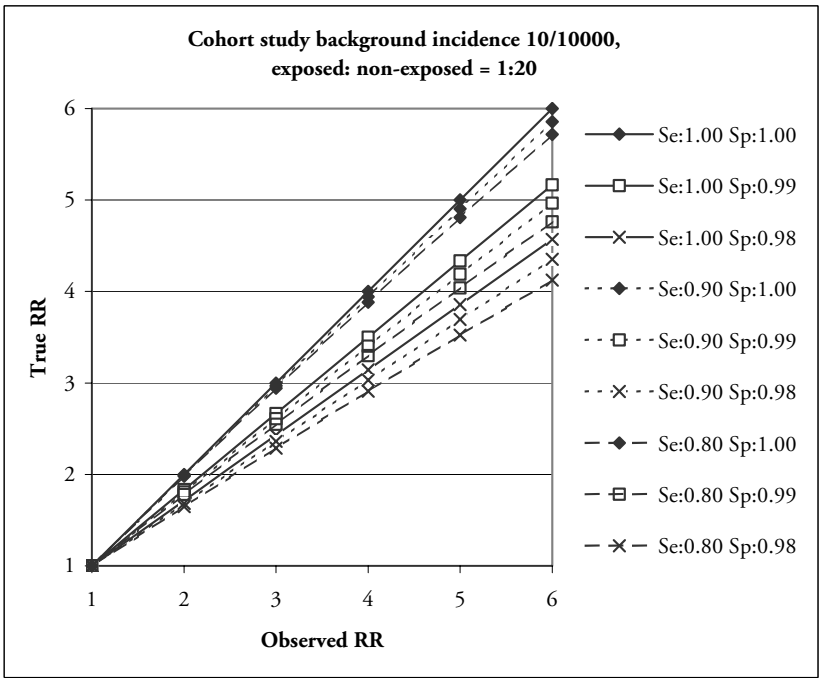


Figure 2a *Effect of sensitivity and specificity on true odds ratio compared with observed odds ratio for case-control studies with a background exposure rate of 5/1000 and 13/1000 and a case to control ratio of 1:4*

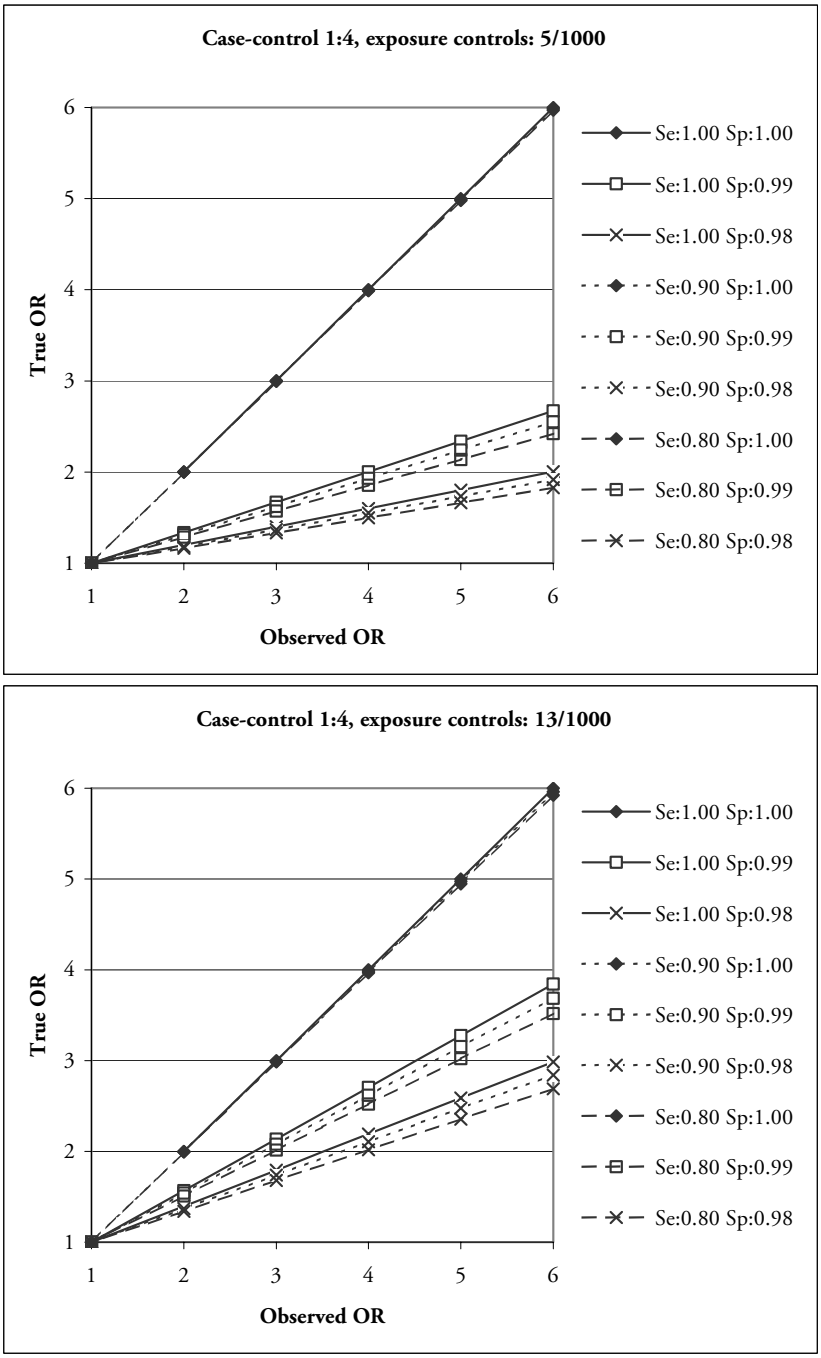
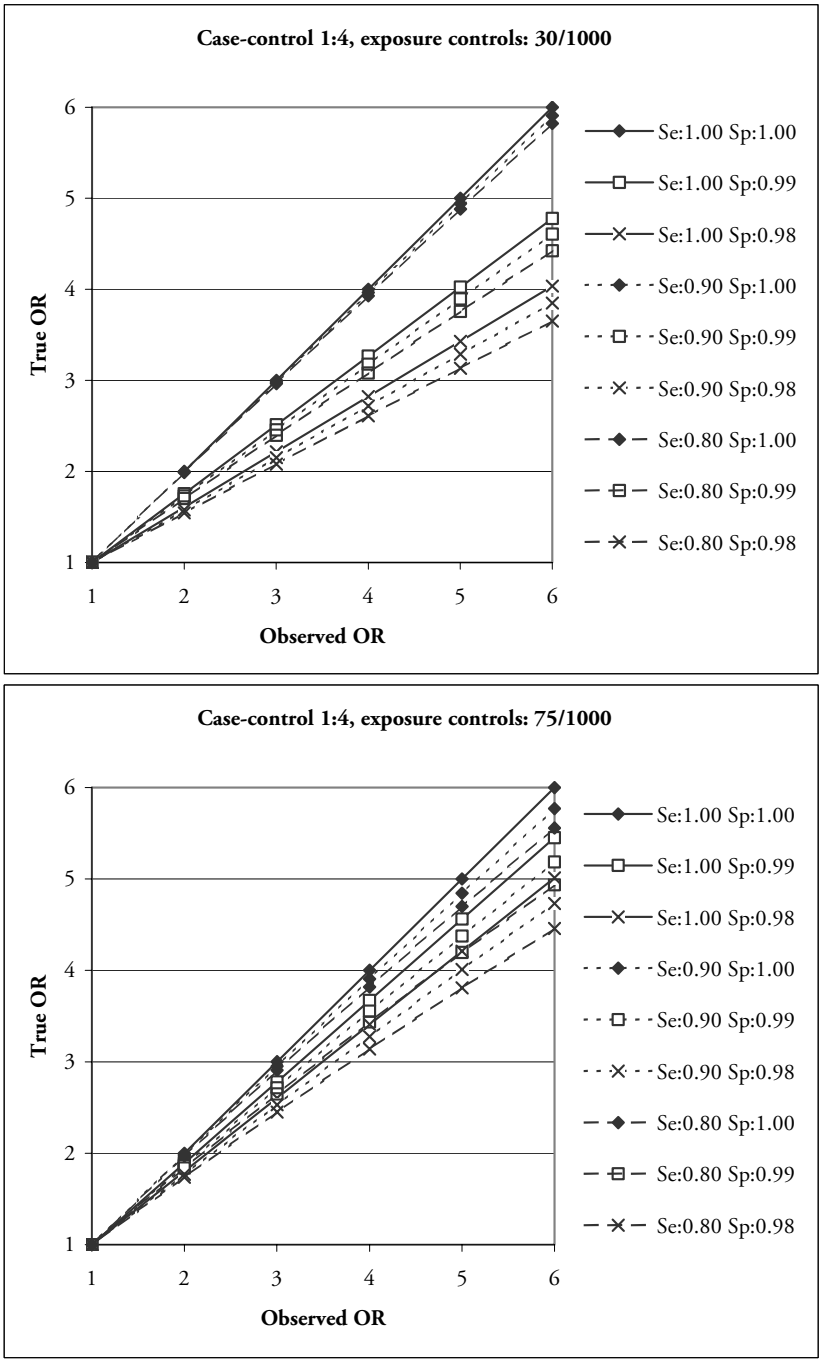


Figure 2b *Effect of sensitivity and specificity on true odds ratio compared with observed odds ratio for case-control studies with a background exposure rate of 30/1000 and 75/1000 and a case to control ratio of 1:4*



Three examples

Data necessary to calculate crude relative risks obtained from the original publications of both the calculated relative risks and odds ratios are presented in Table 4. In the study of de Abajo et al the exposed to nonexposed person days ratio is approximately 1:3, whereas the ratio in the study of Ray et al is 1:20. The exposure among controls in the study of De Bruin et al was 60/1000.

Table 4 *Crude observed data from original publications of three population based studies on drug-induced arrhythmias*

Study	Design	A1*	A0*	B1*/T1*	B0*/T0*	RR or OR
de Abajo et al [5]	Cohort	9	6	47,748	133,761	4.20
Ray et al [11]	Cohort	97	1,337	58,631	1,186,501	1.47
De Bruin et al [13]	Case-control	39	120	462	1,884	1.33

A1: observed exposed cases*

A0: observed non-exposed cases*

B1/T0*: observed exposed controls (case-control), or exposed person time (cohort)*

B0/T0*: observed nonexposed controls (case-control), or nonexposed person time (cohort)*

Table 5 *Misclassification of exposure adjusted true crude risk estimates and underestimation of the observed risk estimates (Δ) according to sensitivity (Se) and specificity (Sp) in three population-based studies on drug-induced arrhythmias*

		Observed	True	Δ	True	Δ	True	Δ
			Se: 1.00		Se: 0.90		Se: 0.80	
de Abajo et al [5]	Sp:1.00	4.20	4.20	0%	4.84	13%	6.12	31%
	Sp:0.99	4.20	4.29	2%	4.95	15%	6.26	33%
	Sp:0.98	4.20	4.40	4%	5.07	17%	6.41	34%
Ray et al [11]	Sp:1.00	1.47	1.47	0%	1.47	0%	1.48	1%
	Sp:0.99	1.47	1.59	8%	1.59	8%	1.60	8%
	Sp:0.98	1.47	1.80	19%	1.80	19%	1.81	19%
De Bruin et al [13]	Sp:1.00	1.33	1.33	0%	1.33	0%	1.33	1%
	Sp:0.99	1.33	1.39	4%	1.39	5%	1.39	5%
	Sp:0.98	1.33	1.48	10%	1.48	11%	1.49	11%

True exposure was calculated and used to obtain a misclassification adjusted relative risk. The study of De Bruin et al, for example, consisted of 501 cases of which 39 were exposed and 2004 controls of which 120 were exposed (Table 2, chapter 2.2). Using the formulas in Table 3, a sensitivity of 0.80 and a specificity of 0.98, the true number of exposed cases was calculated as 39 - (1-0.98)*501 / (0.80+0.98-1) = 37.2. The correspondding number of true unexposed cases was 501-37.2= 463.2. The true number of exposed and non-exposed non-cases were 102.5 and 1901.5 respectively, resulting in a true crude odds ratio of 1.49. The results for all combinations of sensitivity and specificity are presented in Table 5.

In all simulations, the true association was stronger than the observed association. Sensitivity played an important role only in the study of de Abajo et al, for which the true relative risk was more than 30% higher in the scenarios with a sensitivity of 0.80 compared with the scenarios with a sensitivity of 1.00 at equal specificity. Specificity appeared to be the largest concern for the study of Ray et al, for which the true relative risk was approximately 20% higher in the scenarios with a specificity of 0.98 compared with the scenarios with a specificity of 1.00 at equal sensitivity.

DISCUSSION

The results of our analyses indicate that non-differential misclassification of exposure can lead to substantial underestimation of the relative risk. When risks of drug therapy have to be weighed against the benefits, other conclusions could be drawn when non-differential misclassification of exposure is taken into account.

It has been shown previously that misclassification of exposure may play an important role in cohort studies on acute effects of intermittently taken medications [36], as well as in studies where fixed time-intervals were used [37]. However, when drug-exposure is assessed on a day-to-day basis as in the studies discussed in this paper, non-differential misclassification may still strongly bias the study results towards the null.

The effects that sensitivity and specificity have on the difference between observed and true relative risk largely depend on exposure rate in case-control studies and exposed to nonexposed ratio in cohort studies. One should take this into account when designing a study. Figures 1 and 2 in this article may be used to obtain an indication of the magnitude of the problem in certain circumstances. An accurate estimation of the true relative risk is best made by performing a validation study of exposure among a sample of the study population. The sensitivity and specificity

obtained from the validation study can be obtained to calculate the true relative risk, using the formulas in Table 3.

A drawback of the present study is that assumptions on sensitivity and specificity were best estimates based on validation studies in other databases. If it had been possible to use validation data from a substudy, calculations would have been more accurate [30]. We believe, however, that we have simulated realistic estimates of sensitivity and specificity and that results reflect true effects.

Estimations of the effects of non-differential misclassification of exposure on absolute risks and risk differences was not the aim of our study. As an example, however, we simulated a sensitivity of 0.93 and a specificity of 0.97 in the cohort study of Ray et al [18]. The true incidence rates in the index group of the study of Ray et al increased from 165 to 253 events per 100,000 person years, whereas the true incidence rate in the control group decreased from 113 to 112 events per 100,000 person years. The absolute risk difference increased more than 2.5-fold from 52 to 141 events per 100,000 person years, and the 'number needed to harm' decreased from approximately 1,900 to 700.

To summarise, pharmacoepidemiological studies in large pre-existing databases are a powerful tool to study drug-induced disease. In particular when the adverse reaction is rare and risk estimates are required within a short period of time. However, as illustrated by the findings of our study, non-differential misclassification of exposure may result in considerable underestimation of the true effect. This may mislead decision makers when weighing risks versus benefits of drug treatment. We therefore strongly suggest that more attention should be paid to this type of bias in future studies on drug-induced disease.

BIBLIOGRAPHICAL REFERENCES

1. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, Bor DH. Timing of new black box warnings and withdrawals for prescription medications. *JAMA.* 2002; 287: 2215-20.
2. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med.* 2004; 350: 1013-22.
3. Rockenbauer M, Olsen J, Czeizel AE, Pedersen L, Sorensen HT. Recall bias in a case-control surveillance system on the use of medicine during pregnancy. *Epidemiology.* 2001; 12: 461-6.
4. Platt R. Harvard Community Health Plan. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester: John Wiley & Sons Ltd., 1994.
5. Garcia Rodriguez LA, Perez Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. *Br J Clin Pharmacol.* 1998; 45: 419-25.
6. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, Sturkenboom MC. Postmarketing surveillance based on electronic patient record: the IPCI project. *Metgods Inf Med.* 1999; 38: 339-44.
7. Hennessy S, Bilker WB, Weber A, Strom BL. Descriptive analyses of the integrity of a US Medicaid claims database. *Pharmacoepidemiol Drug Saf.* 2003; 12: 103-11.
8. Carson JL, Strom BL. Medicaid databases. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd edition ed. Chichester: John Wiley & Sons Ltd., 1994: 199-216.
9. Strand LM, Downey W. Health databases in Saskatchewan. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd edition ed. Chichester: John Wiley & Sons Ltd., 1994: 217-28.
10. Leufkens HG, Urquhart J. Automated record linkage and other approaches to pharmacoepidemiology in the Netherlands. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd edition ed. Chichester: John Wiley & Sons Ltd., 1994: 231-44.
11. Hanrahan JP, Choo PW, Carlson W, Greineder D, Faich GA, Platt R. Terfenadine-associated ventricular arrhythmias and QTc interval prolongation. A retrospective cohort comparison with other antihistamines among members of a health maintenance organization. *Ann Epidemiol.* 1995; 5: 201-9.
12. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999; 47: 307-13.
13. Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med.* 1999; 107: 356-62.
14. Straus SMJM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the Risk of Sudden Cardiac Death. *Arch Intern Med.* 2004; 164: 1293-7.

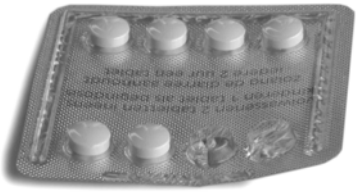
15. Pratt CM, Hertz RP, Ellis BE, Crowell SP, Louv W, Moye L. Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the-counter antihistamines, ibuprofen and clemastine. *Am J Cardiol.* 1994; 73: 346-52.
16. Staffa JA, Jones JK, Gable CB, Verspeelt JP, Amery WK. Risk of selected serious cardiac events among new users of antihistamines. *Clin Ther.* 1995; 17: 1062-77.
17. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *Br Med J.* 2002; 325: 1070.
18. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry.* 2001; 58: 1161-7.
19. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic anidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther.* 2004; 75: 234-41.
20. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *New Engl J Med.* 2004; 351: 1089-96.
21. De Bruin ML, Hoes AW, Leufkens HGM. QTc-prolonging drugs and hospitalizations for cardiac arrhythmias. *Am J Cardiol.* 2003; 91: 69-73.
22. Hartzema AG, Perfetto EM. Misclassification in pharmacoepidemiologic studies. In: Hartzema AG, ed. *Pharmacoepidemiology*. Cincinnati: Harvey Whitney Books Company, 1998: 267-309.
23. West SL, Strom BL. Validity of pharmacoepidemiology drug and diagnosis data. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester: John Wiley & Sons Ltd., 1994: 549-80.
24. Tobi H, van den Heuvel NJN, de Jong - van den Berg LTW. Does uncollected medication reduce the validity of pharmacy dispensing data? *Pharmacoepidemiol Drug Saf.* 2004; 13: 497-500.
25. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* 2001; 23: 1296-310.
26. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. *J Clin Epidemiol.* 1997; 50: 619-25.
27. Monster TB, Janssen WM, de Jong PE, de Jong-van den Berg LT. Pharmacy data in epidemiological studies: an easy to obtain and reliable tool. *Pharmacoepidemiol Drug Saf.* 2002; 11: 379-84.
28. McKenzie DA, Semradek J, McFarland BH, Mullooly JP, McCamant LE. The validity of medicaid pharmacy claims for estimating drug use among elderly nursing home residents: The Oregon experience. *J Clin Epidemiol.* 2000; 53: 1248-57.
29. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol.* 1977; 105: 488-95.

30. Greenland S. Basic methods for sensitivity analysis and external adjustment. In: Rothman KJ, Greenland S, eds. *Modern Epidemiology.* 2nd ed. Philadelphia: Lippincott - Raven Publishers, 1998: 343-57.
31. De Ponti F, Poluzzi E, Vaccheri A, et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. *Br J Clin Pharmacol.* 2002; 54: 171-7.
32. Curtis LH, Ostbye T, Sendersky V, et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *Am J Med.* 2003; 114: 135-41.
33. Myerburg RJ, Interian A, Jr., Mitrani RM, Kessler KM, Castellanos A. Frequency of sudden cardiac death and profiles of risk. *Am J Cardiol.* 1997; 80: 10F-9F.
34. Straus SM, Bleumink GS, Dieleman JP, van der Lei J, Stricker BH, Sturkenboom MC. The incidence of sudden cardiac death in the general population. *J Clin Epidemiol.* 2004; 57: 98-102.
35. Darpo. Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. *Eur Heart J Supplements.* 2001; 3 (suppl K): K70-K80.
36. Ray WA, Thapa PB, Gideon P. Misclassification of current benzodiazepine exposure by use of a single baseline measurement and its effects upon studies of injuries. *Pharmacoepidemiol Drug Saf.* 2002; 11: 663-9.
37. van Staa TP, Abenhaim L, Leufkens HGM. A study of the effects of exposure misclassification due to the time-window design in pharmacoepidemiologic studies. *J Clin Epidemiol.* 1994; 47: 183-9.

Chapter 6

GENERAL DISCUSSION

ON THE SEARCH FOR CLINICALLY RELEVANT DRUG-INDUCED ARRHYTHMIAS, OPTIONS IN STUDY DESIGN



INTRODUCTION

Monitoring safety of marketed drugs is a continuous process which starts, years before marketing, in preclinical studies and should last until the end of their marketing life. Potentially important safety issues can be identified at any stage of drug development. Reasons why they may not be detected until the post-marketing period include [1]:

1. The adverse reaction is rare and therefore undetectable until a large number of patients have been exposed to the drug.
2. There is a long latency period between starting the drug and development of the adverse reaction.
3. The drug has not been studied in day-to-day practice :
    - Patients treated in clinical practice are likely to have different characteristics than trial patients (e.g. demography, comorbidity, comedication) [2, 3]
    - In clinical practice a drug is less likely to be used strictly in accordance with the recommendations either by doctors or patients

Drug-induced cardiac arrhythmias are very rare (approximately 1 per 10,000 to 100,000 [4]) and often occur in patients (notably those with underlying conditions) which may not have been included in pre-marketing studies [5]. Therefore, they are a typical example of a post-marketing drug safety issue.

In order to assess the risks and benefits of drug treatment after a drug safety signal has been raised, epidemiological studies are often initiated to elucidate the adverse event in the context of the exposure [1]. This chapter discusses methodological issues which epidemiologists should consider when investigating rare, potentially fatal adverse reactions, such as drug-induced arrhythmias. Where appropriate, the studies in this thesis are put into perspective.

AIMS - WHAT TO STUDY?

Epidemiological research [6] aims to evaluate the occurrence of a certain health phenomenon of interest (the outcome) as a function of certain determinants (the exposure). The objective can either be to study the causality between outcome and a certain suspect exposure (etiologic research), or to predict the outcome in the context of certain determinants, regardless of causality (diagnostic or prognostic research).
The studies presented in chapter 2.1 and 2.2 aimed to assess the relationship between exposure to several suspected drugs and the occurrence of cardiac arrhythmias in the population at large, whereas the study in chapter 2.3 aimed to determine this relationship in hospitalised patients with underlying diseases. The studies in chapter 4 were also designed to answer etiologic research questions. In chapter 4.1, the association between genetic factors and the occurrence of cardiac arrhythmias among patients using suspected drugs was studied, and in chapter 4.2 the occurrence of cardiac arrhythmias was related to molecular drug-receptor binding properties. The prognostic study presented in chapter 3.2 aimed to predict the occurrence of cardiac arrhythmias given exposure to proarrhythmic drugs.

The determinant - which drugs may be hazardous?

When focusing on a certain adverse drug reaction, one may study a single suspected drug, or a group of drugs, all of which may induce the adverse reaction of interest. Consequently, such a group may consist of a single drug class, or of drugs from multiple classes. In the case of drug-induced arrhythmias, cisapride [7, 8] and erythromycin [9] were studied as a single drug, whereas others focused on class effects of nonsedating antihistamines [10, 11] (chapter 2.1), antipsychotic drugs [12-14], and antidepressants [15]. Chapters 2.2, 2.3, 3.2 and 4.1 of this thesis focused on a group of non-antiarrhythmic proarrhythmic drugs from different classes, to investigate the impact of all drugs for which a clinically relevant association with cardiac arrhythmias has been established [16] on public health.
The next step is to characterise the suspect drug(s) of interest in more detail. Questions such as, 'Is the drug likely to be subject to drug-drug interactions?', 'What is the expected lag time between drug exposure and outcome?', and 'Who prescribes the drugs?' should be answered.

Information on pharmacokinetic drug-drug interactions may be obtained from preclinical and clinical pharmacological research, whereas information on lag time between exposure and outcome may be determined from case reports and other epidemiological studies. Research on drugs which may only be obtained on prescription may require another design to that of studies on drugs which are sold without prescription (over-the-counter: OTC), since information on exposure to the drugs may be obtained differently, with implications for validity.

In this thesis we focused mainly on prescription-only drugs. Exposure to these agents was assessed through prescription (chapter 2.3, 3.2) or dispensing records (chapter 2.2, 3.1). It was assumed that patients took the medication as indicated by the prescribing physician. If a patient is not fully compliant, and takes his or her medication in a dosage or at a time other than instructed, bias may occur. These aspects were addressed in chapter 5.2, which describes how non-differential misclassification of exposure may lead to considerable underestimation of true associations. Exposure to OTC-drugs may be assessed through other, less reliable sources of information, such as questionnaire data [17].

If one wishes to estimate the feasibility of a study on drug-induced disease, techniques from drug-utilization research can be used to estimate the prevalence of drug-use. Several authors have estimated the use of non-antiarrhythmic proarrhythmic drugs. Herings et al [18] estimated the use of terfenadine in the Netherlands by assessing pharmacy records. The use of this drug was also studied in the US by Thompson, Carlson and Burkhart [19-21]. Several researchers performed drug-utilization studies on cisapride in the Netherlands [22] (chapter 3.1), the US [23-25], New Zealand [27], and Mexico [26]. Roe et al [29] focused on antipsychotic drugs, whereas De Ponti et al [30] and Curtis et al [31] estimated the use of a broad range of QTc-prolonging drugs in several European countries and the US, respectively.

The outcome - what to look for?

When signals about a potentially serious adverse reaction first arise, it may not yet be possible to give a well-defined description of the study outcome of interest. In recent years, the mechanism by which drug-induced arrhythmias may manifest has been (partly) unravelled. Through the blockade of HERG potassium channels in cardiac myocytes, drugs may prolong repolarisation, which manifests itself as a prolonged QTc-interval on the surface electrocardiogram. Prolongation of the action potential

may provoke Torsade de Pointes arrhythmias. Clinical manifestations of Torsade de Pointes may range from palpitations to sudden death [32-34].
In case of a rare disease, one may prefer to study an early signature which occurs more often and prior to the outcome of interest, rather than the disease itself. The most widely used early signature for proarrhythmia is prolongation of the corrected QT-interval (QTc) [35]. There is an ongoing discussion, however, on how to measure the QT-interval [35] and how to correct the QT-interval for heart rate [35-37]. In addition, there appears to be no clear dose-response relationship between QTc-prolongation and the proarrhythmic potential of drugs [38, 39]. In general, a drug which prolongs the QTc-interval substantially more compared to another drug is more likely to be proarrhythmic. However, exceptions exist, making it very difficult to propose a safety limit of QTc-interval prolongation [35]. In the latest international conference on harmonisation (ICH) guideline on the clinical evaluation of QT/QTc-interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH E14) [40], it is advised to evaluate both drug effects on mean changes from baseline (> 30ms and > 60ms) as well as an outlier analysis on absolute effects, presenting the number of patients with absolute QTc-intervals over 450ms, 480ms, and 500ms respectively.

In this thesis we did not study QTc-prolongation as an early signature for severe proarrhythmia, but focused solely on arrhythmias, cardiac arrest and sudden death. These 'hard' endpoints were measured using different techniques. In chapter 2.1, 4.1 and 4.2 we made use of spontaneous reports of cardiac arrhythmias and sudden death to identify cases. Cardiac arrhythmias which require hospitalisation were studied in chapter 2.2, whereas chapter 2.3 used information from a hospital registration of cardiopulmonary resuscitations to measure cardiac arrest as the outcome of interest. In chapter 3.2 the occurrence of ventricular arrhythmias and sudden death was measured through medical records from general practices.
Each of the outcome measures we used has its own advantages and drawbacks. The accuracy of outpatient diagnoses, for instance, is thought to be more uncertain than in-patient diagnoses, because hospitals employ experienced persons to code diagnoses for reimbursement purposes, whereas physicians usually do not [41]. In chapter 5.1 we specifically focused on the validity of hospital discharge diagnoses of cardiac arrhythmias. We found that only patients with discharge diagnoses that very specifically refer to ventricular arrhythmias (i.e. paroxysmal ventricular tachycardia,

ventricular fibrillation and/or flutter, and ventricular premature beats) or cardiac arrest were in fact hospitalised for such events. Broadening the case definition may introduce bias. Furthermore, the coding system which is widely applied to code hospital discharge diagnoses diseases, the International Classification of Diseases 9th revision Clinical Modification (ICD-9-CM) [42], has no unique code for Torsade de Pointes arrhythmias.

OPTIONS IN STUDY DESIGN - WHERE, WHEN AND HOW TO LOOK?

After deciding what to study, the next step is to choose the best study design to answer the research question. The major distinction in study design lies between experimental and non-experimental, or observational research. Within these two main study design categories, several options will be discussed in the context of drug-induced arrhythmias. The studies presented in this thesis, however, were all non-experimental.

Experimental drug risk assessment

Randomised trials

The key feature of experimental research is randomisation. Allocation of exposure and nonexposure occurs at random, making both groups of patients comparable regarding the probability of developing the study outcome at the time of randomisation. Therefore, it eliminates bias in treatment assignment [43]. In addition, it facilitates blinding, which is used to keep investigators, participants, and assessors unaware of the assignment intervention, so that they will not be influenced by that knowledge [44], and hence reduces differential assessment of outcomes. Randomised controlled trials have become the gold standard in clinical research. However, they have some disadvantages, making this type of study design not ideal to study rare adverse effects, such as drug-induced arrhythmias.

Pre-marketing trials are mainly performed to confirm or demonstrate a drug's efficacy. They are generally neither large enough nor long enough to provide all the necessary information on the safety of a drug, and tend not to reflect exposure in real life by excluding certain patient groups. At the time of approval, the safety database of a new drug will often only include 3,000 to 4,000 exposed individuals [45]. To detect a relative risk of 2, (with an α of 0.05 and a β of 0.80) of a disease with a

background incidence of 1%, at least 2319 exposed patients and an equal number of unexposed patients are needed [46]. The background incidence rate of Torsade de Pointes, however, is very rare (0.4 per 10,000 per year [4]), and only drugs with a very high relative risk of cardiac arrhythmias can be studied in this type of study. For instance in the case of cisapride, no risk of serious cardiac arrhythmias was observed in pre-marketing studies, while prescribing was later restricted because of pro-arrhythmic potential [45].

Post-marketing trials generally include 'real life' patients that have a different background risk of cardiac arrhythmias of interest as well as a different risk of drug-induced arrhythmias. In most cases, fewer patients need to be included in such a trial to detect a significantly increased risk, compared with pre-marketing randomised trials. The incidence of Torsade de Pointes in the general population is again so low, that even when this background risk in the study population is multiplied by 10 and the relative risk in the study population is 4, more than 10,000 exposed patients and an equal number of controls are needed to detect a statistically significant risk [46].

As mentioned above, the alternative would be to study prolongation of the QTc-interval instead of the cardiac arrhythmias themselves. Detailed electrocardiographic analyses have been introduced in pre-marketing trials in recent years [47, 48]. Analyses such as these are likely to become mandatory in the near future when the ICH guideline for clinical evaluation of QT/QTc-interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs is adopted (ICH E14) [40]. For the majority of non-antiarrhythmic drugs, however, the frequency of QTc-interval prolongation > 500ms (which is mentioned in the guideline) is again too low (< 0,1%) to be detected in clinical trials [49].

In order to increase power, data from multiple trials can be pooled. The cardiac safety of some antibiotics [50, 51], and antipsychotics [52, 53] has been assessed in this way. One should always bear in mind, however, that pre-marketing trials are not primarily designed to study rare adverse drug reactions. Apparent cardiac safety during this phase certainly does not reassure lack of proarrhythmic potential of the investigated drug.

Non-experimental drug risk assessment

In contrast to experimental studies in which exposure is assigned randomly, the occurrence of adverse reactions in patients receiving a certain drug in daily practice can be studied and compared with patients not receiving the drug. Advantages of such observational studies compared to an experimental setting are that rarer adverse reactions can be detected [54], 'real' patients are studied, and costs are lower. However, due to lack of randomisation in non-experimental studies, several types of bias, which have been extensively discussed in the epidemiological literature [55, 56], may affect the validity of the study results. A well-known example is referral bias (e.g. the selective referral of exposed patients, which increases the chance of being identified as a case) which played a role in case-control studies on the association between third generation oral contraceptives and the risk of venous thromboembolism [57]. Another classical example is recall bias, which may occur in case-control studies assessing self-reported exposure, when cases have a different recollection of their past exposures than healthy controls [58].

However, the most important potential problem in non-experimental drug risk assessment is a phenomenon known as 'confounding by indication' [59, 60], which may occur when the prognosis of patients varies according to the exposure. By definition, characteristics differ between those who receive and those who not receive a certain drug, since physicians have a reason to prescribe ('indication') drugs to patients, and tend to 'channel' certain drugs, or certain dosing regimens to specific patients. When these characteristics are related to the occurrence of the outcome, the association between exposure and outcome may be confounded. While in typical type B adverse reactions confounding by indication is a non-issue, the phenomenon may pose insurmountable validity problems in typical type A side effects. Drug-induced arrhythmias by non-antiarrhythmic drugs have characteristics of a type A as well as a type B side effect [61]. They started out as a typical type B adverse drug reaction: uncommon, not related to a pharmacological action of the drug, unpredictable and with high mortality ('all or none' phenomenon). Later, it turned out that the adverse effect was dose-dependent, and that in many cases it could be prevented by avoiding pharmacokinetic drug-drug interactions. In addition, the underlying pharmacological mechanism was unravelled. Consequently, the adverse reaction acquired more and more characteristics of a type A side effect [33]. With increasing predictability of the adverse reaction, the chance of selective (non)prescribing grows, and confounding by (contra)indication will become more of a potential

problem. In recent years, there has been an increase in knowledge about drugs able to induce cardiac arrhythmias, as well as about risk factors for drug-induced arrhythmias [32, 34, 62]. Although this knowledge still shows some deficits [63], it is nevertheless likely to have changed the prescribing behaviour of physicians.
Several non-experimental study designs may be applied to study rare and potentially fatal adverse reactions, including case reports and case series, follow-up studies and case-control studies.

Case reports and case series

When a patient presents him- or herself to a health care professional with a suspected adverse drug reaction, the health care professional may record it in the patient's medical file. The health care provider may also be triggered to report the event to a local or national pharmacovigilance centre, or publish the event in a medical journal. Such case reports are crucial for hypothesis generation.
Spontaneous reporting systems maintained by pharmacovigilance centres are able to detect very rare adverse reactions which occur in less than 1 in 10,000, especially when spontaneous reports are pooled internationally [54]. The Uppsala Monitoring Centre (WHO-UMC), for instance, receives more than 200,000 case reports of suspected adverse drug reactions from more than 70 countries all over the world annually [64]. Spontaneous reporting systems cover the whole population and are relatively cheap. It has to be borne in mind, though, that a registry of this kind is not complete and reporting bias may occur as a result of differential over- and underreporting [65].
Qualitative signal detection on possible causal relations between an adverse event and a drug can be detected through case-by-case assessment [66, 67]. Several decision algorithms have been used for causality assessment, sometimes resulting in different conclusions [68]. Most algorithms require positive dechallenge (disappearance of the adverse reaction after withdrawal of the drug) as well as positive rechallenge (recurrence of the adverse event after re-exposure) to fulfil the criteria of 'certain causality' [66]. Especially in the case of serious or even potentially fatal adverse reactions, such as drug-induced arrhythmias, positive rechallenge may be impossible or unethical [69].
In quantitative signal detection, automated systems select drug-adverse event pairs which stand out against the background of the database, according to prefixed

statistical criteria. The overall reports function as a measure of the drug-use denominator [64]. Individual assessors decide whether a signal deserves further examination and is followed up. Several measures of disproportionality, such as the reporting odds ratio (ROR), or the proportional reporting ratio (PRR), as well as the more sophisticated calculation of information components (IC) using a neural network have been applied [70, 71]. The advantage of these methods is that large numbers of case reports can be studied in a relatively short time span. One of the major drawbacks is the fact that spontaneous reporting systems suffer from underreporting [72]. Selective under- and overreporting of certain adverse drug reactions within the overall underreporting can lead to misinterpretations when comparing drugs in relation to adverse reactions. The studies by De Bruin et al [11] (chapter 2.1) and Lindquist et al [73] gave examples of how media attention to anti-histamine-induced arrhythmias biased the association between drug-exposure and outcome. A similar problem of selective reporting in the case of sertindole was described by Moore et al [74]. The initially high proportional reporting ratio of fatal reactions suggesting arrhythmia, which caused the drug to be suspended, was put into perspective. Factors leading to selective reporting of adverse events (e.g. time since marketing, 'dear doctor' letters, cumulative market exposure) may have distorted the association between drug use and cardiac arrhythmias, when comparing sertindole to other antipsychotic drugs.

Another limitation is that a detailed description of the case and knowledge of (confounding) risk factors is often lacking. In the study presented in chapter 4.1, for instance, an electrocardiographic recording of the arrhythmia was available for only one out of four cases. In the study presented in chapter 4.2, information on potential confounders was only present in part of the study population (age 80%, gender 91%, comedication 50%).

In addition, measures of disproportionality are often mistaken for true relative risks, while in fact they only represent the likelihood of the presence of an association[70].

A completely different application of spontaneous reports of adverse drug reactions to that of signal detection is presented in chapter 4.2. In this study, the predictive value of a pharmacological parameter probably underlying the mechanism of drug-induced arrhythmias was tested. Anti-HERG-activity of drugs is tested for the association with the occurrence of reports of cardiac arrhythmias in the WHO-UMC database. Spontaneous reports may also function as a source for case-finding

in studies assessing risk factors for adverse reactions of drugs, such as genetic predisposition shown in chapter 4.1.

Follow-up studies

Follow-up or cohort studies are studies in which two or more subsets of a defined population, differing in exposure, are followed over time in order to compare the occurrence of the outcome of interest. In drug risk assessment studies, the occurrence of adverse drug reactions is generally compared between a group of patients exposed to a certain drug of interest and a group of unexposed patients. The group of unexposed patients may consist of other patients not taking the drug of interest, other patients taking other comparator drugs, or the same patients at another point in time, when they are taking another comparator drug, or are not taking the drug of interest.

Follow-up studies can be performed prospectively, simultaneously with the events under study, or retrospectively, when the events under study already occurred [75]. One of the most well-known systematic prospective follow-up methods used in drug risk assessment is prescription event monitoring (PEM) [76]. This method aims to identify all patients prescribed selected drugs throughout a certain observation period and to ask prescribers to report subsequent events. The incidence density of events can be calculated by dividing the number of events by the person time of use. Most of the studies include approximately 10,000 patients and are powered to detect adverse drug reactions that occur once in 100 to 5,000 patients [54]. PEM studies may suffer from biases similar to those occurring in spontaneous reporting systems of adverse drug reactions, as a result of underreporting. Although the initial selection of exposed patients is virtually complete, only 60% of the 'green forms' are returned [76]. It is not clear whether the patients whose doctors do return the green forms are in any way different from those whose doctors fail to complete and return the questionnaires, but as in the case of spontaneous reports selective participation may occur. Since most of the PEM studies are performed directly after a new drug has been launched, media attention paid to a specific adverse drug reaction is not very likely to influence participation. It is, however, quite likely that doctors are more likely to fill out green forms when serious events happened, and that this

likelihood varies according to the patient characteristics, time, or order of market entering of different drugs.

In retrospective follow-up studies, researchers often use administrative databases, including routinely documented information on prescription or dispensing of drugs, allowing rapid identification of cohorts of patients taking certain drugs. If these exposure data are linked to outcome information, studies can be performed without requiring additional information from patients or physicians. The advantage of database studies is that large cohorts can be identified, and followed for a relatively long time. The size of cohort studies, however, is limited by the time available to prepare previously stored data for analyses and, even today, by computer capacity to perform the analyses. Since the early 1990s several follow-up studies on drug-induced arrhythmias have been performed in administrative databases which are maintained for pharmacoepidemiological research purposes. These concerned antihistamine drugs [10, 77-79], neuroleptic drugs [12-15], erythromycin [9] and cisapride [7, 8], and included several tens to hundreds of thousands of patients receiving one or more prescriptions of drugs of interest and even more control patients. In chapter 3.2 we performed a retrospective follow-up study to predict the occurrence of drug-induced arrhythmias in diabetic patients. More than 60,000 patients were followed during the period they took non-antiarrhythmic proarrhythmic drugs, until they experienced a ventricular arrhythmia or sudden death. This study was not designed to assess the association between drug exposure and occurrence of arrhythmic events, nor to quantify this risk, but to assess the prognostic value of (combinations of) patient characteristics on the probability of developing an arrhythmic event, among users of proarrhythmic drugs.

Important advantages of follow-up studies, compared with randomised trials include the fact that larger populations are often being followed, and 'real' users are being studied. Confounding by indication, on the other hand, may bias the study results. Ray et al [12], for example, compared the occurrence of sudden cardiac death between patients taking antipsychotic drugs and untreated patients. Psychiatric patients may have an increased risk for sudden death not related to drug-use [80], and the observed association may have been biased due to confounding by indication. Confounding by contra-indication may occur, when it is not the indication for the drug, but another disease which is a relative contraindication for its use that is

associated with the outcome. If doctors refrain from prescribing drugs of interest to high-risk patients with underlying diseases, the observed association will be underestimated. Confounding by contraindication is not very likely in the case of typical Type B adverse drug reactions, because the occurrence of the adverse reaction may not be anticipated by the prescribing physician. However, as mentioned earlier, knowledge concerning risk factors for drug-induced arrhythmias increased during recent years.

A way to limit confounding by (contra)indication is to restrict the study to patients with a similar indication. This can either be obtained by comparing the incidence of events of interest with patients using comparator drugs [77-79], or to compare incidence rates within a single group of patients between the time they used the drug, and the time they did not use the drug of interest [7, 8, 10, 12, 15]. Other means to reduce confounding by indication in follow-up studies include baseline matching of exposed to non-exposed subjects (to simulate randomisation and perform a quasi-experiment), and adjustment for confounders in the analyses (using multivariate regression analyses or propensity scores). These techniques, however, have in common that they can only adjust for known and measured potential confounders [81].

Case-control studies

In case-control studies, patients who develop the outcome of interest (cases) are compared with a sample of the population where the cases emerged from (control patients) regarding the exposure of interest [82]. Case-control studies aim at abstracting the information on determinants in the whole study population from which the cases came, by sampling from that population. It is therefore much more efficient than follow-up studies or randomised trials, in which the determinants are measured in the entire population. The main advantages of this design are that case-control studies are feasible to study rare events, associations with unknown or long latency periods, and multiple exposures (e.g. several different drugs, varying doses, duration of use, or exposure at several points in time before the index date) as risk factors for the disease of interest [75, 82].

Several case-control studies on drug-induced arrhythmias have been performed, either after ad hoc data collection [83] (chapter 2.3) or in administrative databases which are maintained for pharmacoepidemiological research purposes [14, 84] (chapter 2.2). A case-control design was also applied in chapter 4.1 of this thesis. This

study, however, was not designed to assess the association between drug exposure and occurrence of arrhythmic events, but to study genetic predisposition as a risk factor of drug-induced arrhythmias among patients taking non-antiarrhtyhmic proarrhythmic drugs.

Case-control studies may suffer from referral bias. The study presented in chapter 2.2 [84], in which use of QTc-prolonging drugs is compared between patients hospitalised for cardiac arrhythmias and matched controls could have suffered from referral bias when physicians were more likely to refer patients with arrhythmic symptoms to the hospital if they were dispensed one of the suspected drugs. Knowledge about, and media attention paid to drug-induced arrhythmias increased over time. The observed association between exposure and outcome in this study, however, did not increase over time, suggesting that referral bias did not influence the results.

In order to limit confounding by (contra)indication in the pharmacogenetic study presented in chapter 4.1, we selected control patients from the same general practices as the corresponding case. The influence of selective (non-)prescribing of certain drugs to patients with certain (contra)indications on the association between genetic predisposition and the occurrence of cardiac arrhythmias was reduced in this way, since control patients had the same gender and age as the corresponding case and were prescribed the same drug, in the same year, by the same physician. Knowledge about potential adverse reactions that may have influenced the physician's decision to prescribe a certain drug or not was probably comparable between cases and controls in this way. Confounding by (contra)indication in the studies presented in chapters 2.2 and 2.3 was dealt with in the data-analysis. Multivariate regression analyses were performed to adjust for the presence of (contra)indications for treatment with the drugs, that are also known risk factors for the outcome. Potential confounding by indication was nicely assessed by Straus et al [14] in their case-control study on use of antipsychotics and sudden death. Schizophrenia is one of the indications for antipsychotic drugs, and may act as a confounder. The authors, however, found that the risk of sudden death was similarly increased for patients taking antipsychotics for schizophrenia as was for patients taking the drugs for other indications.

As mentioned previously, one can only adjust for known and measurable potential confounders [81], although very rarely 'instrumental variables' may be used to adjust for unmeasured confounders [85]. Residual confounding occurs when one is not able to adjust for all confounding factors. Factors which are generally not measured and collected in administrative databases used for observational pharmacoepidemiological studies include lifestyle factors and food intake. Substances which are able to block HERG potassium channels and cause Torsade de Pointes arrhythmias through the same mechanism as proarrhythmic drugs include cocaine, alcohol, and tobacco [86]. In addition, farmacokinetic drug-food interactions through CYP3A4 metabolism have been reported for various foods and beverages, including grapefruit juice and red wine [87].

Another special type of case-control design is the case-crossover study. In this design cases are used as their own controls, at another point in time [88]. The idea behind this design is that cases themselves are the best representatives of the study base from which the cases emerged. In a way, it resembles the principle of dechallenge and rechallenge applied in causality assessment of case reports of adverse drug reactions [66]. The method is only feasible as long as the drug effects are acute and exposure is transient. Drug-induced arrhythmias appear to fulfil these criteria, as patients are often intermittently exposed to drugs, and the onset of cardiac arrhythmias is acute. Although the proarrhythmic effect of QTc-prolonging drugs is likely to disappear after discontinuation of therapy [89], carry-over effects can not be ruled out in most cases, making a case-crossover design less suitable. This design may appear an attractive option for studying at least some drug-induced arrhythmias. Nevertheless, no such studies have as yet been published to our knowledge. It would be interesting to compare this design methodologically with a traditional case-control design, in order to evaluate the additional value of such studies in the case of drug-induced arrhythmias.

FINAL CONSIDERATIONS

Pharmacoepidemiological research will continue to play an important role in drug-risk assessment and management. It helps to tackle drug safety issues generated by pharmacovigilance, and may provide crucial information for patients, health professionals, industry and regulatory authorities. A diversity of interests may be at stake, however, in the intriguing field between regulatory affairs, pharmaceutical industry and clinical practice, while objectivity and transparency are of the utmost importance. Balancing drug risks against benefits is a human activity inevitably involving substantial subjective, cultural and political variability. This subjectivity is illustrated by the measures taken in response to reports on the arrhythmogenicity of the antihistamine drug terfenadine: American regulators decided that it was better to take terfenadine off the market as soon as the safer alternative fexofenadine became available. In the Netherlands, on the other hand, terfenadine is still available on prescription. Similarly, cisapride was withdrawn in the United States, shortly after drug safety issues were first raised, while in the Netherlands the drug is still available under a restricted policy. Apparently, risk assessment and perception vary between countries, and different regulatory decisions are being made on the basis of the same scientific information.

Although the results of this thesis add useful pieces to the puzzle of drug-induced arrhythmias, a number of issues remain unsolved. Firstly, one can argue about the most relevant outcome definition. As depicted in figure 3 in chapter 1, the clinical manifestations of drug-induced arrhythmias vary from asymptomatic alterations of the electrocardiogram to sudden cardiac death. These different manifestations make precise quantification of the problem complex. For example, asymptomatic patients are difficult to identify and assessment of a cardiac origin of sudden death is often impossible. Epidemiologists use different case definitions, according to their best current knowledge and practical applicability. Due to strict definitions and criteria, absolute incidences of drug-induced arrhythmias may be underestimated. In addition, it would be relevant to study the correlation between the various endpoints in relation to drug exposure. A database in which drug exposure data are linked to electrocardiographic information, data from general practices, results from outpatient cardiology-visits, hospitalisation records and death certificates would be ideal to study all possible endpoints ranging from vague symptoms to causes of death.

Drug-induced arrhythmias appear very rare, making it very difficult to quantify their occurrence and determinants in the population at large. In addition, these side effects seem to occur in selective groups of high-risk patients prone to adverse reaction. In order to detect, for instance, a statistically significant increased relative risk of hospitalisation for cardiac arrhythmias of 1.2 in a population with a background exposure among controls of 6%, 4,744 cases and four times as many controls are required [46]. With an annual incidence of 16 outcome events per 100,000 inhabitants per year (chapter 2.2), almost 30 million person years of follow-up are needed to identify enough cases. Such studies are virtually impossible, and a challenge for future epidemiologists may be to focus primarily on the high-risk groups in more detail. For instance, we found that patients with asthma (chapter 2.2), are prone to drug-induced arrhythmias. Hopefully other researchers, with a special interest in pulmonary diseases, will study this problem in more detail. Nowadays, molecular strategies are increasingly applied to understand and predict toxicity of drugs. The anti-HERG activity of drugs and the pharmacogenetics of drug-induced arrhythmias, both addressed in this thesis, appear promising, but do not perfectly predict proarrhythmia. The interaction between various molecular parameters and environmental factors underlying the susceptibility for drug-induced arrhythmias needs to be further unravelled in the near future.

With regard to the options in study design for assessing rare, potentially fatal adverse reactions, such as drug-induced arrhythmias, no paradigm method exists. A case-control approach enables us to study the rarest adverse reactions, while follow-up studies in administrative databases with sufficient power are a good alternative. However, neither of these methods may be capable of quantifying minuscule risks in the population at large. We may have arrived at a point in time where the level of safety that is required in drug safety is greater than the resources and techniques we have available to quantify this risk and identify its determinants.

BIBLIOGRAPHICAL REFERENCES

1. Waller PC, Lee EH.Responding to drug safety issues.*Pharmacoepidemiol Drug Saf.*1999;8:535-52.
2. Wieringa NF, de Graeff PA, van der Werf GT, Vos R. Cardiovascular drugs: discrepancies in demographics between pre- and post-registration use. *Eur J Clin Pharmacol.* 1999; 55: 537-44.
3. Wieringa NF, Vos R, van der Werf GT, van der Veen WJ, de Graeff PA. Co-morbidity of 'clinical trial' versus 'real-world' patients using cardiovascular drugs. *Pharmacoepidemiol Drug Saf.* 2000; 9: 569-79.
4. Darpo. Spectrum of drugs prolonging QT interval and the incidence of torsades de pointes. *Eur Heart J Supplements.* 2001; 3 (suppl K): K70-K80.
5. Viskin S, Justo D, Halkin A, Zeltser D. Long QT syndrome caused by noncardiac drugs. *Prog Cardiovasc Dis.* 2003; 45: 415-27.
6. Grobbee DE, Miettinen OS. Clinical epidemiology. Introduction to the discipline. *Neth J Med.* 1995; 47: 2-5.
7. Walker AM, Szneke P, Weatherby LB, et al. The risk of serious cardiac arrhythmias among cisapride users in the United Kingdom and Canada. *Am J Med.* 1999; 107: 356-62.
8. Enger C, Cali C, Walker AM. Serious ventricular arrhythmias among users of cisapride and other QT-prolonging agents in the United States. *Pharmacoepidemiol Drug Saf.* 2002; 11: 477-86.
9. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM. Oral erythromycin and the risk of sudden death from cardiac causes. *New Engl J Med.* 2004; 351: 1089-96.
10. de Abajo FJ, Rodriguez LA. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999; 47: 307-13.
11. De Bruin ML, van Puijenbroek EP, Egberts AC, Hoes AW, Leufkens HGM. Non-sedating antihistamine drugs and cardiac arrhythmias -- biased risk estimates from spontaneous reporting systems? *Br J Clin Pharmacol.* 2002; 53: 370-4.
12. Ray WA, Meredith S, Thapa PB, Meador KG, Hall K, Murray KT. Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry.* 2001; 58: 1161-7.
13. Hennessy S, Bilker WB, Knauss JS, et al. Cardiac arrest and ventricular arrhythmia in patients taking antipsychotic drugs: cohort study using administrative data. *Br Med J.* 2002; 325: 1070.
14. Straus SMJM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the Risk of Sudden Cardiac Death. *Arch Intern Med.* 2004; 164: 1293-7.
15. Ray WA, Meredith S, Thapa PB, Hall K, Murray KT. Cyclic anidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther.* 2004; 75: 234-41.

16. De Ponti F, Poluzzi E, Montanaro N. Organising evidence on QT prolongation and occurrence of Torsades de Pointes with non-antiarrhythmic drugs: a call for consensus. *Eur J Clin Pharmacol.* 2001; 57: 185-209.
17. Tobi H, Meijer WM, de Jong-van den Berg LTW, Tuinstra J. Socio-economic differences in prescription and OTC drug use in Dutch adolescents. *Pharm World Sci.* 2003; 25: 203-6.
18. Herings RM, Stricker BH, Leufkens HG, Bakker A, Sturmans F, Urquhart J. Public health problems and the rapid estimation of the size of the population at risk. Torsades de pointes and the use of terfenadine and astemizole in The Netherlands. *Pharm World Sci.* 1993; 15: 212-8.
19. Thompson D, Oster G. Use of terfenadine and contraindicated drugs. *JAMA.* 1996;275:1339-41.
20. Carlson AM, Morris LS. Coprescription of terfenadine and erythromycin or ketaconazole: an assessment of potential harm. *J Am Pharm Assoc (Wash).* 1996; NS36: 263-9.
21. Burkhart GA, Sevka MJ, Temple R, Honig PK. Temporal decline in filling prescriptions for terfenadine closely in time with those for either ketoconazole or erythromycin. *Clin Pharmacol Ther.* 1997; 61: 93-6.
22. De Bruin ML, Panneman MJM, Leufkens HGM, Hoes AW, Herings RMC. Use of cisapride with contraindicated drugs in the Netherlands. *Ann Pharmacother.* 2002; 36: 338-43.
23. Jones JK, Fife D, Curkendall S, Goehring E, Jr., Guo JJ, Shannon M. Coprescribing and codispensing of cisapride and contraindicated drugs. *JAMA.* 2001; 286: 1607-9.
24. Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of food and drug administration regulatory action. *JAMA.* 2000; 284: 3036-9.
25. Weatherby LB, Walker AM, Fife D, Vervaet P, Klausner MA. Contraindicated medications dispensed with cisapride: temporal trends in relation to the sending of 'Dear Doctor' letters. *Pharmacoepidemiol Drug Saf.* 2001; 10: 211-8.
26. Viramontes-Madrid JL, Jerjes-Sanchez C, Pelaez-Ballestas I, Aguilar-Chiu A, Hernandez-Garduno AG. Risk of drug interactions. Combinations of drugs associated with ventricular arrhythmias. *Rev Invest Clin.* 2002; 54: 192-7.
27. de la Porte M, Reith D, Tilyard M. Impact of safety alerts upon prescribing of cisapride to children in New Zealand. *N Z Med J.* 2002; 115: U24.
28. Raschetti R, Maggini M, Da Cas R, Popoli P, Rossi A. Time Trends in the Coprescribing of Cisapride and Contraindicated Drugs in Umbria, Italy. *JAMA.* 2001; 285: 1840-1.
29. Roe CM, Odell KW, Henderson RR. Concomitant use of antipsychotics and drugs that may prolong the QT interval. *J Clin Psychopharmacol.* 2003; 23: 197-200.
30. De Ponti F, Poluzzi E, Vaccheri A, et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. *Br J Clin Pharmacol.* 2002; 54: 171-7.

31. Curtis LH, Ostbye T, Sendersky V, et al. Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients. *Am J Med.* 2003; 114: 135-41.
32. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med.* 2004; 350: 1013-22.
33. Shah RR. Pharmacogenetic aspects of drug-induced torsade de pointes: potential tool for improving clinical drug development and prescribing. *Drug Saf.* 2004; 27: 145-72.
34. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart.* 2003; 89: 1363-72.
35. Malik M, Camm AJ. Evaluation of drug-induced QT interval prolongation: implications for drug approval and labelling. *Drug Saf.* 2001; 24: 323-51.
36. Moss AJ. The QT interval and torsade de pointes. *Drug Saf.* 1999; 21: 5-10.
37. de Bruyne MC, Hoes AW, Kors JA, et al. Prolonged QT interval: a tricky diagnosis? *Am J Cardiol.* 1997; 80: 1300-4.
38. Eckardt L, Breithardt G, Haverkamp W. Electrophysiologic characterization of the antipsychotic drug sertindole in a rabbit heart model of torsade de pointes: low torsadogenic potential despite QT prolongation. *J Pharmacol Exp Ther.* 2002; 300: 64-71.
39. Belardinelli L, Antzelevitch C, Vos MA. Assessing predictors of drug-induced torsade de pointes. *Trends Pharmacol Sci.* 2003; 24: 619-25.
40. ICH Steering Committee. *The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH E14) draft consensus guideline.*Geneva: International Conference on Harmonization, 2004.
41. West SL, Strom BL. Validity of pharmacoepidemiology drug and diagnosis data. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester: John Wiley & Sons Ltd., 1994: 549-80.
42. World Health Organisation. *International Classification of Diseases, ninth revision (ICD9)*. Geneva, Switzerland: World Health Organisation, 1977.
43. Schulz KF, Grimes DA. Generation of allocation sequences in randomised trials: chance, not choice. *Lancet.* 2002; 359: 515-9.
44. Schulz KF, Grimes DA. Blinding in randomised trials: hiding who got what. *Lancet.* 2002; 359: 696-700.
45. Layton D, Key C, Shakir SA. Prolongation of the QT interval and cardiac arrhythmias associated with cisapride: limitations of the pharmacoepidemiological studies conducted and proposals for the future. *Pharmacoepidemiol Drug Saf.* 2003; 12: 31-40.
46. Schlesselman JJ. Sample size requirements in cohort and case-control studies of disease. *Am J Epidemiol.* 1974; 99: 381-4.

47. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry.* 2003; 60: 681-90.
48. Bernstein DI, Schoenwetter WF, Nathan RA, Storms W, Ahlbrandt R, Mason J. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 1997; 79: 443-8.
49. Shah RR. The significance of QT interval in drug development. *Br J Clin Pharmacol.* 2002; 54: 188-202.
50. Lipsky BA, Dorr MB, Magner DJ, Talbot GH. Safety profile of sparfloxacin, a new fluoroquinolone antibiotic. *Clin Ther.* 1999; 21: 148-59.
51. Jaillon P, Morganroth J, Brumpt I, Talbot G. Overview of electrocardiographic and cardiovascular safety data for sparfloxacin. Sparfloxacin Safety Group. *J Antimicrob Chemother.* 1996; 37 Suppl A: 161-7.
52. Czekalla J, Beasley CM, Jr., Dellva MA, Berg PH, Grundy S. Analysis of the QTc interval during olanzapine treatment of patients with schizophrenia and related psychosis. *J Clin Psychiatry.* 2001; 62: 191-8.
53. Pezawas L, Quiner S, Moertl D, et al. Efficacy, cardiac safety and tolerability of sertindole: a drug surveillance. *Int Clin Psychopharmacol.* 2000; 15: 207-14.
54. Meyboom RH, Egberts AC, Edwards IR, Hekster YA, de Koning FH, Gribnau FW. Principles of signal detection in pharmacovigilance. *Drug Saf.* 1997; 16: 355-65.
55. Rothman KJ. *Modern epidemiology*. Boston, MA: Little, Brown & Co, 1986.
56. Grimes DA, Schulz KF. Bias and causal associations in observational research. *Lancet.* 2002; 359: 248-52.
57. Dunn N, White I, Freemantle S, Mann R. The role of prescribing and referral bias in studies of the association between third generation oral contraceptives and increased risk of thrombo-embolism. *Pharmacoepidemiol Drug Saf.* 1998; 7: 3-14.
58. Rockenbauer M, Olsen J, Czeizel AE, Pedersen L, Sorensen HT. Recall bias in a case-control surveillance system on the use of medicine during pregnancy. *Epidemiology.* 2001; 12: 461-6.
59. Walker AM. Confounding by indication. *Epidemiology.* 1996; 7: 335-6.
60. Grobbee DE, Hoes AW. Confounding and indication for treatment in evaluation of drug treatment for hypertension. *Br Med J.* 1997; 315: 1151-4.
61. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet.* 2000; 356: 1255-9.

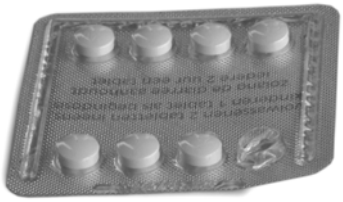
62. De Ponti FD, Poluzzi E, Cavalli A, Recanatini M, Montanaro N. Safety of Non-Antiarrhythmic Drugs that Prolong the QT Interval or Induce Torsade de Pointes: An Overview. *Drug Saf.* 2002; 25: 263-86.
63. LaPointe NM, Al-Khatib SM, Kramer JM, Califf RM. Knowledge deficits related to the QT interval could affect patient safety. *Ann Noninvasive Electrocardiol.* 2003; 8: 157-60.
64. Meyboom RH, Lindquist M, Egberts AC, Edwards IR. Signal selection and follow-up in pharmacovigilance. *Drug Saf.* 2002; 25: 459-65.
65. Wilson AM, Thabane L, Holbrook A. Application of data mining techniques in pharmacovigilance. *Br J Clin Pharmacol.* 2004; 57: 127-34.
66. Meyboom RH, Hekster YA, Egberts AC, Gribnau FW, Edwards IR. Causal or casual? The role of causality assessment in pharmacovigilance. *Drug Saf.* 1997; 17: 374-89.
67. Meyboom RH. Causality assessment revisited. *Pharmacoepidemiol Drug Saf.* 1998; 7 Suppl 1: S63-5.
68. Macedo AF, Marques FB, Ribeiro CF, Teixeira F. Causality assessment of adverse drug reactions: comparison of the results obtained from published decisional algorithms and from the evaluations of an expert panel, according to different levels of imputability.*J Clin PharmTher.*2003;28:137-43.
69. Po AL, Kendall MJ. Causality assessment of adverse effects: when is re-challenge ethically acceptable? *Drug Saf.* 2001; 24: 793-9.
70. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Saf.* 2002; 11: 3-10.
71. Hauben M, Zhou X. Quantitative methods in pharmacovigilance: focus on signal detection. *Drug Saf.* 2003; 26: 159-86.
72. Lumley CE, Walker SR, Hall GC, Staunton N, Grob PR. The under-reporting of adverse drug reactions seen in general practice. *Pharmaceut. Med.* 1986; 1: 205-12.
73. Lindquist M, Edwards IR. Risks of non-sedating antihistamines. *Lancet.* 1997; 349: 1322.
74. Moore N, Hall G, Sturkenboom M, Mann R, Lagnaoui R, Begaud B. Biases affecting the proportional reporting ratio (PPR) in spontaneous reports pharmacovigilance databases: the example of sertindole. *Pharmacoepidemiol Drug Saf.* 2003; 12: 271-81.
75. Strom BL. Study designs available for pharmacoepidemiology studies. In: Strom BL, ed. *Pharmacoepidemiology*. 2nd ed. Chichester: John Wiley & Sons Ltd., 1994: 15-27.
76. Mann RD. Prescription-event monitoring--recent progress and future horizons. *Br J Clin Pharmacol.* 1998; 46: 195-201.
77. Hanrahan JP, Choo PW, Carlson W, Greineder D, Faich GA, Platt R. Terfenadine-associated ventricular arrhythmias and QTc interval prolongation. A retrospective cohort comparison with

other antihistamines among members of a health maintenance organization. *Ann Epidemiol.* 1995; 5: 201-9.

78. Pratt CM, Hertz RP, Ellis BE, Crowell SP, Louv W, Moye L. Risk of developing life-threatening ventricular arrhythmia associated with terfenadine in comparison with over-the-counter antihistamines, ibuprofen and clemastine. *Am J Cardiol.* 1994; 73: 346-52.
79. Staffa JA, Jones JK, Gable CB, Verspeelt JP, Amery WK. Risk of selected serious cardiac events among new users of antihistamines. *Clin Ther.* 1995; 17: 1062-77.
80. Appleby L, Thomas S, Ferrier N, Lewis G, Shaw J, Amos T. Sudden unexplained death in psychiatric in-patients. *Br J Psychiatry.* 2000; 176: 405-6.
81. Collet JP, Boivin JF. Bias and confounding in pharmacoepidemiology. In: Strom BL, ed. *Pharmacoepidemiology*. third ed. Chichester: John Wiley & Sons Ltd., 2000: 765-84.
82. Hoes AW. Case-control studies. *Neth J Med.* 1995; 47: 36-42.
83. Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SH. Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry.* 2002; 180: 515-22.
84. De Bruin ML, Hoes AW, Leufkens HGM. QTc-prolonging drugs and hospitalizations for cardiac arrhythmias. *Am J Cardiol.* 2003; 91: 59-62.
85. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol.* 2000; 29: 722-9.
86. Karle CA, Kiehn J. An ion channel 'addicted' to ether, alcohol and cocaine: the HERG potassium channel. *Cardiovasc Res.* 2002; 53: 6-8.
87. Offman EM, Freeman DJ, Dresser GK, Munoz C, Bend JR, Bailey DG. Red wine-cisapride interaction: comparison with grapefruit juice. *Clin Pharmacol Ther.* 2001; 70: 17-23.
88. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. *Am J Epidemiol.* 1991; 133: 144-53.
89. van Haarst AD, van 't Klooster GA, van Gerven JM, et al. The influence of cisapride and clarithromycin on QT intervals in healthy volunteers. *Clin Pharmacol Ther.* 1998; 64: 542-6.

Chapter 7

SUMMARY



Cardiac arrhythmias as an adverse reaction to the use of non-antiarrhythmic drugs have attracted much attention during recent years. In the last decades, they have been the single most common reason to withdraw drugs from the market or to restrict their use. Drug-induced arrhythmias may occur through blockade of the HERG (human ether a go-go related gene) potassium channels in cardiac myocytes, leading to a prolonged action potential, which manifests itself as a prolonged QTc-interval on the surface electrocardiogram. They are very rare (approximately 1 per 10,000 to 100,000). However, they are of regulatory concern, mainly because they can be fatal, the occurrence is rather unpredictable, and many patients use these potentially harmful drugs. The research presented in this thesis aimed to quantify the risk of drug-induced arrhythmias and to identify high-risk groups of patients. In addition, methodological aspects and validity issues of epidemiological research on rare adverse reactions, such as drug-induced arrhythmias, have been addressed.

In **chapter 2** the risk of drug-induced arrhythmias was quantified using various data sources and several definitions of cardiac arrhythmias. Groups of patients prone to develop the adverse reaction have been identified. In **chapter 2.1** the association between nonsedating antihistamine drugs and cardiac arrhythmias was determined using data from the spontaneous adverse drug reactions reporting system maintained by the Netherlands Pharmacovigilance Centre 'Lareb'. In general, nonsedating antihistamines were associated with cardiac arrhythmias to a higher extent in comparison with other drugs (ADR reporting odds ratio 2.05, 95%CI 1.45 to 2.89). However, the association between arrhythmias and nonsedating antihistamine drugs calculated before 1998 was not significantly higher than 1 (OR 1.37, 95%CI 0.85 to 2.23), whereas the risk estimate calculated after the government's decision did significantly differ from 1 (OR 4.19, 95%CI 2.49 to 7.05). These findings strongly suggest that the increased risk identified may at least partly be explained by reporting bias as a result of publications about, and mass media attention paid to, antihistamine-induced arrhythmias, which occurred in the first months of 1998. We therefore suggested that the method of reaction proportion signalling, used to relate adverse reactions to certain drugs, should be applied cautiously while taking into account the dynamics of risk communication, regulatory action, and other erratic features of the pharmaceutical marketplace over time. In **chapter 2.2** cardiac arrhythmias which require hospitalisation were studied. Data from the PHARMO record linkage system were obtained to perform a case-control study in which

patients (cases), hospitalised for nonatrial cardiac arrhythmias, were compared with their matched controls regarding current use of several QTc-prolonging drugs. Overall, a statistically nonsignificant increased risk of arrhythmias (OR 1.2, 95%CI 0.8 to 1.9) was observed in patients who received QTc-prolonging drugs. A clearly increased risk of arrhythmias was found, however, in patients with a history of asthma (OR 9.9, 95%CI 1.0 to 100) and in patients using potassium lowering drugs (OR 5.3, 95%CI 1.1 to 25.9). Our data do not suggest that there is a strong overall association between the use of QTc-prolonging drugs and hospitalisation for cardiac arrhythmias. However, some specific groups of patients may experience clinically relevant risks, and may need extra attention. In **chapter 2.3** cardiac arrest requiring cardiopulmonary resuscitation in a university hospital setting was studied as the outcome of interest. A statistically significant increased risk of cardiac arrest (OR 2.1, 95%CI 1.2 to 3.5) was observed in patients who received proarrhythmic drugs. The risk was more pronounced in patients receiving more than the standard dose (OR 2.5, 95%CI 1.1 to 5.9), patients taking more than one proarrhythmic drug simultaneously (OR 4.8, 95%CI 1.6 to 14), and patients taking pharmacokinetic interacting drugs concomitantly (OR 4.0, 95%CI 1.2 to 13). We concluded that the use of non-antiarrhythmic proarrhythmic drugs in hospitalised patients with several underlying diseases is associated with an increased risk of cardiac arrest. Physicians caring for in-patients should be made aware of this, so that potential risks can be weighed against treatment benefits and additional cardiac surveillance can be requested if necessary.

Chapter 3 focused on groups of patients at increased risk of drug-induced arrhythmias. In **chapter 3.1** the influence of official warnings for potentially hazardous drug-drug interactions concerning proarrhythmogenicity among cisapride users on prescribing practice was studied. Between 1995 and 1997 three label changes were issued, regarding warnings for QTc-prolongation with respect to concomitant use of a total of nine CYP3A4 inhibiting drugs. In addition, a 'Dear Doctor' letter was posted in 1995 to emphasize the importance of the label changes. From 1994 to 1998, the relative prevalence rate of the observed versus expected use of any potentially interacting drug decreased significantly over time ($p<0.01$). However, the absolute number of days-at-risk and number of coprescriptions of potentially interacting drugs among patients taking cisapride increased on average 13% and 9% per year, respectively. So, although it appeared that health care professionals have

refrained from dispensing potentially interacting drugs to patients who use cisapride, the absolute effects were limited. The study presented in **chapter 3.2** aimed to develop a decision tool to be applied in general practice, to predict the risk of serious ventricular arrhythmias and sudden death among diabetic patients taking non-antiarrhythmic proarrhythmic drugs. We focused on diabetic patients, because they have relatively long baseline QTc-interval by nature, and a subsequent increase in QTc-interval by proarrhythmic drugs may lead to cardiac arrhythmias and sudden cardiac death. The absolute risk of serious ventricular arrhythmias and sudden death among diabetic patients taking proarrhythmic drugs is low (24 events per 100,000 prescriptions). Independent predictors of serious ventricular arrhythmias and sudden death were age, male gender, ischaemic heart disease and nonventricular arrhythmias. We derived a scoring rule which may be used to identify patients with a 4 times higher risk of the study outcome, compared to the whole study population.

Chapter 4 provided new insights into molecular strategies in the research on drug-induced arrhythmias. In **chapter 4.1** the feasibility of a pharmacogenetic study using spontaneous reporting data as a source of identifying case patients was discussed. It has been hypothesised that there may be some genetic predisposition for drug-induced arrhythmias. The rareness of this disease, however, may hamper patient recruitment in a hospital setting for example. Spontaneous reporting systems may form a useful source of patients. We were able to include four out of 45 potential cases, of whom the occurrence of drug-induced arrhythmias was reported to the Netherlands Pharmacovigilance Centre 'Lareb' during the previous seven years, as well as five matched controls. We concluded that spontaneous reporting systems for adverse drug reactions may be used for pharmacogenetic research. However, the described methods need to be improved to increase patient participation, and international collaboration may be required.
The study presented in **chapter 4.2** linked the preclinical molecular HERG-blocking properties of drugs to post-marketing drug safety data. The method of reaction proportion signalling and calculation of reporting odds ratios were used to associate the ratio of therapeutic and toxic plasma levels of 52 different drugs to the occurrence of case reports of suspected adverse drug reactions regarding cardiac arrest, sudden death, Torsade de Pointes, ventricular fibrillation, and ventricular tachycardia among all case reports received by the International Drug Monitoring Program of the World Health Organisation (WHO-UMC). We identified a statisti-

cally significant association of 1.93 (95%CI 1.89 to 1.98) between the anti-HERG-activity of drugs, measured as $\log^{10}$ ($ETCP_{unbound}/IC_{50}$), and the outcome. These findings support the value of preclinical HERG testing to predict proarrhythmic effects of medicines.

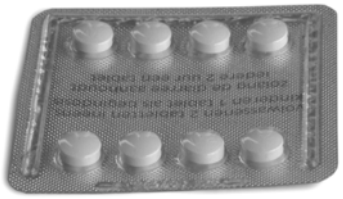
Chapter 5 addressed the validity of pharmacoepidemiological research on drug-induced arrhythmias and may be used to improve future research on this topic. **Chapter 5.1** reported on the validity of hospital discharge diagnoses of cardiac arrhythmias. The positive predictive value (PPV) of hospital discharge diagnosis of cardiac arrhythmias as a measure for ventricular arrhythmias or cardiac arrest was assessed. A distinction was made between well-defined diagnoses (paroxysmal ventricular tachycardia, ventricular fibrillation and/or flutter, cardiac arrest, and ventricular premature beats), and other cardiac arrhythmias which may also include ventricular arrhythmias (unspecified paroxysmal tachycardia, unspecified premature beats, other cardiac dysrhythmias, and unspecified cardiac dysrhythmias). The PPV of well-defined diagnoses was 82% (95%CI 72% to 92%), whereas the PPV of other diagnoses was as low as 10% (95%CI 2% to 18%), giving an overall PPV of 50% (95%CI 40% to 59%). Among the well-defined diagnoses, true positive results were associated with male gender (p=0.09) and younger age (p=0.05). We concluded that well-defined hospital discharge diagnosis of ventricular cardiac arrhythmias and sudden death are useful to identify cases, whereas other diagnoses are not. In **chapter 5.2** we simulated the influence of non-differential misclassification of exposure (expressed as the sensitivity and specificity of the measurement tool) on effect estimates of hypothetical and previously published studies on drug-induced arrhythmias, because pharmacoepidemiological studies in large pre-existing databases are a powerful tool to study drug-induced disease and non-differential misclassification may lead to underestimation of true effects. In cohort studies, observed relative risks generally decreased with decreasing sensitivity, whereas specificity had less influence. With increasing exposed to nonexposed person time ratio, the influence of sensitivity decreased, whereas the influence of specificity increased. In case-control studies, specificity was the most important factor in the association between observed and true odds ratio. When the background exposure increased, the influence of the specificity decreased, whereas the influence of sensitivity increased. Three simulations of the potential impact, using previously published studies on drug-induced arrhythmias from daily epidemiological practice, were in concordance with

this theory. We observed underestimations of up to almost 35% for a sensitivity of 0.80 and a specificity of 0.98, and warned against misleading results, when estimating the public health impact of a drug-induced disease.

Chapter 6 provided a general discussion and options in study design, when studying rare, potentially fatal, adverse reactions, using drug-induced arrhythmias as a case example. The advantages and limitations of various experimental as well as non-experimental designs were discussed, together with methodological issues to be considered. Although no paradigm method exists, a case-control approach enables us to study the rarest adverse reactions and follow-up studies in administrative databases with sufficient power are a good alternative. Nevertheless, we may have arrived at a point in time when the level of drug safety that is required is greater than the resources and techniques we have available to quantify this risk and identify its determinants.

Chapter 8

SAMENVATTING



Geneesmiddel-geïnduceerde hartritmestoornissen staan de laatste jaren zeer in de belangstelling. In het afgelopen decennium is deze bijwerking de belangrijkste reden geweest om geneesmiddelen uit de handel te nemen of hun gebruik te beperken tot uitzonderlijke gevallen. Verlenging van het QTc-interval, een maat voor de repolarisatie van de ventrikels van het hart, kan resulteren in ernstige, soms fatale hartritmestoornissen. Bij geneesmiddelen die worden gegeven bij hartritmestoornissen, waar verlenging van het QTc-interval tot het werkingsmechanisme behoort, is een dergelijke bijwerking te verwachten. Het komt echter ook voor bij andere geneesmiddelen, die veelal voor vrij milde aandoeningen, zoals bijvoorbeeld hooikoorts, worden gebruikt. In die laatste gevallen is de bijwerking meestal zeer zeldzaam (circa 1 op de 10.000 à 100.000), maar aangezien het middelen betreft die veel voorgeschreven worden en tot verschillende therapeutische klassen behoren, betreft het een klinisch relevant probleem.
Gezien deze complexiteit, is het kwantificeren van het risico op een dergelijke zeldzame bijwerking een epidemiologische uitdaging. Kwantificering van het risico en identificatie van patiënten met een extra verhoogd risico zijn de centrale thema's van dit proefschrift. Nadruk wordt daarbij gelegd op de methodologische aspecten van farmacoepidemiologisch onderzoek.
In dit proefschrift wordt de associatie tussen diverse, potentieel proaritmogene, geneesmiddelen en het optreden van hartritmestoornissen bestudeerd. Er wordt gebruik gemaakt van verschillende gegevensbronnen en er is speciale aandacht voor groepen patiënten met een extra verhoogd risico, zoals patiënten met diabetes mellitus en patiënten die meerdere (mogelijk interacterende) geneesmiddelen tegelijkertijd gebruiken. Daarnaast worden enkele moleculaire parameters als risicofactor van geneesmiddel-geïnduceerde hartritmestoornissen bestudeerd en worden een aantal methodologische vraagstukken behandeld, welke relevant zijn voor zeldzame geneesmiddel-bijwerkingen in het algemeen.

In **hoofdstuk 2** wordt gebruik gemaakt van verschillende gegevensbronnen en verschillende definities van de uitkomst om de associatie tussen het gebruik van diverse, potentieel proaritmogene, geneesmiddelen en hartritmestoornissen te kwantificeren. In **hoofdstuk 2.1** wordt de relatie tussen niet-sederende antihistaminica en hartritmestoornissen bestudeerd met behulp van de gegevens van het Nederlands Bijwerkingen Centrum 'Lareb'. Er wordt een statistisch significant verband gevonden (reporting odds ratio 2.05, 95% betrouwbaarheidsinterval (BI)

1.45 tot 2.89). Begin 1998 is er veel te doen geweest over antihistaminica-geïnduceerde hartritmestoornissen, naar aanleiding van het opnieuw recept-plichtig maken van terfenadine en astemizol, twee antihistaminica die tot dan toe vrij verkrijgbaar waren. Wanneer het verband tussen het geneesmiddel en de bijwerking apart bekeken wordt in de periode vóór en na 1 januari 1998, wordt in de vroege periode (voor 1998) geen significante associatie gevonden (OR 1.37, 95%BI 0.85 tot 2.23), terwijl de associatie na 1998 bijzonder sterk was (OR 4.19, 95%BI 2.49 tot 7.05). Deze bevinding suggereert dat de totale significante associatie hoogstwaarschijnlijk vertekend is door de aandacht die de media heeft geschonken aan de bijwerking en het feit dat verschillende artsen en apothekers 'getriggered' zijn geweest deze bijwerking specifiek te melden aan Lareb. Het onderzoek toont wederom aan dat er haken en ogen zitten aan de veel gebruikte methode van kwantitatieve signaaldetectie, die wordt toegepast in geneesmiddelenbewaking. In **hoofdstuk 2.2** worden hartritmestoornissen die leiden tot een ziekenhuisopname bestudeerd. Gegevens van het PHARMO Instituut worden gebruikt voor het uitvoeren van een patiënt-controle onderzoek. Patiënten opgenomen voor ventriculaire of niet-gespecificeerde hartritmestoornissen worden vergeleken met controle patiënten voor wat betreft het gebruik van QTc-verlengende medicatie. In de onderzoekspopulatie als geheel wordt er geen significante relatie gevonden tussen geneesmiddelgebruik en hartritmestoornissen (OR 1.2, 95%BI 0.8 tot 1.9). Patiënten met astma en patiënten die gelijktijdig kaliumverlagende medicatie gebruikten daarentegen hebben een aanzienlijk verhoogd risico op de bijwerking (OR 9.9, 95%BI 1.0 tot 100 en OR 5.3, 95%BI 1.1 tot 25.9, respectievelijk). Extra oplettendheid lijkt derhalve vereist wanneer QTc-verlengende medicatie aan dergelijke patiënten voorgeschreven wordt. In **hoofdstuk 2.3** is de uitkomstmaat hartstilstand waarvoor reanimatie benodigd is bestudeerd als functie van proaritmogene geneesmiddelen. Er is een statistisch significant verhoogd risico op hartstilstand in het ziekenhuis bij patiënten die proaritmogene geneesmiddelen (m.u.v. antiaritmica) voorgeschreven krijgen (OR 2.1, 95%BI 1.2 tot 3.5). Het risico neemt toe wanneer patiënten meer dan de standaard dosering gebruiken (OR 2.5, 95%BI 1.1 tot 5.9), wanneer patiënten meerdere proaritmogeen geneesmiddellen tegelijkertijd gebruiken (OR 4.8, 95%BI 1.6 tot 14) en wanneer patiënten naast de proaritmogene geneesmiddelen andere middelen gebruiken die het metabolisme kunnen remmen (OR 4.0, 95%BI 1.2 tot 13). We concluderen hieruit dat patiënten die in het ziekenhuis liggen een verhoogd risico hebben op hartstilstand wanneer zij pro-

aritmogene geneesmiddelen gebruiken. Specialisten dienen hierop attent gemaakt te worden, zodat zij een weloverwogen keuze kunnen maken dergelijke geneesmiddelen al dan niet voor te schrijven en eventueel extra voorzorgsmaatregelen te nemen.

Hoofdstuk 3 richt zich in het bijzonder op enkele patiëntengroepen die mogelijk een extra hoog risico hebben op geneesmiddel-geïnduceerde hartritmestoornissen. In **hoofdstuk 3.1** wordt de invloed van waarschuwingen voor farmacokinetische geneesmiddel interacties, die het risico op hartritmestoornissen kan doen toenemen tijdens het gebruik van cisapride, onderzocht in de dagelijkse praktijk. Tussen 1995 en 1997 is de bijsluitertekst van cisapride drie maal gewijzigd, om te waarschuwen voor CYP3A4-gemediëerde geneesmiddelinteracties met erythromicine, clarithromycine, fluconazol, itraconazol, ketoconazol, miconazol, nefazodon, ritonavir en troleandomycine. Tevens is er eind 1995 een brief verstuurd naar alle artsen en apothekers om de ernst van de nieuw vermeldde interacties te benadrukken. De apotheekbestanden van het PHARMO Instituut laten zien dat het gelijktijdig gebruik van cisapride en deze gecontraïndiceerde middelen relatief gezien afnam tussen 1994 en 1998. Dit wil zeggen dat de middelen in mindere mate gelijktijdig gebruikt zijn dan op basis van toeval is te verwachten. Daarentegen namen zowel het absolute aantal dagen dat patiënten in Nederland gelijktijdig blootgesteld waren aan cisapride en interacterende middelen, als het aantal voorschriften voor cisapride dat overlapte met een voorschift een gecontraïndiceerd middel toe in dezelfde periode met respectievelijk 13% en 9%. Alhoewel dus ogenschijnlijk het gecontraïndiceerd gebruik van cisapride minder is dan het zou kùnnen zijn, wellicht door oplettendheid van artsen en apothekers, is het absolute gezondheidsrisico dat deze geneesmiddel interactie in Nederland veroorzaakt in de onderzoeksperiode toegenomen. **Hoofdstuk 3.2** wordt speciale aandacht besteed aan patiënten met diabetes mellitus. Diabetici hebben vaker een verlengd QTc-interval dan niet-diabetici en een verdere verlenging door middel van geneesmiddelen kan mogelijk hartritmestoornissen induceren. Er is een, in de dagelijkse praktijk toepasbare, beslisregel ontwikkeld die het risico op ventriculaire hartritmestoornissen en plotse dood bij diabetici die proaritmogene geneesmiddelen gebruiken kan voorspellen. Het absolute risico op deze bijwerking is laag (24 gevallen per 100.000 voorschriften). Onafhankelijke voorspellers voor ventriculaire ritmestoornissen en plotse dood zijn leeftijd, mannelijk geslacht, ischemische hartziekten en niet-ventriculaire hartritmestoornissen. De van het statistisch model

afgeleidde beslisregel is in staat patiënten te identificeren met een vier maal verhoogd risico.

Hoofdstuk 4 behandelt enkele nieuwe moleculaire strategieën in het onderzoek naar geneesmiddel-geïnduceerde hartritmestoornissen. In **hoofdstuk 4.1** wordt een farmacogenetisch haalbaarheidsonderzoek beschreven. Genetische factoren spelen hoogstwaarschijnlijk een rol in de gevoeligheid van patiënten voor geneesmiddel-geïnduceerde hartritmestoornissen. De bijwerking is echter zo zeldzaam, dat het includeren van patiënten in een dergelijk onderzoek erg moeizaam kan zijn. Een spontaan meldingssysteem voor bijwerkingen zoals dat van het Nederlands Bijwerkingen Centrum 'Lareb' biedt wellicht een belangrijke bron van patiënten. Van de 45 patiënten van wie arts of apotheker in de afgelopen zeven jaar bij Lareb heeft gemeld dat zij een geneesmiddel-geïnduceerde hartritmestoornis hebben ondervonden zijn er vier opgenomen in ons onderzoek, evenals vijf benaderde controlepatiënten. De voornaamste zaken die de inclusie bemoeilijken zijn het tijdsgebrek van de artsen en het feit dat de bijwerkingen vaak reeds enkele jaren geleden hebben plaatsgevonden en de betreffende patiënt niet meer te traceren is. Na optimalisatie van de beschreven methode, kan een spontaan meldingssysteem voor bijwerkingen waarschijnlijk een belangrijke rol spelen bij het identificeren van patiënten voor farmacogenetisch onderzoek. In **hoofdstuk 4.2** wordt er een epidemiologische link gelegd tussen preklinische bepaalde HERG-blokkerende eigenschappen van geneesmiddelen en post-marketing farmacovigilantie gegevens. Zogenaamde 'adverse drug reaction reporting odds ratio's' worden berekend om de associatie te bepalen tussen therapeutisch/toxische plasmaconcentraties van 52 verschillende geneesmiddelen en meldingen van geneesmiddel geïnduceerde hartritmestoornissen (hartstilstand, plotse dood, Torsade de Pointes, ventrikelfibrilleren en ventriculaire tachycardie), verzameld door het International Drug Monitoring Program van de Wereld Gezondheid Organisatie (WHO-UMC). Een statistisch significantie associatie wordt gevonden tussen de anti-HERG-activiteit, gemeten als $\log^{10}$ ($ETCP_{unbound}$/ IC_{50}), en de meldingen (OR 1.93, 95%BI 1.89 tot 1.98). Deze bevinding ondersteunt het nut van het preklinisch testen van nieuwe geneesmiddelen op HERG blokkerende eigenschappen.

In **hoofdstuk 5** komen enkele validiteits-aspecten van onderzoek naar geneesmiddel-geïnduceerde hartritmestoornissen aan bod. **Hoofdstuk 5.1** omvat een

valideringsonderzoek van ziekenhuisontslagdiagnoses. Het percentage van de ontslagdiagnoses, die ook bij bestudering van de patiëntengegevens ventriculaire hartritmestoornissen of hartstilstand bleken te omvatten, is bepaald (positief voorspellende waarde (PVW)). Onderscheid is gemaakt tussen goed gedefinieerde diagnoses (paroxysmale ventriculaire tachycardie, vetrikelfibrilleren en -flutter, hartstilstand en ventriculaire premature hartslagen) en diagnoses voor minder duidelijk omschreven hartritmestoornissen, die ook ventriculaire stoornissen zouden kunnen omvatten (niet-gespecificeerde paroxysmale tachycardie, niet-gespecificeerde premature hartslagen, overige hartdysritmieën en niet-gespecificeerde hartdysritmieën). De gevonden PVW van goed gedefinieerde diagnoses bedraagt 82% (95%BI 72% tot 92%), terwijl de PVW van de overige diagnoses slechts 10% (95%BI 2% tot 18%) is, resulterend in een overall PVW van 50% (95%BI 40% tot 59%). De juistheid van de duidelijk omschreven diagnoses is positief geassocieerd met mannelijk geslacht (p=0,09) en afnemende leeftijd (p=0.05). De goed gedefinieerde diagnoses lijken derhalve geschikt om patiënten met ventriculaire hartritmestoornissen en hartstilstand te identificeren door middel van ziekenhuisontslagdiagnoses.
In **hoofdstuk 5.2** wordt de invloed van niet-differentiële misclassificatie van blootstelling aan geneesmiddelen in database-onderzoeken (uitgedrukt in sensitiviteit en specificiteit) gemodelleerd op de uitkomsten van hypothetische en drie eerder gepubliceerde onderzoeken naar geneesmiddel-geïnduceerde hartritmestoornissen. Dit omdat database-onderzoeken veelvuldig worden toegepast om bijwerkingen van geneesmiddelen te kwantificeren en de genoemde misclassificatie, welke niet ondenkbaar is, kan leiden tot een onderschatting van het risico op de bijwerking. We vinden dat in cohort-onderzoeken de geobserveerde relatieve risico's afnemen met afnemende sensitiviteit, terwijl de specificiteit van de expositiemaat minder van invloed is. Als de verhouding tussen blootgestelde en niet-blootgestelde persoonstijd toeneemt, neemt de relatieve invloed van de sensitiviteit af en die van de specificiteit toe. In patiënt-controle onderzoeken heeft de specificiteit het meeste invloed op de relatie tussen de geobserveerde en werkelijke odds ratio. Wanneer de blootstelling in de onderzoekspopulatie toeneemt, neemt de relatieve invloed van de specificiteit af en die van de sensitiviteit toe. De drie bestudeerde voorbeelden bevestigen deze theorie. We observeren mogelijke onderschattingen tot wel 35% bij een sensitiviteit van 0,80 en een specificiteit van 0,98. Bij het inschatten van de effecten van bijwerkingen op de volksgezondheid, dient men bedacht te zijn op dergelijke mogelijk misleidende resultaten.

In **hoofdstuk 6** worden diverse opties in onderzoeksopzet besproken en gerelateerd aan onderzoek uit dit proefschrift. De voor- en nadelen van verschillende experimentele en niet-experimentele mogelijkheden worden behandeld, evenals methodologische aspecten welke in ogenschouw genomen dienen te worden. Hoewel geen van de beschreven methoden perfect is, stelt de patiënt-controle methode ons in staat de meest zeldzame bijwerkingen te bestuderen en vormen cohort-onderzoeken in grote databestanden een goed alternatief. Desondanks zijn we momenteel wellicht aangekomen op het punt waar het epidemiologisch arsenaal tekortschiet om de toenemende verlangens omtrent veiligheid van geneesmiddelen te waarborgen.

APPENDIX 1

Different criteria used to define drugs with relevant proarrhythmic properties

Researchers	Definition
De Ponti et al [1, 2]	Clinically relevant proarrhythmic risk: drugs with published clinical studies and/or case reports associated with the occurrence of Torsade de Pointes / ventricular tachyarrhythmias.
Al-Khatib et al [3]	Very probable risk of QTc-prolongation: drugs for which more than 50% of the respondents at an expert meeting on long-QT syndrome stated that they would always check an ECG when starting this medication. Probable risk: 40-49% of the respondents would check an pretherapy ECG. Possible risk in high-risk patients: > 40% of the respondants would always check an ECG in high-risk patients
Redfern et al [4]	Drugs with torsadogenic properties: a) drugs that have been withdrawn or suspended from the marked in at least one major regulatory territory due to unacceptable risk of Torsade de Pointes for the condition being treated, b) drugs that have a measurable incidence of Torsade de Pointes in humans, or for which numerous case reports exist in the published literature
Crouch et al [5]	Definite association with QTc-prolongation: positive temporal concordance of drug administration and the event is documented (per published data retrieved from MEDLINE searches), the event disappears or lessens with drug discontinuation, and the event recurs with rechallenge. Additional evidence may include in vitro or in vivo data showing the drug's effects on cardiac ion channels
Woosley et al [6]	Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes: expert opinion, criteria not clearly described

1. De Ponti F, Poluzzi E, Vaccheri A, et al. Non-antiarrhythmic drugs prolonging the QT interval: considerable use in seven countries. *Br J Clin Pharmacol.* 2002; 54: 171-7.
2. De Ponti F, Poluzzi E, Montanaro N. Organising evidence on QT prolongation and occurrence of Torsades de Pointes with non-antiarrhythmic drugs: a call for consensus. *Eur J Clin Pharmacol.* 2001; 57: 185-209.
3. Al-Khatib SM, LaPointe NM, Kramer JM, Califf RM. What clinicians should know about the QT interval. *JAMA.* 2003; 289: 2120-7.
4. Redfern WS, Carlsson L, Davis AS, et al. Relationships between preclinical cardiac electrophysiology, clinical QT interval prolongation and torsade de pointes for a broad range of drugs: evidence for a provisional safety margin in drug development. *Cardiovasc Res.* 2003; 58: 32-45.
5. Crouch MA, Limon L, Cassano AT. Clinical relevance and management of drug-related QT interval prolongation. *Pharmacotherapy.* 2003; 23: 881-908.
6. Woosley RL. Drugs that prolong the QT interval and/or induce Torsade de Pointes. Available at: www.qtdrugs.org; Accessed June 1, 2004.

Drugs with clinically relevant proarrhythmic risks according to De Ponti [1, 2], Al-Khatib [3], Redfern [4], Crouch [5] and Woosley [6]

	De Ponti	Al-Khatib	Redfern	Crouch	Woosley
GI-prokinetics					
Cisapride	X		X	X	X
Domperidone	X				X
Cardiovascular					
Bepridil			X	X	X
Indapamide	X				
Ketanserin	X				
Lidoflazine	X		X		
Prenylamine			X		
Probucol	X			X	
Antibacterials					
Clarithromycin	X	X			X
Clindamycin	X*				
Erythromycin	X	X	X	X	X
Gatifloxacin		X			
Grepafloxacin	X		X	X	
Levofloxacin	X*				
Sulfamethoxazole /Trimethoprim	X				
Sparfloxacine		X		X	X
Spiramycin	X*				
Antipsychotics					
Chlorpromazine	X	X	X		X
Droperidol	X	X	X	X	X
Haloperidol	X	X	X	X	X
Mesoridazine				X	X
Olanzapine		X			
Pimozide	X	X	X	X	X
Risperidone		X			
Sertindole			X		
Sultopride	X				
Thioridazine	X	X	X	X	X
Ziprasidone		X		X	

** Clinical data do not provide a strong signal for these drugs*

Drugs with clinically relevant proarrhythmic risks according to De Ponti [1, 2], Al-Khatib [3], Redfern [4], Crouch [5] and Woosley [6], continued

	De Ponti	Al-Khatib	Redfern	Crouch	Woosley
Antidepressants					
Amitriptyline	X	X		X	
Clomipramine	X				
Desipramine		X		X	
Doxepine	X			X	
Fluoxetine	X*				
Imipramine		X		X	
Maprotiline			X	X	
Mianserine	X				
Nortriptyline				X	
Protriptyline	X				
Sertraline		X			
Venlafaxine		X			
Zimeldine	X				
Antimalarials					
Chloroquine	X				X
Halofantrine	X		X	X	X
Antihistamines					
Astemizole	X		X	X	
Fexofenadine	X*				
Diphenhydramine/ dimenhydrinate	X				
Promethazine	X				
Terfenadine	X		X	X	
Miscellanea					
Arsenic trioxide				X	X
Fluconazole	X*				
Levomethadyl			X		X
Pentamidine	X	X	X	X	X
Tacrolimus	X				
Terodiline	X		X		

* *Clinical data do not provide a strong signal for these drugs*

APPENDIX 2

Drugs having a clinically relevant proarrhythmic risk

Drug	Defined Daily Dose	Substrate of cytochrome P450
Antibacterials		
Clarithromycin	500 mg	CYP3A4
Erythromycin	1000 mg	CYP3A4
Grepafloxacin	400 mg	
Cotrimoxazole	1920 mg	
Sulfamethoxazole	2000 mg	CYP2C9
Trimethoprim	400 mg	
Antidepressant		
Amitriptyline	75 mg	CYP2C19, CYP2D6
Clomipramine	100 mg	CYP2C19, CYP2D6
Doxepine	100 mg	
Mianserine	60 mg	
Protriptyline	30 mg	
Zimeldine	200 mg	
Antihistamines		
Astemizole	10 mg	CYP3A4
Diphenhydramine/dimenhydrinate	200 mg	
Promethazine	25 mg	
Terfenadine	120 mg	CYP3A4
Antimalarials		
Chloroquine	500 mg	
Halofantrine	1500 mg	
Antipsychotics		
Chlorpromazine	300 mg	
Droperidol	15 mg	
Haloperidol	8 mg	CYP2D6, CYP3A4
Pimozide	4 mg	CYP3A4
Sultopride	1200 mg	
Thioridazine	300 mg	CYP2D6
Cardiovascular		
Indapamide	2.5 mg	
Ketanserin	40 mg	
Lidoflazine	180 mg	
Probucol	250 mg	
GI-prokinetics		
Cisapride	30 mg	CYP3A4
Domperidone	30 mg	
Miscellanea		
Pentamidine	280 mg	
Tacrolimus	5 mg	
Terodiline	50 mg	

APPENDIX 3

*Inhibitors of cytochrome P450 isoenzymes **

Drug	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Amiodarone		X	X	X
Chlorpheniramine			X	
Cimetidine			X	X
Clarithromycin				X
Clomipramine			X	
Diltiazem				X
Erythromycin				X
Fluconazole		X		
Fluoxetine	X		X	X
Fluvoxamine	X			X
Haloperidol			X	
Indinavir				X
Isoniazid		X		
Itraconazole				X
Ketoconazole	X			X
Lansoprazole	X			
Methadone			X	
Mibefradil			X	X
Nefazodone				X
Nelfinavir				X
Omeprazole	X			
Paroxetine			X	
Quinidine			X	
Ritonavir			X	X
Saquinavir				X
Ticlopidine	X	X		
Troleandomycin				X
Verapamil				X

* *Flockhart DA. Clinically relevant D-I table. Available at: http://medicine.iupui.edu/flockhart/clinlist.htm; Accessed June 28, 2004*

DANKWOORD

Wie dit proefschrift doorbladert, ziet dat ik samengewerkt heb met allerhande mensen, overal vandaan. Mede daarom zijn er een groot aantal mensen die ik hier zou willen bedanken.

Ten eerste mijn promotoren Bert Leufkens en Arno Hoes, die mij zonder hulp van co-promotoren de afgelopen jaren hebben begeleid. Bert, we hebben elkaar ontmoet toen ik in 1996 besloot bijvak te komen doen op de 8ste. Jij gaf aan dat de deur altijd voor me open stond wanneer ik verder wilde in het onderzoek. Na m'n apothekers-examen heb ik dankbaar gebruik gemaakt van dit aanbod. Je was vaak weg, maar wist toch meestal op het juiste moment de juiste sturing te geven. Ook gunde je mij veel wetenschappelijke vrijheid die ik erg waardeer. Ik geloof wel dat je beseft dat ik, hoewel op mijn eigen initiatief, gemengde gevoelens heb bij mijn afscheid. De situatie in Utrecht bevalt me prima, maar toch kan het er me niet van weerhouden eens ergens anders te gaan kijken wat er nog meer in epidemiologisch Nederland omgaat. Ik weet zeker dat we elkaar nog geregeld tegen zullen komen in de toekomst. En wie weet,…….. ooit samen naar Maastricht?
Beste Arno, op advies van Bert raakte jij ook betrokken bij mijn onderzoek en werd je mijn promotor. Je bent volgens mij misschien nog wel drukker dan Bert en nog minder makkelijk te bereiken. Toch ben je minstens even waardevol voor het tot stand komen van dit proefschrift. Jouw kijk als arts en lid van het College, samen met je uitgebreide methodologische kennis hebben me veel geleerd.

Vervolgens alle mensen waar ik tijdens de verschillende onderzoeken mee heb samengewerkt en die mijn werk kritisch hebben bekeken. Twee studies deed ik samen met Lareb. Eugene van Puijenbroek wil ik hartelijk danken voor de altijd snelle reacties, het meedenken en uitvoeren van de pilot studie en de prettige samenwerking. Verder dank ik Kees van Grootheest voor het openstaan voor nieuwe toepassingen met de gegevens die Lareb verzamelt en Fanny Verbunt voor de hulp bij het benaderen van alle artsen en apothekers. Met student Mark Korving begon ik samen aan het allereerste hoofdstuk voor dit proefschrift.
Drie maanden zat ik ook bij PHARMO op kantoor voor het cisapride onderzoek. Martien Panneman, bedankt voor het samen uitpluizen van de data en een goed gesprek. Ron Herings, dank voor de discussies over de analyses en het samen

opschrijven van het stuk en Ernst de Graag, bedankt voor de open ontvangst binnen jullie instituut. Ook voerde ik nog de validatie studie uit samen met PHARMO. Patricia Croes, hartelijk dank voor de vele telefoontjes die je hebt moeten plegen om de verschillende ziekenhuizen over te halen mee te werken aan het onderzoek.
Another project was in collaboration with the Uppsala Monitoring Centre in Sweden. Professor I Ralph Edwards, I would like to thank you very much for the opportunity to make use of the incredible amount of information you and your team have collected during the past decades. In addition, thank you for your critical comments. Hopefully further collaboration with Utrecht will be fruitful. Kristina Star and Monica Pettersson, thank you very much for the data extractions and comments.
Ook was er nog het project waarvoor ik gedurende enkele maanden één dag in de week naar de apotheek van het AMC ging. Richard Koopmans, hartelijk dank voor het contact met Bert, waaruit deze samenwerking is voortgekomen en alle andere contacten binnen het AMC, die het verzamelen van data van verschillende afdelingen zeer zeker hebben vergemakkelijkt. Pim Langendijk, voor jouw gevoel was je misschien niet altijd even voldoende betrokken bij de uitvoering van het onderzoek. Naar mijn mening heb je toch zeker belangrijke invloed gehad op het geheel en ervoor gezorgd dat wij er beiden een prachtig hoofdstuk bij hebben voor in ons proefschrift. Wouter Holtzer, vele malen stond jij voor me klaar als ik weer eens met een verzoek om gegevens kwam of vastliep op onduidelijkheden in de data, bedankt.
En dan natuurlijk nog Sabine Straus, mijn lotgenote in Rotterdam. Veel hebben we gesproken en gedacht over mogelijke onderzoeken samen. Jammer genoeg is er minder gerealiseerd. Mijn boekje ligt hier nu en ik hoop dat jouwe er binnen afzienbare tijd ook is.
Verder wil ik ook nog alle andere co-auteurs bedanken voor hun bijdragen aan de verschillende onderzoeken.
Prof. dr I. R. Edwards, prof. dr A.C.G. Egberts, prof. dr P.A. de Graeff, prof. dr D.E. Grobbee, and prof. dr N.M. van Hemel, members of the thesis committee, are gratefully acknowledged for their assessment of this thesis.

Dan zijn er natuurlijk nog de collega's, familie, vrienden en bekenden. Ik heb het op de 8ste altijd erg naar mijn zin gehad. Kamer Z8.25 heb ik met vele mensen uit alle windstreken gedeeld. Had ik wat beter opgelet, dan had ik nu misschien wel Russisch, Duits, Sloveens, Haags, Twents, IJslands, Vlaams en Turks gesproken. Svetlana, Annette, Mitja, Matthijs, Karin, Helga en Özlem, bedankt voor de gezelligheid van de afgelopen jaren, de tips en discussies over het onderzoek en het lief en leed. Voor een praatje kon ik natuurlijk ook altijd terecht bij één van de anderen. Een rondje door de gang: eerst buurman Rob voor de nieuwste Prince CD, dan naar Aukje om herinneringen op te halen over een congres, of het uitje dat we samen organiseerden, naar Patrick voor een goeie FoxPro-tip of de laatste sportuitslagen en Willem om m'n waarzegster te doen verdwijnen, dan langs het secretariaat om te kletsen in de 'wachtkamer van Bert', Bert op de hoogte brengen van de laatste bevindingen, naar Lyda voor een pleister, even bij Ton een proefschrift uit de kast trekken, bij Diane wat postzegels lenen, dan naar Menno en Marnix om de borrel te plannen, langs Svetlana voor een statistisch advies, op de jongenskamer een dropje pikken, bij Madelon een beetje babypraat, even naar Frank om de boodschappen van albert.nl op te halen en tot slot in N8.13 neerploffen om te vragen of het al tijd is om naar huis te gaan.

Addy, Ineke en Suzanne verdienen nog een extra opmerking, omdat zij naast het sociale steunpunt van de afdeling, natuurlijk ook nog de dagelijkse gang van zaken op rolletjes weten te houden. Chapeau!

Ook wil ik wat langer stilstaan bij mijn paranimfen Menno en Marnix. Jullie symboliseren voor mij mijn jaren op de 8ste: een combinatie van hard werken en tijd voor ontspanning, e-mail en borrels, data opschonen en M&M productions, vereniging Mensa en de Parade, IQ en EQ. Bedankt dat jullie me bij willen staan bij deze bekroning op m'n werk. En geloof me, het is niet alleen 'voor het plaatje'.

Beste vrienden uit Amsterdam, (ex)Utrecht en Maastricht, veel heb ik met jullie nooit over de inhoud mijn onderzoek gesproken. Jullie zijn er dan ook voornamelijk voor gezelligheid in de vorm van etentjes, feestjes, vakanties en een goed gesprek op zijn tijd. Hier het bewijs dat ik al die jaren toch echt wel iets heb uitgevoerd!
Lieve Barbara, Marieke, Laurens en rest van de familie. Op jullie kon ik altijd rekenen en jullie hebben me gesteund tijdens de mindere periodes in de laatste jaren. Het is fijn om te weten dat dat ik zo'n goede basis heb om op terug te vallen. Hup Har, nu jij ook nog even!
Lieve Mamma, van jou kreeg ik de liefde voor getallen. Lieve Pappa, van jou de kritische blik. Wat had ik jullie graag nog eens trots zien kijken……

Lieve Lieven, nog te klein om er veel van te snappen waarom ik toch zo veel achter de computer zat de laatste tijd. Jouw glimlach is betoverend, als je op m'n schoot klimt om ook op het toetsenbord te tikken.
Lieve Tom, mijn liefste Lief, het is niet de eerste keer in de geschiedenis dat een architect en een apotheker een goed koppel blijken. Zoals gewoonlijk wisselen wij elkaar af in pieken en dalen. Mijn drukste tijd zit er voorlopig weer even op en de jouwe is al weer in volle gang. Jouw steun, liefde en vertrouwen zijn fantastisch. Wat zullen we nog allemaal gaan meemaken samen?

Marieke

LIST OF PUBLICATIONS

1. Volksgezondheid Toekomst Verkenning 2002 - Geneesmiddelen nu en in de toekomst. Bilthoven: RIVM, 2001:111-122, 156-166, 178-187, 259-270, 283-293, 330-346, 359-370.
2. Bouvy ML, Heerdink ER, De Bruin ML, Herings RM, Leufkens HG, Hoes AW. Use of sympathomimetic drugs leads to increased risk of hospitalization for arrhythmias in patients with congestive heart failure. *Arch Intern Med.* 2000; 160: 2477-80.
3. De Bruin ML, Panneman MJM, Leufkens HGM, Hoes AW, Herings RMC. Use of cisapride with contraindicated drugs in The Netherlands. *Ann Pharmacother* 2002; 36: 338-343.
4. De Bruin ML, van Puijenbroek EP, Egberts ACG, Hoes AW, Leufkens HGM. Non-sedating antihistamine drugs and cardiac arrhythmias - biased risk estimates from spontaneous reporting systems? *Br J Clin Pharmacol* 2002; 53: 370-374.
5. De Bruin ML, Hoes AW, Leufkens HGM, QTc-prolonging Drugs and Hospitalizations for Cardiac Arrhythmias. *Am J Cardiol* 2003; 91: 59-62.
6. De Bruin ML, Oraal erythromycine en acute hartdood. *Ned Tijdschr Geneeskd. [in press]*
7. De Bruin ML, Pettersson M, Meyboom RHB, Hoes AW, Leufkens HGM. Anti-HERG activity and the risk of drug-induced arrhythmias and sudden death. *Eur Heart J [provisionally accepted]*
8. De Bruin ML, van Staa TP, Belitser SV, Leufkens HGM, Hoes AW. Predicting arrhythmias and sudden death in diabetic patients taking non-antiarrhythmic proarrhythmic drugs. *Submitted for publication*
9. De Bruin ML, van Hemel NM, Leufkens HGM, Hoes AW. Validation of hospital discharge diagnosis for cardiac arrhythmias. *Submitted for publication*
10. Straus SMJM, Kors JA, De Bruin ML, van der Hooft CS, Hofman A, Heeringa J, Kingma JH, Witteman JCM, Sturkenboom MCJM, Stricker BHCh. Prolonged QTc-interval and the risk of sudden cardiac death in a general population. *Submitted for publication*

11. De Bruin ML, Langendijk PNJ, Koopmans RP, Wilde AAM, Leufkens HGM, Hoes AW. Proarrhythmic drugs and cardiac arrest, a hospital based case-control study. *Submitted for publication*
12. De Bruin ML, van Puijenbroek EP, Bracke M, Hoes AW, Leufkens HGM. Pharmacogenetics of drug-induced arrhythmias, a feasibility study using spontaneous adverse drug reaction reporting data. *Submitted for publication*
13. De Bruin ML, Hoes AW, Leufkens HGM. Non-differential misclassification in pharmacoepidemiological studies, the example of drug-induced arrhythmias. *Submitted for publication*

Marie Louise De Bruin was born on April 1, 1974 in Haarlem, the Netherlands.
She graduated in 1992 at the 'Stedelijke Scholengemeenschap' (gymnasium). in Maastricht In 1997, she obtained her Master's degree in Pharmacy at the Utrecht University, and in 1999 she became a pharmacist. In the same year she started as a junior researcher at the Department of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences, Faculty of Pharmaceutical Sciences of the Utrecht University, where she worked on the third Dutch Public Health Status and Forecasts (PHSF) report in collaboration with the National Institute of Public Health and Environment (RIVM). From 2000 to 2004 she worked on the studies described in this PhD thesis. In addition, she obtained a Master of Science degree in clinical epidemiology at the Netherlands Institute for Health Sciences in Rotterdam in 2003. In November 2004 she will start working on a post-doc project on late effects of therapy for Hodgkin's disease at the department of Psychosocial Research and Epidemiology of the Netherlands Cancer Institute in Amsterdam.