LABORATORY MARKERS IN DRUG SAFETY RESEARCH

STUDIES ON DRUG-INDUCED THROMBOCYTOPENIA

MAARTEN JAAP TEN BERG

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LABORATORY MARKERS IN DRUG SAFETY RESEARCH: STUDIES ON DRUG-INDUCED THROMBOCYTOPENIA

LABORATORIUMPARAMETERS BIJ DE BESTUDERING VAN BIJWERKINGEN VAN GENEESMIDDELEN: ONDERZOEKEN NAAR GENEESMIDDEL-GEÏNDUCEERDE TROMBOCYTOPENIE

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. J.C. Stoof, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op woensdag 17 juni 2009 des middags te 2.30 uur

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IF YOU DON'T KNOW WHERE YOU ARE GOING, YOU WILL WIND UP SOMEWHERE ELSE

Lawrence Peter 'Yogi' Berra (1925, St. Louis, Mo., USA),
a former Major League Baseball player,
who, based on his style of speaking, was named
"Wisest Fool of the Past 50 Years" by
The Economist magazine in January 2005

AAN
MIJN OUDERS
AAN LAUREEN

CONTENTS

1

GENERAL INTRODUCTION, AIMS, AND OUTLINE OF THE THESIS

GENERAL INTRODUCTION

Adverse drug reactions

The unintended effects of drugs can be a major threat to the health of individual patients, drug manufacturers and society as a whole. Thirty years ago the World Health Organization (WHO) defined an adverse drug reaction as a response to a drug which is unintended and noxious and occurs at doses normally used in man.[1] The mechanisms underlying adverse drug reactions are various, i.e. pharmacological, immunological, metabolic or genetic.[2] Whereas a drug is often intended to treat a single or a few similar illnesses or complaints, the clinical manifestations of adverse drug reactions can be very diverse in nature. Despite this variety, adverse drug reactions can be classified into two major groups based on their mechanism, i.e. unintended reactions directly related to the pharmacological mechanism of a drug, so-called type A adverse reactions, and adverse reactions caused by a hypersensitive response of the human biosystem (immunologic or non-immunologic) to the presence of a drug, so-called type B adverse reactions.[2] Characteristic for type A adverse reactions is the common occurence (> 1%), a dose relationship, a suggestive time relationship and reproducibility.[2] An example of a type A adverse reaction is suppression of the hematopoietic function of the bone marrow by cytostatic drugs, which is caused by interference of the drug with cell replication, the same mechanism that is intended in treating cancer.[3] Characteristic for type B adverse reactions is the uncertain underlying mechanism, the rare occurrence (< 1%), the acute and unexpected onset and the severity.[2] An example of a type B adverse drug reaction is the increased destruction of peripheral blood cells caused by immune reactions involving drug-related antibodies.[4]

During the premarketing phases of the development process a drug is extensively tested for adverse drug reactions, including toxicity experiments using in vitro models, healthy volunteers and a selection of patients for whom the drug is under development. Only drugs with a positive ratio between efficacy and adverse reactions will be granted access to the market by licensing authorities. An unacceptable frequency and severity of adverse reactions given the severity of the treated disease will lead to termination of the drug development. Because of their commonness and their relationship with the pharmacological mechanism, type A adverse reactions are often identified during drug development. Type B reactions are seldomly detected in the premarketing phase, because the sample size of clinical trials is often too small to detect these rare effects in addition to the highly selected sample of patients included in clinical research and the limited duration.[2] In general, type B adverse reactions are detected after regulatory approval when the drug is used in large numbers of patients in clinical practice.[2] It has been estimated that

about 3% of new drugs are withdrawn from the market due to safety issues, mainly type B reactions.[5] Withdrawal of a drug is problematic for the manufacturer who has spent large resources developing the drug; the total pre-approval process of a new drug costing several hundred million dollars.[6] In addition, drug withdrawal is potentially problematic for patients when alternative effective treatments are not available. To make informed decisions on issuing recommendations for monitoring adverse drug reactions, restricted use or withdrawal of a drug reliable evidence on the adverse effects of a drug is needed. This evidence concerns the underlying mechanisms, the prognosis (severity, reversibility), the absolute incidence in patient populations, the relative risk compared to alternative drugs, types of patients at high risk and the availability of risk management strategies.

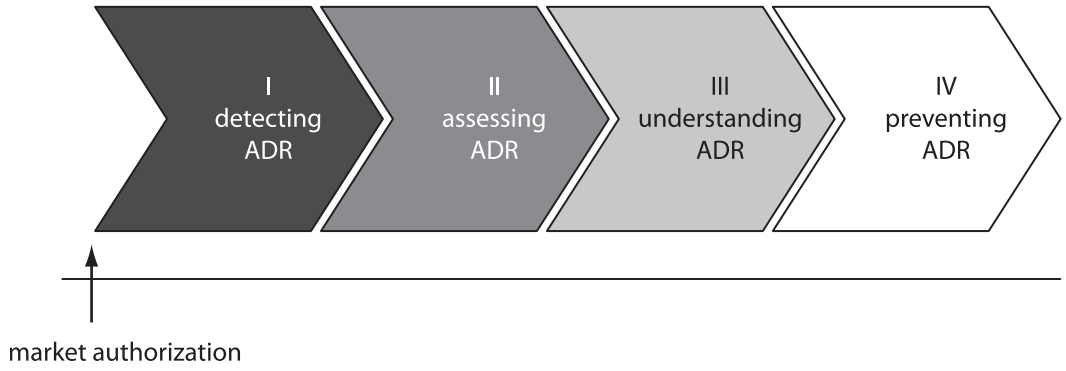
Pharmacovigilance and pharmacoepidemiology

The search for evidence on adverse drug reactions is within the scope of pharmacovigilance and pharmacoepidemiological research. The goals of pharmacovigilance are to identify new information about hazardous associations with medicines and to prevent harm to patients treated with drugs in clinical practice.[7] Four steps can be identified in pharmacovigilance research: detection of a possible association between drug exposure and an adverse reaction, confirmation and quantitative assessment of the possible association, understanding of the mechanism and nature of a confirmed association and prevention of the occurrence of adverse drug reactions, e.g. investigating possible risk management strategies (Figure 1). Pharmacoepidemiology is the study of the use and the effects of drugs in large numbers of people.[8] With regard to drug safety, pharmacoepidemiology can be considered as the science that aims to develop and to apply the methodology that is needed for the practice of pharmacovigilance.[8]

Epidemiological database studies to assess suspected adverse drug reactions

Signals of a possible association between drug exposure and adverse drug reactions often originate from descriptions of a changed clinical picture in individual patients considered to be caused by drug treatment. Such signals derived from collections of suspicions reported in biomedical literature or to spontaneous reporting systems, such as the WHO Uppsala monitoring center, can be considered as hypotheses that need further testing and unraveling with formal epidemiological studies including a population denominator and a control group to confirm or to reject the hypothesis (phase II, Figure 1).[2] For this purpose epidemiological designs such as follow-up, case-control or case-crossover can be used.[7] To investigate a possible association

Figure 1 **Four phases of drug safety research in follow-up of signals of possible adverse drug reactions**



detailed data on drug exposure as well on disease for a large population is required. Over the past 30 years, the availability of such data in automated form within health information registration systems has led to the development of several large patient-oriented database systems comprising data on medication exposure such as physician prescriptions and pharmacy dispensings and disease diagnoses such as hospital discharge diagnoses or general practitioners diagnoses.[9,10] These databases allow the conduct of epidemiological studies on adverse drug reactions relatively fast and against reasonable costs compared to for example prospective cohort studies.[11] Often the required data of the same patient are not available within the same information system, and data from different systems need to be linked on the level of the individual patient. The technique used to relate data on drug exposure and diagnoses within different automated databases is called record linkage. Over the past decades many successful epidemiological database studies aimed to confirm and quantify associations between drug exposure and adverse reactions have been performed.[12] Despite these successes the available data on disease within database systems have potential limitations for investigating adverse drug reactions. First, hospital discharge diagnoses and general practioners diagnoses lack clinical detail and must be considered as a crude marker for disease. In addition, the registration process of hospital discharge diagnoses has been reported to be prone to incompleteness and misclassification.[13] Finally, one hospital discharge diagnosis often codes for different manifestations or causes of a condition. These characteristics possibly limit the use of hospital discharge diagnoses for identifying possible adverse drug reactions, and thereby possibly limit the assessment of suspected adverse drug reactions with database studies. For the assessment of

Table 1	Examples of drugs [a] for which serious blood disorders resulted in intervention in the registration status in the period 1960 to 2007 [b]	
Year	**Generic drug name (type of drug)**	**Type of blood disorder**
	Black box warnings	
1950	chloramphenicol (antibiotic)	aplastic anemia
1990	tocainide (anti-arrhythmic)	agranulocytosis, leukopenia, neutropenia and hypoplastic anemia
1994	felbamate (anti-epileptic)	aplastic anemia
2000	ticlopidine (anti platelet)	neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura, aplastic anemia
2000	clopidogrel (anti platelet)	thrombotic thrombocytopenic purpura
unknown	azathioprine (DMARD)	aplastic anemia
unknown	auranofin (DMARD)	aplastic anemia
unknown	carbamazepine (anti-epileptic)	aplastic anemia and agranulocytosis
unknown	procainamide (anti-arrhythmic)	agranulocytosis, thrombocytopenia, neutropenia, hypoplastic anemia
unknown	cidofovir (antiretroviral)	neutropenia
unknown	valganciclovir and its metabolite ganciclovir (antiretroviral)	granulocytopenia, anemia and thrombocytopenia
unknown	zidovudine (antiretroviral)	neutropenia and serious anemia
	Market withdrawals	
1960	thenalidine (antihistaminic)	agranulocytosis
1970	aminopyrine (NSAID)	agranulocytosis
1975	clozapine (antipsychotic)	agranulocytosis
1975	metamizole (NSAID)	agranulocytosis
1981	nomifensine (antidepressant)	hemolytic anemia
1984	nitrefazole (alcohol deterrent)	hematologic toxicity
1984	oxyphenbutazone (NSAID)	aplastic anemia
1985	indalpine (antidepressant)	agranulocytosis
1985	phenylbutazone (NSAID)	aplastic anemia
1985	cianidanol (free radical scavenger)	hemolytic anemia, thrombocytopenia
1986	sulfamethoxypyridazine (antibiotic)	non-specified hematologic reactions
1987	vincamine (vasodilator)	hematologic toxicity
1987	cinepazide (vasodilator)	agranulocytosis
1988	sulfacarbamide (antibiotic)	non-specified hematologic reactions
1992	temafloxacin (antibiotic)	among others hemolytic anemia
1993	remoxipride (antipsychotic)	aplastic anemia
1998	proxibarbal (barbiturate)	thrombocytopenia

DMARD = disease-modifying antirheumatic drug; NSAID = non-steroidal anti-inflammatory drugs

a) A drug was included if withdrawn from the market because of serious hematological adverse effects, or if labelled with a 'black box warning' by the Food and Drug Administration (FDA). Antineoplastic drugs were not included, considering that bone marrow toxicity is in line with expectation based on their mechanisms of action; nearly all of these drugs have a black box warning.

b) Adapted from an unpublished paper on the consequences of signals of drug-induced blood disorders, written by Ms. Ellen Derissen, student in Pharmaceutical Sciences.

associations between drug exposure and adverse reactions as soon as possible after a suspected association is reported, the development of methods and tools for investigating adverse drug reactions with epidemiological database studies in needed. Automated laboratory data collected in patient care may be a valuable additional data source for this purpose. Laboratory data can be considered as an objective and valid indicator of disease. In addition, many adverse drug reactions, including hepatic, hematological or nephrologic toxicity can be detected with biochemical tests.[2,14]

Linking laboratory and medication data in drug safety research

Laboratory data can be considered to be valuable for investigating the safety of drugs for several reasons. First, laboratory data may be used to detect and quantify associations between drug exposure and adverse reactions that can be detected with a biochemical test. The results from previous research in our group suggested that laboratory parameters are more sensitive in identifying possible cases of adverse drug reactions (e.g. hyponatremia) compared to hospital discharge diagnoses.[15-17] In addition to testing hypotheses on signals for possible adverse drug reactions, laboratory data may be a useful tool for identification of possible patient characteristics that predict the patient's susceptibility for adverse drug reactions, since some laboratory parameters can be considered as objective measurement of a patients health status. Furthermore, laboratory data may be useful for identification of early warning markers of adverse drug reactions. Many adverse drug reactions take time to develop. Laboratory parameters that reflect changes in organ function may be early warning signals for the occurrence of adverse drug reactions. For example a change in reticulocyte count could be a signal for an early change in bone marrow activity following drug exposure.[18] Finally, linking laboratory and medication data might be useful for evaluating compliance to laboratory monitoring which is recommended for many drugs for early detection of adverse drug reactions.[19,20]

Drug-induced blood disorders

A type of adverse drug reaction for which laboratory medication record linkage holds great potential are drug-induced blood disorders, including aplastic anemia, granulocytopenia (including agranulocytosis) and thrombocytopenia. Drug-induced blood disorders are generally type B adverse reactions.[21] Drug-induced blood disorders are among the adverse drug reactions that are most feared by physicians and drug manufacturers because of their unpredictability and the high rate of fatality.[22] Their unpredictability makes them difficult to manage in clinical

practice.[22] Many drugs have been reported to cause blood disorders. For example over 300 drugs have been reported to cause thrombocytopenia, possibly due to immune-mediated mechanisms.[23-26] Demonstration of an association with blood disorders has let to black box warnings and withdrawal of many drugs.[22,27] In Table 1 examples of drug-induced blood disorders that led to black box warnings or withdrawals in the past decades are presented. The detection of chloramphenicol-induced aplastic anemia in the early 1950s led to an increased interest in adverse drug reactions and was, together with the thalidomide-associated phocomelia disaster in the 1960s, one of the main triggers for the worldwide establishment of drug monitoring schemes.[8]

Because of the potential severity of drug-induced blood disorders it is important to follow up these signals by epidemiological studies to corfirm or reject the suspected association. Over the past decades several epidemiological studies have been performed to investigate the incidence and the risk factors of drug-induced blood disorders,[28-33] of which the International Agranulocytosis and Aplastic Anemia Study (IAAAS) is probably the best known example.[34] However, many signals have not been investigated, for example for medication most often reported to cause thrombocytopenia the association has not been confirmed and

Table 2	Drug-induced thrombocytopenia related issues that warrant investigation
Drug-induced immune thrombocytopenia	Many drugs reported to cause immune thrombocytopenia. However, limited evidence on size of the associations and on risk factors.
Chemotherapy-induced thrombocytopenia	Current knowledge on incidence, relative risk and risk factors for patients treated in clinical care is scarce. In general considered to be caused by bone marrow suppression (type A adverse drug reaction), however immune-mediated mechanisms (type B adverse drug reaction) can also play a role. Although expected to be rare, the frequency of immune-mediated chemotherapy-induced thrombocytopenia is unknown. Immune-mediated thrombocytopenia requires different clinical management than thrombocytopenia caused by bone marrow suppression. A simple parameter that could be used to discriminate between these types of mechanisms could be valuable for clinical practice.
Heparin-induced thrombocytopenia	Reported to occur in up to 5% of patients treated with unfractionated heparin and 0.9% of patients treated with low molecular weight heparin, nevertheless more research is needed on the incidence in specific patient populations. Tools for prediction, diagnosis and early-warning of HIT would be useful. Close monitoring of the platelet count is recommended for early detection of HIT. Unknown whether these recommendations are abided by in clinical practice.

quantified.[23] In addition, the incidence of thrombocytopenia in medication well known to cause thrombocytopenia, e.g. heparin and cytostatic drugs, has not been well defined. Moreover, little is known on risk factors and management of drug-induced thrombocytopenia. For many drugs platelet count monitoring is recommended for early detection of thrombocytopenia, but the compliance with these recommendations is unknown as is the effect of monitoring on clinical outcome. In Table 2 specific drug-induced thrombocytopenia related issues that warrant further investigation are presented. Pharmacoepidemiological studies using linked laboratory data and medication data collected in patient care may provide valuable knowledge on these issues.

THESIS AIMS

The aim of the studies presented in this thesis is to investigate the additional value of laboratory data collected in patient care for drug safety research, with a focus on drug-induced thrombocytopenia. The specific aims of this thesis are to investigate:

1) the sensitivity and specificity of case-finding of drug-induced thrombocytopenia using clinical laboratory parameters compared to using hospital discharge diagnoses;
2) the incidence and potential biomarkers for drug-induced thrombocytopenia;
3) compliance with laboratory monitoring for drug-induced thrombocytopenia.

THESIS OUTLINE

This thesis consists of five distinct chapters. In the first chapter (the introduction) the scope, aims and outline of the thesis are presented.

In **Chapter 2** a new patient-oriented automated database comprising laboratory data and medication data collected in patient care at the University Medical Center Utrecht (UMC Utrecht), the **Utrecht Patient Oriented Database (UPOD)**, is described. We present the structure and content of UPOD and discuss its potential application for pharmacoepidemiological research.

Chapter 3 concerns the comparison of the use of **laboratory markers and hospital discharge diagnoses** for the identification of patients with possible adverse drug reactions from health care data. In *Chapter 3.1* a population-based study into the relative risk for thrombocytopenia following exposure to drugs that are often reported to cause immune-mediated thrombocytopenia is presented. The study

is conducted using data from the PHARMO Record Linkage System and hospital discharge diagnoses will be used as identifiers for patients with thrombocytopenia. In the study presented in *Chapter 3.2* the use of hospital discharge diagnoses for thrombocytopenia for the identification of patients with possible drug-induced thrombocytopenia will be compared to using platelet measurements for this purpose. This is done by a cross-sectional study design and data from UPOD.

In **Chapter 4** three studies on different aspects of drug safety research in which laboratory markers may have value are presented: assessment of the risk in populations, identification of biomarkers and monitoring of pharmacotherapy in patient care. The first two studies in Chapter 4 address **chemotherapy-induced thrombocytopenia**. In the study presented in *Chapter 4.1.1* the incidence and relative risk of thrombocytopenia will be determined in the population of oncology patients treated with non-experimental cytostatic drugs at the UMC Utrecht. In the study presented in *Chapter 4.1.2* the value of the platelet indices mean platelet volume and platelet distribution width for discriminating between immune-mediated versus bone marrow suppression-related thrombocytopenia is analysed. *Chapter 4.2.1* concerns a study on **heparin-induced thrombocytopenia**. The compliance with recommendations for platelet count monitoring for heparin-induced thrombocytopenia in clinical patients receiving low molecular weight heparin will be investigated, as well as the compliance with recommendations for managing possible heparin-induced thrombocytopenia.

In the final chapter, the general discussion, the results of the different studies are discussed in a broader perspective of the current needs of drug safety research and patient care and directions for further research are given.

REFERENCES

1. International drug monitoring: the role of national centres. Report of a WHO meeting. World Health Organ Tech Rep Ser 1972;498:1-25.
2. Meyboom RH, Lindquist M, Egberts AC. An ABC of drug-related problems. Drug Saf 2000;22:415-23.
3. Cairo MS. Dose reductions and delays: limitations of myelosuppressive chemotherapy. Oncology (Williston Park) 2000;14:21-31.
4. Aster RH. Drug-induced immune cytopenias. Toxicology 2005;209:149-53.
5. Lasser KE, Allen PD, Woolhandler SJ, Himmelstein DU, Wolfe SM, et al. Timing of new black box warnings and withdrawals for prescription medications. JAMA 2002;287:2215-20.
6. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ 2003;22:151-85.

7. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet 2000;356:1255-9.
8. Strom BL. What is Pharmacoepidemiology? In: Strom BL, editor. Pharmacoepidemiology. 3rd ed. Chichester: John Wiley & Sons, LTD; 2000. p. 4-15.
9. Herings RMC. PHARMO: A record linkage system for postmarketing surveillance of prescription drugs in the Netherlands [dissertation]. Utrecht: Utrecht University; 1993.
10. Vlug AE, van der Lei J, Mosseveld BM, van Wijk MA, van der Linden PD, et al. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods Inf Med 1999;38:339-44.
11. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 2005;58:323-37.
12. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004;329:44-7.
13. Iezzoni LI. Using administrative diagnostic data to assess the quality of hospital care. Pitfalls and potential of ICD-9-CM. Int J Technol Assess Health Care 1990;6:272-81.
14. Kelly WN. Potential risks and prevention, Part 1: Fatal adverse drug events. Am J Health Syst Pharm 2001;58:1317-24.
15. Movig KL, Leufkens HG, Lenderink AW, Egberts AC. Serotonergic antidepressants associated with an increased risk for hyponatraemia in the elderly. Eur J Clin Pharmacol 2002;58:143-8.
16. 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.
17. Movig KL, Leufkens HG, Lenderink AW, van den Akker VG, Hodiamont PP, et al. Association between antidepressant drug use and hyponatraemia: a case-control study. Br J Clin Pharmacol 2002;53:363-9.
18. Flow cytometric reticulocyte quantification in the evaluation of hematologic recovery. Spanish Multicentric Study Group for Hematopoietic Recovery. Eur J Hematol 1994;53:293-7.
19. Derijks HJ, Oosterhuis WP, de Koning GHP, Egberts ACG. Geneesmiddelgebruik gekoppeld aan klinisch-chemische parameters. Een nieuwe dimensie in medicatiebegeleiding. Pharm Weekbl 2002;137
20. Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. Arch Intern Med 2003;163:893-900.
21. De Gruchy GC. Drug-induced blood disorders. 1st ed. Oxford: Blackwell Scientific Publications; 1975.
22. Carey PJ. Hematological ADR. In: Mann RD, Andrews EB, editors. Pharmacovigilance. 2nd ed. Chichester: Wiley; 2007.
23. Van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. Drug Saf 2004;27:1243-52.
24. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998;129:886-90.
25. Rizvi MA, Kojouri K, George JN. Drug-induced thrombocytopenia: an updated systematic review. Ann Intern Med 2001;134:346.

26. Rizvi MA, Shah SR, Raskob GE, George JN. Drug-induced thrombocytopenia. Curr Opin Hematol 1999;6:349-53.

27. Fung M, Thornton A, Mybeck K, Hsiao-Hui Wu J, Hornbuckle K, et al. Evaluation of the characteristics of safety withdrawals of prescription drugs from worldwide pharmaceutical markets-1960 to 1999. Drug Inf J 2001;35:293-317.

28. Risks of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special reference to analgesics. The International Agranulocytosis and Aplastic Anemia Study. JAMA 1986;256:1749-57.

29. Kaufman DW, Kelly JP, Johannes CB, Sandler A, Harmon D, et al. Acute thrombocytopenic purpura in relation to the use of drugs. Blood 1993;82:2714-8.

30. 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.

31. Van der Klauw MM, Goudsmit R, Halie MR, van't Veer MB, Herings RM, et al. A population-based case-cohort study of drug-associated agranulocytosis. Arch Intern Med 1999;159:369-74.

32. Huerta C, Garcia Rodriguez LA. Risk of clinical blood dyscrasia in a cohort of antibiotic users. Pharmacotherapy 2002;22:630-6.

33. Van Staa TP, Boulton F, Cooper C, Hagenbeek A, Inskip H, et al. Neutropenia and agranulocytosis in England and Wales: incidence and risk factors. Am J Hematol 2003;72:248-54.

34. Kramer MS, Lane DA, Hutchinson TA. The International Agranulocytosis and Aplastic Anemia Study (IAAAS). J Clin Epidemiol 1988;41:613-6.

2

LINKING LABORATORY AND MEDICATION DATA

2.1

Linking laboratory and medication data: new opportunities for pharmacoepidemiological research

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ABSTRACT

Transfer of automated laboratory data collected during routine clinical care from the laboratory information system into a database format that enables linkage to other administrative (e.g. patient characteristics) or clinical (e.g. medication, diagnoses, procedures) data provides a valuable tool for clinical epidemiological research. It allows the investigation of biochemical characteristics of diseases, therapeutic effects and diagnostic and/or prognostic markers for disease with easy access and at relatively low cost. To this end, the Utrecht Patient Oriented Database (UPOD), an infrastructure of relational databases comprising data on patient characteristics, laboratory test results, medication orders, hospital discharge diagnoses and medical procedures for all patients treated at the University Medical Center Utrecht since January 2004, was established. Current research within UPOD is focused on the innovative linkage of laboratory and medication data, which, for example, makes it possible to assess the quality of pharmacotherapy in clinical practice, to investigate interference between laboratory tests and drugs, to study the risk of adverse drug reactions, and to develop diagnostic and prognostic markers or algorithms for adverse drug reactions. Although recently established, we believe that UPOD broadens the opportunities for clinical pharmacoepidemiological research and can contribute to patient care from a laboratory perspective.

INTRODUCTION

Since the introduction of the first computers to process and capture laboratory data in the 1960s,[1] enormous progress has been made in laboratory automation. Currently, the majority of biochemical laboratory tests are performed by fully automated analyzers, and test results are processed and stored electronically within advanced laboratory information systems. These automated laboratory data are primarily used in patient care and for management purposes. However, transfer of data from the laboratory information system into a database format that allows questioning and linkage to administrative (e.g. patient characteristics) or other clinical data (e.g. disease and medical treatment) would provide a valuable tool for clinical epidemiological research, i.e. the application of epidemiological principles and methods to problems encountered in clinical medicine.[2]

Until now, most clinical epidemiological research with laboratory data was only possible after elaborate gathering of data for a specific research question. A structurally available data linkage system that provides complete and well-defined research data that can be questioned at any time would increase the possibilities for conducting clinical epidemiological research with laboratory data. Therefore, the Utrecht Patient Oriented Database (UPOD), an infrastructure of relational databases comprising data on patient characteristics, laboratory test results, medication orders, hospital discharge diagnoses and medical procedures for all patients treated at the University Medical Center Utrecht (UMC Utrecht) was recently established. In this paper the structure, current content and potential applications of UPOD are presented. Because of the innovative character and clinical relevance of the linkage of laboratory and medication data, which increases the opportunities to study the use and effects of drugs in a clinical setting (i.e. clinical pharmacoepidemiological research), this specific feature is used as an example to illustrate the potential of UPOD.

UTRECHT PATIENT ORIENTED DATABASE: UPOD

Setting

The UMC Utrecht is a 1042-bed academic medical center located in the center of The Netherlands. Approximately 165 000 patients are treated annually during more than 28 000 clinical hospitalizations, 15 000 day-care treatments and 333 000 outpatient visits (Table 1). At UMC Utrecht all administrative and clinical information on in- and outpatients is registered and processed electronically and

Table 1 Number of data within UPOD from the year 2005	
Type of data	**Number**
Inpatient admissions	28 561
Day-care treatments	15 305
Outpatient visits	333 858
Laboratory test results	3 812 756
Medication orders	289 878
Discharge diagnoses	88 216
Procedures	148 499

UPOD = Utrecht Patient Oriented Database

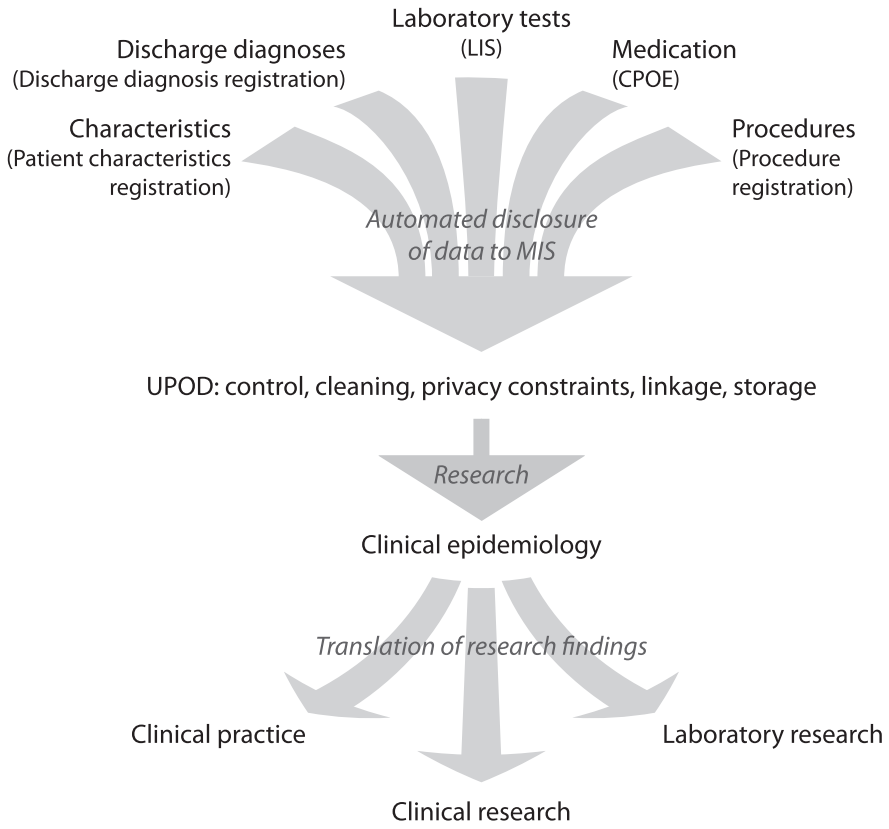
stored at patient level within systems that are integrated in the hospital information system.

Research database

UPOD is a relational database infrastructure capturing complete and detailed data on patient characteristics, laboratory test results, medication orders, hospital discharge diagnoses and therapeutic procedures for all patients treated at UMC Utrecht since January 2004 (Figure 1). Periodically all relevant data are automatically transferred from the specific registration systems into tables in the management information system, which is an environment (SQL [Structured Query Language] server) that allows checking, cleaning, storing, maintaining, questioning and linking of data (Figure 1). All data contain a patient identifier and an index date, allowing selection of unique patients or events and deterministic linkage between tables comprising different types of data. Researchers who are granted access to the data can make data selections in the management information system using SQL syntaxes. Subsequently, data can be downloaded from the management information system to the researcher's personal computer.

Data on patient characteristics are extracted from the hospital's central electronic patient registry and consist of gender and dates of birth, death, hospitalization and discharge. Laboratory data originate from the laboratory information system, and include all tests concerning clinical chemistry, hematology, endocrinology, immunology and therapeutic drug monitoring. The records contain information on the collection date, type of material and the result. Medication data concern drugs that are ordered in the computerised physician order entry (CPOE) system for medication. Medication records contain information on the start and stop date, duration, prescriber (type of medical specialty), amount administered, dosage

Figure 1 **UPOD: clinical epidemiological research with a relational database system comprising patient-oriented clinical and administrative data**



UPOD = Utrecht Patient Oriented Database; LIS = laboratory information system; CPOE = computerized physician order entry system

regimen, and route of administration for each drug prescription. Drugs are coded with regard to the different national (generic product code, trade code)[3] and international (Anatomical Therapeutic Chemical classification, ATC)[4] classification schemes. Diagnostic data concern the full list of discharge diagnoses (up to 10 diagnoses per admission) that are registered primarily for reimbursement purposes. Discharge diagnoses are coded according to the International Classification of Diseases, 9th edition Clinical Modification (ICD-9-CM).[5] Likewise, data on therapeutic procedures performed by medical specialists are registered. Procedures are coded according to the Classification of Procedures by Medical Specialists, published by the Dutch CBV (Centraal Beheer Verrichtingenbestand) Foundation.[6]

In addition to the laboratory data described above, UPOD contains a specific database with hematology data on automated blood cell analyses performed with

Abbott Cell-Dyn Sapphire automated blood cell analyzers used at UMC Utrecht. A feature of this type of blood cell analyzer is that it not only reports the parameters requested by the physician, but all hematological parameters that it is capable of measuring.[7] For example, when a physician requests a hemoglobin measurement, the analyzer also automatically determines the platelet count. Although this platelet count is not reported to the clinician, the analyzer stores the data. Periodically, all data captured within the blood cell analyzers are manually downloaded to a database format, and are cleaned and checked for integrity, making the data available for research. These hematological data include the collection date, type of material and the results, including flagging parameters.

Ethical and privacy considerations

The collection, storage and use of administrative and clinical patient information for scientific research is subject to ethical and privacy regulations.[8,9] The establishment and utilisation of UPOD is in accordance with guidance of the Institutional Review Board (IRB) and privacy board of UMC Utrecht, which allows the use of clinical data from patients who did not object to use of their data for scientific purposes, as long as the patients cannot be identified directly from the data.

Within UPOD, only data are captured that were initially registered during routine care and not for research purposes. Because no extra material, for example, blood samples, is taken from patients, there is not a requirement to obtain informed consent from individual patients or seek IRB approval for every study protocol.

At our institution, patients are informed at the time of admission that their data can be used for scientific research purposes. Patients can object to the use of their data within UPOD according to a general procedure for objecting to the use of data for scientific research that is available at UMC Utrecht.

To prohibit the identification of individual patients within the database, sensitive patient data must be encoded before they are processed outside the protective environment of the hospital and management information systems. For this purpose, the original patient identification number for UMC Utrecht is encrypted into a unique UPOD patient identifier within the database. Decrypting the patient identifier is possible in case it is essential to retrieve additional information from the patient's medical record. However, decryption is only possible after approval of the protocol by the IRB.

Linking laboratory and medication data

Laboratory data are often essential for selection, dosing and monitoring of drug therapy. Currently, many hospitals implement CPOE systems for ordering

prescriptions or laboratory tests that contain decision support tools involving linkage of laboratory and pharmacy information at the time of ordering medication. This so-called real-time linkage of laboratory and medication information is considered an important contribution to reducing prescription errors and improving patient care [10] since, in the absence of such computerised support systems, patient safety hinges on the ability of the physician to recall a particular warning concerning a specific drug in relation to the clinical characteristics of the patient.[11]

In addition to the benefits of real-time linkage for clinical practice, laboratory and medication data can also be linked retrospectively for research purposes within a database,[10] as is done within UPOD. This innovative technique provides numerous opportunities to conduct pharmacoepidemiological studies in which the role of the clinical laboratory is considered. These include evaluating the quality of pharmacotherapy with regard to laboratory monitoring, studying therapeutic and adverse effects of drugs, and investigating drug-test interference.[10]

Table 2 Examples of current research projects within UPOD

Subject	Type of epidemiology	
Laboratory monitoring for heparin-induced thrombocytopenia (HIT)	Descriptive	In patients at risk for HIT, close monitoring of the platelet count and an anti-heparin platelet factor 4 antibody test are advised to rule out HIT in case of suspicion;[12] it is investigated if there is a need to intensify laboratory monitoring within our institution
Epidemiology of drug-associated blood dyscrasias	Etiologic	Blood dyscrasias following exposure to non-cytotoxic drugs are rare; however, the outcome can be severe, especially since they often occur unexpected and are diagnosed after symptoms occurred; trombocytopenia, agranulocytosis, and aplastic anemia are among the most reported and fatal adverse drug reactions,[13] but research into the frequency, risk factors and mechanisms is still scarce.[14,15]
Laboratory markers for early-warning for drug-induced blood dyscrasias	Prognostic	Haematological parameters can possibly serve as early-warning markers for drug-induced blood dyscrasias; some haematological parameters reflect blood dyscrasias in an early stage and thus may be useful as indicators for predicting drug toxicity.[16]

UPOD = Utrecht Patient Oriented Database

In the following, examples of pharmacoepidemiological studies concerning the clinical laboratory are presented to illustrate the relevance of linking laboratory and medication data within a research database. We consider etiological (causality of an association between exposure and outcome), descriptive (pattern and frequency of the disease), prognostic (prediction of an outcome from factors that can be obtained before or at a certain time of treatment) and diagnostic (development of tests that allow accurate diagnosis of health status) epidemiological studies. Table 2 presents examples of pharmacoepidemiological studies currently being conducted within UPOD.

Etiological epidemiology: adverse drug reactions and drug-test interference

Adverse drug reactions Adverse drug reactions are considered a major threat to patient safety.[17] Depending on the definition, adverse drug reactions occur in up to 5%–30% of hospitalized patients.[18] Laboratory testing can be helpful in managing the risk of adverse drug reactions, as it has been shown that 60%–65% of clinically relevant adverse drug reactions can be detected with a biochemical test.[13,19-21] Several studies have shown that linking laboratory and medication data for large groups of patients is a powerful tool for studying the association between adverse events that can be detected with a biochemical test and drug exposure.[22-25] Two recent examples are the assessment of the incidence of drug-induced liver injuries based on serum values for liver enzymes during hospitalization and the quantification of the association between hyponatraemia and the use of serotonergic antidepressants in elderly patients.[26,27] In addition to evidence on the association between drug exposure and an adverse event, epidemiological studies can provide knowledge on risk factors for adverse drug reactions. An example of such a study is the recent identification of treatment-related risk factors for hospital-acquired hyponatraemia.[28] Knowledge of risk factors is important for the identification of patients at high risk of adverse drug reactions to initiate prophylactic treatment or close monitoring for the development of adverse drug reactions.[18,29]

Drug-test interference With more than 40 000 drugs described that affect laboratory test results,[30,31] drug-test interference is a relevant issue in clinical chemistry.[32] The interference can be due either to a biological effect, e.g. the increase in serum concentration of the thyroid hormone FT4 by valproic acid,[33] or to analytical interference, e.g. interference by aminoglycoside in total protein determination in urine.[34] Drug-test interference can lead to misinterpretation of laboratory data, potentially resulting in unnecessary medical services and costs.

Gronroos et al. extensively evaluated the literature on drug-test interference and recommended the development of a database system comprising linked laboratory and medication data for appropriate investigation of drug-test interference.[35]

Descriptive epidemiology: quality of pharmacotherapy

In selecting a drug, the patient's physical condition can be a contraindication. By linking laboratory and medication data, it can be investigated whether the drug is appropriately prescribed to the patient. Using this approach, Schiff et al. revealed that at their institutions a large proportion of patients received potassium supplementation while hyperkalemic.[36] By linking prescription claim data and hospital admission records, Juurlink et al. showed that publication of the results of the Randomised Aldactone Evaluation Study (RALES) was associated with an abrupt increase in the rate of prescriptions for spironolactone and in hyperkalemia-associated morbidity and mortality in heart failure patients also treated with ACE (angiotensin-converting enzyme) inhibitors.[37]

On the other hand, laboratory measurements can also reveal conditions that require treatment. Schiff et al. uncovered patients who were not treated with levothyroxine after abnormal levels of thyroid-stimulating hormone (TSH) were found.[38] Patient groups with altered drug metabolism, such as patients with renal insufficiency, often require dose adjustments of specific drugs. Epidemiological studies can be used to evaluate the adherence to dosing instructions with regard to renal insufficiency, as shown by Chertow et al.,[39] who reported that 70% of medication orders were written for an inappropriately high dose or frequency, increasing the risk of developing adverse drug reactions.

For a number of drugs, laboratory monitoring for drug toxicity, e.g. drug-induced liver damage, blood dyscrasias and nephrotoxicity is warranted.[40] In several cases of adverse drug reactions that have led to withdrawal of drugs from the market, a lack of appropriate laboratory monitoring played an important role.[41] Several recent studies considering laboratory monitoring during drug exposure in outpatients showed that essential monitoring was performed in only a minority of patients at risk of severe adverse drug reactions.[42-44]

Laboratory monitoring can also be warranted for efficacy of drug therapy, for example, measuring cholesterol goal attainment in statin treatment. Goettsch et al. linked outpatient laboratory data to prescription histories from community pharmacies and found that the percentage of patients who achieved the cholesterol level recommended in guidelines was low in practice.[45]

Prognostic and diagnostic epidemiology: markers for drug effects

Several adverse drug reactions develop unexpectedly and are diagnosed when symptoms occur, for example, drug-induced thrombocytopenia is often detected after spontaneous/excessive bleeding occurs.[14] For the patient (irreversible harm) and for society (increased medical costs), it is relevant to investigate whether the risk of such adverse drug reactions can be predicted before initiation of the medication and hence even guide the choice of medication, or if these adverse drug reactions can be diagnosed at an early stage (i.e. before clinical symptoms occur). Laboratory parameters could potentially serve as prognostic or diagnostic markers for adverse drug reactions,[46] for example, the occurrence of the typical drop in platelet count associated with heparin-induced thrombocytopenia (HIT).[47] Epidemiological studies within databases linking laboratory and medication data can contribute to the identification of predictive or prognostic markers and/or the development of algorithms for adverse drug reactions.

DISCUSSION

Application of UPOD for clinical epidemiological research

Transfer of automated laboratory data from the laboratory information system into a relational database infrastructure makes laboratory data available for clinical epidemiological research. Linking laboratory data to other clinical data provides numerous opportunities to study the biochemical characteristics of diseased populations, the effects of medical therapy that can be detected with laboratory tests and contribute to the development of predictive and diagnostic markers and/or algorithms for disease.

The application of automated database systems comprising observational data on patient characteristics, diagnoses, disease and therapy is already an established and widely used approach in the study of the effects of drugs in clinical settings,[48] in particular with regard to the detection, verification and quantification of adverse drug reactions.[49] The linkage of laboratory and medication data is especially innovative for database systems comprising data on in-hospital patients, such as UPOD. With regard to the general population, laboratory data have recently become available within some of the automated database systems used in pharmacoepidemiological research, for example the insurance-based Kaiser Permanente database,[40,43] and the Dutch population-based PHARMO Record Linkage System.[45] However, until recently, most database systems used to study drug use in populations comprised

drug histories from community pharmacies or hospitals linked to registrations of morbidity or hospital-discharge diagnoses,[48] but lacked laboratory data, thereby limiting the possibilities for conducting studies on adverse drug reactions that can be detected biochemically, as illustrated in a recent study carried out by our group.[50] It was found that the underlying disease overshadows many clinical conditions and that comorbidity is seldom registered in the case of severe illness. This could result in underestimation of the number of cases and potential bias when using hospital discharge diagnoses only in (pharmaco)epidemiological research. Because laboratory data allow more sensitive detection of the outcome and thereby increase the study power, the potential of investigations regarding, for example, the association between drug exposure and hyponatraemia would be increased if cases were sampled from laboratory data.[50] Taking this into account and considering the elevated risk of adverse drug reactions in hospitalized patients, the importance of laboratory information in drug therapy and the continuing introduction of new drugs with innovative mechanisms of action, a research platform that allows the linkage of laboratory and medication data for hospitalized patients promises to be a valuable tool for clinical epidemiological studies aimed at investigating the (adverse) effects of drugs.

Quality and data management

The use of database systems such as UPOD for clinical epidemiological research has several advantages. In contrast to ad hoc data collection, database systems allow the study of complete and validated data on a patient level for a large population over a prolonged period of time with relatively easy access and at low cost.[51] Furthermore, the collection of data using electronic registration systems and by automated transfer can be considered less prone to mistakes and less expensive compared to manual data collection. In addition, the real-life setting makes the population representative of patients actually being treated in clinical practice.[51]

Although the potential advantages of a database comprising clinical data are numerous, potential threats to epidemiological research using observational data should be considered, for example, missing data and misclassification that are to a certain extent inherent to the use of retrospectively gathered data.[52] To ensure maximum completeness and integrity, the data within UPOD are collected automatically and are extensively checked by data processing experts, administrative personnel and researchers. Furthermore, a data dictionary in which the database content is described in detail is available for researchers.

UPOD was established after the introduction of a CPOE system for ordering medication in our hospital and currently comprises complete data for a period of

two years for one institution. This may possibly limit the study of rare outcomes in the short term and the extrapolation of findings to other hospitals. However, the population covered will increase rapidly over time (Table 1), and cooperation with other hospitals will extend the possibilities.

We believe that the institutional basis of the database has several advantages. The setting within a large academic hospital guarantees optimal synergy between clinical and both diagnostic and basic research laboratories. In this way, the translation of research findings to clinical practice and the experimental laboratory becomes relatively easy and efficient. For example, when novel associations between drug exposure and abnormal blood-cell parameters reflecting damage to blood cells are found in epidemiological research, mechanistic hypotheses can be further investigated within the experimental laboratory setting using blood cell-specific in vitro systems.[53] In addition, the institutional basis makes it possible to validate data relatively easily or gather additional data, for example, by retrieving information that is currently not available within UPOD, such as radiology reports or electrocardiograms, from the original patient chart or by contacting the patient through his or her physician.

UPOD can be further expanded with data on extramural patient care, e.g. medication histories from community pharmacies or visits to general practitioners, and potentially other important types of clinical information such as pathology and genetic data. With regard to the latter, worldwide initiatives are currently undertaken to collect genetic data within population databases to study gene-disease relationships to characterise individual patients with regard to disease subtype based on their genetic profile.[54] Adding genetic data to UPOD will provide interesting research possibilities such as pharmacogenetics, i.e. investigating the role of genetic variation in th patient's response to pharmacotherapy.[55]

CONCLUSIONS

Facilitating the linkage of laboratory data collected during routine clinical care within a database system to other patient-oriented records broadens the opportunities for clinical pharmacoepidemiological research. Although recently established, UPOD promises to be invaluable for this type of research and should be exploited fully.

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REFERENCES

1. Porth AJ, Lubke B. History of computer-assisted data processing in the medical laboratory. Eur J Clin Chem Clin Biochem 1996;34:215-29.
2. Sackett D, Haynes RB, Tugwell P, Guyatt GH, editors. Clinical epidemiology: a basic science for clinical medicine. 2nd ed. Boston (MA): Little, Brown & Co.; 1991.
3. Z-Index. About the G-standard. http://www.zindex.nl/(in Dutch). Accessed July 6, 2006.
4. WHO Collaborating Centre for Drug Statistics Methodology. About the ATC/DDD system. http://www.whocc.no/atcddd/atcsystem.html. Accessed July 6, 2006.
5. CDC National Center for Health Statistics. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Available from: http://www.cdc.gov/nchs/icd9.htm (Accessed February 19, 2006).
6. CBV Foundation. About the classification of medical specialist procedures (CMSV). Available from: http://www.cbv.nl (in Dutch) (Accessed February 19, 2006).
7. Muller R, Mellors I, Johannessen B, Aarsand AK, Kiefer P, et al. European multi-center evaluation of the abbott cell-dyn sapphire hematology analyzer. Lab Hematol 2006;12:15-31.
8. Ohno-Machado L, Silveira PS, Vinterbo S. Protecting patient privacy by quantifiable control of disclosures in disseminated databases. Int J Med Inform 2004;73:599-606.
9. Hodge JG, Jr., Gostin LO, Jacobson PD. Legal issues concerning electronic health information: privacy, quality, and liability. JAMA 1999;282:1466-71.
10. Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. Arch Intern Med 2003;163:893-900.
11. Gurwitz JH. Serious Adverse Drug Effects -- Seeing the Trees through the Forest. N Engl J Med 2006;354:1413-5.
12. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126(3 Suppl):311S-37S.
13. Kelly WN. Potential risks and prevention, Part 1: Fatal adverse drug events. Am J Health Syst Pharm 2001;58:1317-24.
14. Van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. Drug Saf 2004;27:1243-52.

15. Van Staa TP, Boulton F, Cooper C, Hagenbeek A, Inskip H, et al. Neutropenia and agranulocytosis in England and Wales: incidence and risk factors. Am J Hematol 2003;72:248-54.

16. Wyrick-Glatzel J, Conway-Klaassen J. Clinical utility of the IRF: assessment of erythroid regeneration following parvo B19 infection. Clin Lab Sci 2002;15:208-12.

17. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998;279:1200-5.

18. Van den Bemt PM, Egberts AC, de Jong-van den Berg LT, Brouwers JR. Drug-related problems in hospitalised patients. Drug Saf 2000;22:321-33.

19. Azaz-Livshits T, Levy M, Sadan B, Shalit M, Geisslinger G, et al. Computerized survelliance of adverse drug reactions in hospital: pilot study. Br J Clin Pharmacol 1998;45:309-14.

20. Tegeder I, Levy M, Muth-Selbach U, Oelkers R, Neumann F, et al. Retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. Br J Clin Pharmacol 1999;47:557-64.

21. Levy M, Azaz-Livshits T, Sadan B, Shalit M, Geisslinger G, et al. Computerized surveillance of adverse drug reactions in hospital: implementation. Eur J Clin Pharmacol 1999;54:887-92.

22. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. JAMA 1991;266:2847-51.

23. Dormann H, Muth-Selbach U, Krebs S, Criegee-Rieck M, Tegeder I, et al. Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. Drug Saf 2000;22:161-8.

24. Jha AK, Kuperman GJ, Teich JM, Leape L, Shea B, et al. Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. J Am Med Inform Assoc 1998;5:305-14.

25. Honigman B, Lee J, Rothschild J, Light P, Pulling RM, et al. Using computerized data to identify adverse drug events in outpatients. J Am Med Inform Assoc 2001;8:254-66.

26. Bagheri H, Michel F, Lapeyre-Mestre M, Lagier E, Cambus JP, et al. Detection and incidence of drug-induced liver injuries in hospital: a prospective analysis from laboratory signals. Br J Clin Pharmacol 2000;50:479-84.

27. Movig KL, Leufkens HG, Lenderink AW, van den Akker VG, Hodiamont PP, et al. Association between antidepressant drug use and hyponatraemia: a case-control study. Br J Clin Pharmacol 2002;53:363-9.

28. Hoorn EJ, Lindemans J, Zietse R. Development of severe hyponatraemia in hospitalized patients: treatment-related risk factors and inadequate management. Nephrol Dial Transplant 2006;21:70-6.

29. Van den Bemt PM, Egberts AC, Lenderink AW, Verzijl JM, Simons KA, et al. Risk factors for the development of adverse drug events in hospitalized patients. Pharm World Sci 2000;22:62-6.

30. Tryding N, Tufvesson C, Sonntag O. Drug effects in clinical chemistry. 7th ed. Stockholm: AB Realtryck; 1996.

31. Salway JG. Drug-test interactions handbook. 1st ed. London: Chapman and Hall Medical; 1990.

32. Kroll MH, Elin RJ. Interference with clinical laboratory analyses. Clin Chem 1994;40(11 Pt 1):1996-2005.

33. Kailajarvi M, Takala T, Gronroos P, Tryding N, Viikari J, et al. Reminders of drug effects on laboratory test results. Clin Chem 2000;46:1395-400.

34. Marshall T, Williams KM. Total protein determination in urine: aminoglycoside interference. Clin Chem 2003;49:202-3.

35. Gronroos P, Irjala K, Heiskanen J, Torniainen K, Forsstrom. Using computerized individual medication data to detect drug effects on clinical laboratory tests. Scand J Clin Lab Invest Suppl 1995;222:31-6.

36. Schiff GD, Aggarwal HC, Kumar S, McNutt RA. Prescribing potassium despite hyperkalemia: medication errors uncovered by linking laboratory and pharmacy information systems. Am J Med 2000;109:494-7.

37. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543-51.

38. Schiff GD, Kim S, Krosnjar N, Wisniewski MF, Bult J, et al. Missed hypothyroidism diagnosis uncovered by linking laboratory and pharmacy data. Arch Intern Med 2005;165:574-7.

39. Chertow GM, Lee J, Kuperman GJ, Burdick E, Horsky J, et al. Guided medication dosing for inpatients with renal insufficiency. JAMA 2001;286:2839-44.

40. Raebel MA, Lyons EE, Chester EA, Bodily MA, Kelleher JA, et al. Improving laboratory monitoring at initiation of drug therapy in ambulatory care: a randomized trial. Arch Intern Med 2005;165:2395-401.

41. Meyboom R, Gribnau F, Hekster Y, de Koning G, Egberts A. Characteristics of topics in pharmacovigilance in The Netherlands. Clin Drug Invest 1996;12:207-19.

42. Simon SR, Andrade SE, Ellis JL, Nelson WW, Gurwitz JH, et al. Baseline laboratory monitoring of cardiovascular medications in elderly health maintenance organization enrollees. J Am Geriatr Soc 2005;53:2165-9.

43. Raebel MA, McClure DL, Simon SR, Chan KA, Feldstein AC, et al. Frequency of serum creatinine monitoring during allopurinol therapy in ambulatory patients (March). Ann Pharmacother 2006;40:386-91.

44. Derijks HJ, De Koning GH, Mantel-Teeuwisse AK, Egberts AC. Limited adherence to safety instructions in drug leaflets. Br J Clin Pharmacol 2002;54:678-9.

45. Goettsch WG, Yin DD, Alemao E, Klungel OH, Stalenhoef AF, et al. Statins are less effective in common daily practice among patients with hypercholesterolemia: the REALITY-PHARMO study. Curr Med Res Opin 2004;20:1025-33.

46. Kane-Gill SL, Dasta JF, Schneider PJ, Cook CH. Monitoring abnormal laboratory values as antecedents to drug-induced injury. J Trauma 2005;59:1457-62.

47. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. Arch Intern Med 2003;163:2518-24.

48. Strom BL, Carson JL. Use of automated databases for pharmacoepidemiology research. Epidemiol Rev 1990;12:87-107.

49. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004;329:44-7.

50. 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.

51. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 2005;58:323-37.

52. Zwetsloot-Schonk JH, Snitker P, Vandenbroucke JP, Bakker AR. Using hospital information systems for clinical epidemiological research. Med Inform (Lond) 1989;14:53-62.

53. Van Wijk R, van Wesel AC, Thomas AA, Rijksen G, van Solinge WW. Ex vivo analysis of aberrant splicing induced by two donor site mutations in PKLR of a patient with severe pyruvate kinase deficiency. Br J Haematol 2004;125:253-63.

54. Potter JD. Epidemiology informing clinical practice: from bills of mortality to population laboratories. Nat Clin Pract Oncol 2005;2:625-34.

55. Maitland-van der Zee AH, de Boer A, Leufkens HG. The interface between pharmacoepidemiology and pharmacogenetics. Eur J Pharmacol 2000;410:121-30.

3

LABORATORY MARKERS VERSUS DISCHARGE DIAGNOSES IN STUDIES ON DRUG-INDUCED THROMBOCYTOPENIA

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Drug-induced thrombocytopenia: a population study

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ABSTRACT

Background

Drug-induced immune thrombocytopenia, excluding heparin-induced thrombocytopenia, is a rare adverse drug reaction for which the evidence about frequency, relative risk and risk factors mainly originates from case reports and case studies. This study aims to quantify the risk for thrombocytopenia following exposure to drugs that are most often reported to cause thrombocytopenia in the general population.

Methods

A retrospective case-control study was conducted within the PHARMO record linkage system. Cases were defined as patients hospitalized for thrombocytopenia in the period 1 January 1990 to 31 December 2002. For each case, up to four controls were matched based on age, sex and geographical area. Exposure on the index date to anticonvulsants, β-lactam antibacterials, cinchona alkaloids, disease modifying antirheumatic drugs (DMARDs), diuretics, nonsteroidal antiinflammatory drugs (NSAIDs), sulfonamide antibacterials and tuberculostatics was assessed and categorised into mutually exclusive groups of current, recent, past and non-use. The risk was quantified with multivariate conditional logistic regression analysis.

Results

The study population comprised 705 cases and 2658 controls. Current use of β-lactam antibacterials was associated with an increased risk for thrombocytopenia (adjusted odds ratio 7.4, 95% confidence intervals 1.8-29.6). Increased risk estimates, although not significant, were found for current exposure to DMARDs and the sulfonamide antibacterial cotrimoxazole (trimethoprim/sulfamethoxazole). No increased risk was found for anticonvulsants, cinchona alkaloids, diuretics, NSAIDs or tuberculostatics.

Conclusion

More evidence for an increased risk for thrombocytopenia in current use of β-lactam antibacterials in the general population was provided. The expected increase in risk could not be confirmed for the other drugs investigated, which is possibly a result of the limited statistical power. Future studies including more patients and with laboratory data should confirm our findings before drawing definite conclusions.

BACKGROUND

If not recognised in time, thrombocytopenia is a potential life-threatening disorder. Thrombocytopenia is commonly defined as a fall in platelet count to $<100\times10^9$ platelets/L of blood or a drop in platelet count of >50% compared with baseline. Although it may initially be asymptomatic, thrombocytopenia is often diagnosed by the occurrence of bruising, petechiae, ecchymosis and epistaxis. When the thrombocytopenia persists, bleeding from mucous membranes and severe purpura can occur.[1]

Drugs can cause thrombocytopenia, either through a direct toxic effect on the thrombopoietic mechanism in the bone marrow resulting in decreased platelet production or through immune-mediated mechanisms resulting in increased platelet destruction.[2,3] Thrombocytopenia, together with other blood dyscrasias, is a frequent adverse effect of treatment with chemotherapeutics that cause bone-marrow toxicity by direct interference with cell formation.[3] Another relatively well studied type of immune-mediated drug-induced thrombocytopenia is heparin-induced thrombocytopenia, which is reported to occur in up to 2.6% of hospitalized patients exposed to unfractionated heparin and in 0.2-0.8% of patients exposed to low-molecular weight heparins.[4,5]

A review of the literature on drug-induced immune thrombocytopenia, which was published in Drug Safety last year, concluded that other drugs that are most frequently reported as possible causes of thrombocytopenia are anticonvulsants, β-lactam antibacterials, cinchona alkaloid derivates, disease modifying antirheumatic drugs (DMARDs), diuretics, sulfonamide antibacterials, nonsteroidal antiinflammatory drugs (NSAIDs), and tuberculostatics.[2] However, the current evidence about the frequency and possible risk factors for thrombocytopenia induced by these drugs was found to be limited and mainly to originate from case reports and studies with spontaneous-reporting databases.[6-12]

These limited data revealed that the overall incidence of drug-induced thrombocytopenia in the general population is considered to be approximately 10 cases per 1 million inhabitants per year. However, this estimate might be much higher for specific populations such as hospitalized patients.[2] Although case reports and studies with spontaneous-reporting databases provide detailed information on the etiology of adverse drug reactions, it is not possible to quantify the strength of the association between drug exposure and the adverse reaction and to identify risk factors in the absence of a control group. Therefore, studies with a controlled design, e.g. a case-control study, are preferred when studying the risk of rare adverse drug reactions, such as thrombocytopenia.[13] To our knowledge, only one case-control study has been performed to provide quantitative risk estimates for the association

between drug exposure and hospitalization for acute thrombocytopenic purpura, in which increased risks were reported for several drugs, for example the sulfonamide antibacterial cotrimoxazole (trimethoprim/sulfamethoxazole) and quinine/quinidine.[14] To quantify the risk for thrombocytopenia following exposure to drugs that are most frequently reported as a possible cause for thrombocytopenia, a case-control study was conducted in a well defined population of community-dwelling patients.

METHODS

Data collection

Data were obtained from the PHARMO record linkage system, a database that since 1985 has linked dispensing records of prescription drugs from a representative sample of Dutch community pharmacies to hospital discharge data from individual patients,[15] and currently contains data for >2 million residents. Since the majority of patients in The Netherlands are registered in a single community pharmacy, the patient's drug exposure history is virtually complete with regard to prescription drugs.[16]

The computerised drug-dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen and the estimated duration of use. The duration was estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs were coded according to the Anatomical Therapeutic Chemical (ATC) classification.

The hospital-discharge records were obtained from the Dutch National Medical Registry (LMR database, Prismant), which covers all hospital-discharge records from The Netherlands since the 1960s in a standardised format. These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists, and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases (9th Edition), Clinical Modification (ICD-9-CM).[17]

Patients

The source population comprised all subjects that were registered in the PHARMO database during the study period that started on 1 January 1990 and ended on 31 December 2002. All patients who were hospitalized at least once for

thrombocytopenia during the study period were identified. Although drug-induced thrombocytopenia is considered as a secondary cause of thrombocytopenia according to the ICD-9-CM classification, all three defined categories of thrombocytopenia, i.e. primary (ICD-9-CM code 287.3), secondary (287.4) and non-specified thrombocytopenia (287.5), were considered.[17] The index date was defined as the date of admission to the hospital. Patients with a history of <180 days in the PHARMO database prior to the index date were excluded from the study. If patients were hospitalized more than once for thrombocytopenia, the first hospitalization in time was selected.

This study aimed to quantify the risk for drug-induced thrombocytopenia following drug exposure in the general population. Therefore, cases that were likely to be related to other causes were excluded. To prevent the inclusion of patients who were treated with chemotherapy, cases with a discharge diagnosis for agranulocytosis (ICD-9-CM code 288.0) at the index date were excluded. Additionally, cases with a discharge diagnosis for thrombocytopenia-related medical conditions at the index date were excluded. The following conditions were excluded: cancer (014.0-023.9); aplastic anemia (284.8-9); vitamin B12 deficiency (281.1); folate deficiency (281.2); alcohol abuse (305.0); splenomegaly (289.4-5); systemic lupus erythematosus (695.4, 710.0); human immunodeficiency virus (HIV) infection (044.9, 795.8); measles (055.9); mononucleosis infectiosa (075.0-9); malaria (084.1, 4.6); thrombotic thrombocytopenia purpura (446.6); and hemolytic uremic syndrome (283.1). The remaining cases were included in the study population.

For each case, up to four control patients were randomly selected from the source population and matched to cases based on sex, age (5-year intervals) and geographical area. Controls were assigned the same index date as the cases. Controls were only eligible for inclusion if they had ≥180 days of history in the PHARMO database prior to the index date of the matched case. The same exclusion criteria were used for cases and controls.

Exposure definition

From the drug-dispensing histories, all prescriptions for the following drugs, which were *a priori* considered as the drug classes that are most frequently reported in the literature to cause thrombocytopenia [2] and were available on the Dutch market during the study period, were selected: anticonvulsants; β-lactam antibacterials; cinchona alkaloids; DMARDs; diuretics; NSAIDs; the sulfonamide antibacterial cotrimoxazole; and tuberculostatics.

Exposure at the index date was assessed and categorised into mutually exclusive groups of current, recent, past and non-use. Current use was defined as exposure

to the drug in the period of four weeks before or at the index date, recent use was defined as exposure in the period of three months through four weeks before the index date, past use was defined as exposure in the period of six months through three months before the index date and non-use was defined as having dispensed a prescription >6 months before the index date or not having dispensed a prescription at all. The drug exposure window was defined as the period between the dispensing date and the theoretical end date, which was calculated by adding the estimated duration of use to the start date.

Potential confounding factors

By restricting the selection of cases to patients hospitalized for thrombocytopenia without discharge diagnoses for agranulocytosis and other thrombocytopenia-related conditions at the index date, potential confounding by these risk factors was eliminated. However, it was investigated if potential confounding was introduced by the presence of thrombocytopenia-related morbidity in the period of six months before the index date. Hospitalizations for the following conditions were considered: malignant disease, aplastic anemia, vitamin B12 deficiency, folate deficiency, alcohol abuse, splenomegaly, systemic lupus erythematosus, HIV infection, measles, mononucleosis infectiosa, malaria, thrombotic thrombocytopenia purpura and hemolytic uremic syndrome. Additionally, the use of unfractionated heparin or low-molecular weight heparins, antineoplastic and immunosuppressive drugs, dispensed by the community pharmacy in the 6-month period prior to the index date was considered as a potential confounder.

Data analysis

The association between drug exposure and thrombocytopenia was estimated with conditional logistic regression and expressed as relative risk by calculating odds ratios (ORs) with 95% confidence intervals (95%CI). Power calculations with α=0.05, suggested that the study would give an 80% chance of detecting a significant OR >2.7 based on 705 cases and assuming, on average, a proportional drug exposure in the control group of 1 in 100 patients.[18]

Initially, crude ORs were calculated with univariate conditional logistic regression. Additionally, multivariate conditional logistic regression was used to adjust crude odds ratios for concurrent exposure to other drugs most frequently reported to cause drug-induced thrombocytopenia, and for potential confounders. Potential confounders were included in the final model when they changed the point estimate by >10%.[19]

In case a significant adjusted risk estimate was found, sensitivity analyses were performed regarding four different definitions of current exposure to the drug: (1) within 7 days of the index date; (2) within 14 days of the index date; (3) within 28 days of the index date; and (4) within 42 days of the index date.

RESULTS

In the source population, 1213 patients with at least one hospitalization for thrombocytopenia were identified during the study period. Of those patients, 233 were excluded because they had a history of <180 days in the PHARMO database prior to the index. Additionally, 179 cases were excluded because they had a diagnosis for agranulocytosis at the index date, and another 96 cases were excluded because they had a diagnosis for aplastic anemia, cancer, hemolytic uremic syndrome, malaria or systemic lupus erythematosus at the index date.

Table 1 Characteristics of the study population

Characteristics	Cases n=705 (100%)	Controls n=2658 (100%)
Demographics		
female	461 (65.4%)	1753 (66.0%)
mean age in years (sd)	48.7 (24.1)	47.9 (23.8)
Discharge diagnosis		
primary thrombocytopenia	162 (23.0%)	NA
secondary thrombocytopenia	79 (11.2%)	NA
unspecified thrombocytopenia	464 (65.8%)	NA
Potential confounders [a,b]		
cancer	55 (7.8%)	10 (0.4%)
aplastic anemia	10 (1.4%)	0 (0.0%)
SLE	0 (0.0%)	1 (0.0%)
TTP	1 (0.1%)	0 (0.0%)
use of UFH or LMWH	1 (0.1%)	0 (0.0%)
use of antineoplastic drugs	3 (0.4%)	0 (0.0%)

sd = standard deviation; NA = not applicable; SLE = systemic lupus erythematosus; TTP = thrombotic thrombocytopenic purpura; UFH = unfractionated heparin; LMWH = low-molecular weight heparin

a) Presence of thrombocytopenia-related morbidity in the period of six months before the index date.

b) No cases and controls were identified for the other potential confounders that were investigated (i.e. vitamin B12 deficiency, folate deficiency, alcohol abuse, splenomegaly, SLE, HIV infection, measles, mononucleosis infectiosa, malaria, hemolytic uremic syndrome, and exposure to immunosuppressants drugs).

Table 2 Risk for thrombocytopenia following drug exposure				
Drug exposure[a]	**Cases n=705 (100%)**	**Controls n=2658 (100%)**	**Crude OR (95%CI)**	**Adj[b] OR (95%CI)**
Anticonvulsants				
non-use	701 (99.4%)	2646 (99.5%)	1.0 (reference)	1.0 (reference)
past use	1 (0.1%)	0 (0.0%)	NA	NA
recent use	1 (0.1%)	2 (0.1%)	2.0 (0.2–22.1)	2.0 (0.2–22.2)
current use	2 (0.3%)	10 (0.4%)	0.7 (0.2–3.3)	0.8 (0.2–3.5)
Beta-lactam antibiotics				
non-use	688 (97.6%)	2626 (98.8%)	1.0 (reference)	1.0 (reference)
past use	6 (0.9%)	15 (0.6%)	1.5 (0.5–3.8)	1.0 (0.3–3.1)
recent use	5 (0.7%)	14 (0.5%)	1.4 (0.5–3.9)	1.1 (0.3–3.6)
current use	6 (0.9%)	3 (0.1%)	7.8 (1.9–31.1)	7.4 (1.8–29.6)
Cinchona alkaloids				
non-use	699 (99.1%)	2650 (99.7%)	1.0 (reference)	1.0 (reference)
past use	2 (0.3%)	2 (0.1%)	4.0 (0.6–28.4)	3.0 (0.4–25.6)
recent use	2 (0.3%)	1 (0.0%)	8.0 (0.7–88.2)	9.1 (0.8–102.2)
current use	2 (0.3%)	5 (0.2%)	1.3 (0.2–6.9)	1.3 (0.2–8.0)
Diuretics				
non-use	675 (95.7%)	2603 (97.9%)	1.0 (reference)	1.0 (reference)
past use	6 (0.9%)	7 (0.3%)	3.4 (1.1–10.8)	3.0 (0.9–10.0)
recent use	4 (0.6%)	5 (0.2%)	3.2 (0.9–12.0)	2.5 (0.6–10.1)
current use	20 (2.8%)	43 (1.6%)	1.8 (1.0–3.2)	1.7 (0.9–3.0)
DMARDs				
non-use	703 (99.7%)	2655 (99.9%)	1.0 (reference)	1.0 (reference)
past use	0 (0.0%)	1 (0.0%)	NA	NA
recent use	1 (0.1%)	1 (0.0%)	4.0 (0.2–63.9)	2.3 (0.1–52.3)
current use	1 (0.1%)	1 (0.0%)	4.0 (0.2–63.9)	4.3 (0.3–69.3)
NSAIDs				
non-use	675 (95.7%)	2553 (96.1%)	1.0 (reference)	1.0 (reference)
past use	9 (1.3%)	33 (1.2%)	1.0 (0.5–2.1)	1.0 (0.5–2.3)
recent use	9 (1.3%)	34 (1.3%)	1.0 (0.5–2.1)	1.0 (0.5–2.3)
current use	12 (1.7%)	38 (1.4%)	1.2 (0.6–2.4)	1.3 (0.6–2.6)
Tuberculostatics				
non-use	705 (100%)	2657 (100%)	1.0 (reference)	1.0 (reference)
past use	0 (0.0%)	0 (0.0%)	NA	NA
recent use	0 (0.0%)	0 (0.0%)	NA	NA
current use	0 (0.0%)	1 (0.0%)	NA	NA
TMP/SMX				
non-use	701 (99.4%)	2647 (99.6%)	1.0 (reference)	1.0 (reference)
past use	1 (0.1%)	5 (0.2%)	0.8 (0.1–6.8)	0.8 (0.1–7.3)
recent use	0 (0.0%)	4 (0.2%)	NA	NA
current use	3 (0.4%)	2 (0.1%)	5.7 (0.9–34.0)	3.7 (0.5–24.3)

(*legend Table 2*)
OR = odds ratio; NA = not applicable; DMARDs = disease modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs; TMP/SMX = trimethoprim/sulfamethoxazole

a) N*on-use* was defined as having dispensed a prescription >6 months before the index date or not having dispensed a prescription at all; *past use* was defined as exposure in the period of 6 months through 3 months before the index date; *recent use* was defined as exposure in the period of 3 months through 4 weeks before the index date; and *current use* was defined as exposure to the drug in the period of 4 weeks before or at the index date.
b) Adjusted for hospitalization for cancer in the period of six months before the index date and concurrent exposure to the other drugs investigated in this study.

After matching, the final study population comprised 705 cases and 2658 controls. The characteristics of the study population are presented in Table 1. The majority of the cases (65.8%) were classified as hospitalized for unspecified thrombocytopenia. Hospitalization for cancer during the period of six months before the index date was the only potential confounder found to be associated with an increased risk for thrombocytopenia (crude OR 22.5, 95%CI 11.1-45.5).

Current use of β-lactam antibacterials (crude OR 7.8; 95%CI 1.9-31.1) was associated with an increased risk for thrombocytopenia (Table 2). After adjusting for potential confounding by concurrent exposure to one of the other drugs most frequently reported to cause thrombocytopenia and a hospitalization for cancer in the period of six months before the index date, the current use of β-lactam antibacterials was associated with a >7-fold increase (adjusted OR 7.4; 95%CI 1.8-29.6) in the risk for thrombocytopenia. No increase in the risk for thrombocytopenia was found for past and recent use of β-lactam antibacterials. The specific β-lactam antibacterials used by the six cases identified as currently exposed were amoxicillin (n=4), pheneticillin (n=1) and cefaclor (n=1). Sensitivity analysis concerning different exposure windows revealed that the risk for thrombocytopenia in exposure to β-lactam antibacterials increased with narrowing the exposure window (Table 3).

An increased point estimate for the risk for thrombocytopenia was found for current exposure to DMARDs (adjusted OR 4.3; 95%CI 0.3-69.3) and cotrimoxazole (adjusted OR 3.7; 95%CI 0.5-24.3), although both did not reach statistical significance (Table 2). No increased risk for thrombocytopenia was found for current exposure to anticonvulsants, cinchona alkaloids, NSAIDs and tuberculostatics. Past use of diuretics was found to be associated with an increased risk for thrombocytopenia in univariate analysis. However, after adjusting for potential confounding the risk estimate became non-significant (Table 2).

Table 3 Sensitivity analysis current exposure to β-lactam antibacterials				
Exposure window in days to the index date	**Cases n=705 (100%)**	**Controls n=2658 (100%)**	**Crude OR (95%CI)[b]**	**Adjusted[a] OR (95%CI)[b]**
7	3 (0.4%)	0 (0.0%)	NA	NA
14	4 (0.6%)	1 (0.0%)	15.2 (1.7–136.0)	14.2 (1.6–127.8)
28	6 (0.8%)	3 (0.1%)	7.8 (1.9–31.1)	7.4 (1.8–29.6)
42	7 (1.0%)	6 (0.2%)	4.6 (1.6–13.6)	3.8 (1.2–11.7)

OR = odds ratio; NA = not applicable

a) Adjusted for hospitalization for cancer in the period of six months before the index date and concurrent exposure to the other drugs investigated in this study.

b) Non-use taken as reference category.

DISCUSSION

The results of this study, one of the few large epidemiological studies designed to quantify the association between drug exposure and thrombocytopenia, indicate that the current use of β-lactam antibacterials is associated with a 7-fold increased risk for thrombocytopenia in the general population. β-Lactam antibacterials have been reported to cause thrombocytopenia by immune-mediated mechanisms [2,20] and by bone-marrow suppression.[21,22] Furthermore, β-lactam antibacterials were found to be associated with an increased risk for blood dyscrasias in a cohort study using data from the British General Practice Research Database.[23] However, the authors suggested that confounding by indication has to be considered when an association is found between the use of antibacterials and blood dyscrasias, because the antibacterial drug might be prescribed to treat an infection that could be considered as early manifestation of a blood dyscrasia related to the underlying disease.[23,24] In the current study, we cannot rule out confounding by indication. However, by excluding patients with thrombocytopenia that also had agranulocytosis and/or thrombocytopenia-related medical conditions at the index date, we believe it is not likely that confounding by indication can explain our results.

From the results of this study the expected increased risk for thrombocytopenia could not be confirmed for the other drug classes investigated. This is in contrast with findings of a previous case-control study that reported an increased risk for hospitalization for acute thrombocytopenic purpura and the use of cotrimoxazole (multivariate relative risk 124; 95%CI 19-821) and quinine/quinidine (multivariate relative risk 101; 95%CI 31-324).[14]

The lack of statistical power resulting from the low number of cases is a possible explanation for the current findings, such as in the case of cotrimoxazole. Considering the study design, a matched retrospective case-control study, the a priori defined criteria for significance (α=0.05) and power (80%; β=0.2), the increased point estimate of 5.4 that was found for current exposure to cotrimoxazole could only have been statistically confirmed for this number of exposed controls (2 of 2658) if >2350 cases were identified, i.e. three times more then were included in the study.[18] Therefore, future studies including more patients are necessary to confirm our findings.

The extensive information on drug exposure, potential confounders and patient characteristics that is available within the PHARMO database is the strength of this study. Nevertheless, the study design and the available resources introduce potential limitations. It is quite possible that patients who developed drug-induced thrombocytopenia, who were identified by including those with thrombocytopenia who required hospitalization, were only the tip of the iceberg, leaving patients who recovered after termination of therapy and patients who died unidentified.[25]

Incomplete and inaccurate coding of discharge diagnosis could have introduced misclassification of outcome.[25] Inaccurate coding might be reflected by the finding that two-thirds of the identified hospitalizations for thrombocytopenia were classified as unspecified. Since no data were available on medication administered during hospitalization, we might have included patients who developed thrombocytopenia related to drug exposure (e.g. chemotherapy, immunosuppressants, unfractionated heparin or low-molecular weight heparins) administered during hospitalization. On the other hand, by excluding patients with a diagnosis for agranulocytosis or thrombocytopenia-related medical conditions at the index date and by adjusting for confounding, this bias, if existing, seems relatively small. Nevertheless, additional studies including cases that are validated by retrieving all detailed information on all etiologic causes of thrombocytopenia from the original patient records remain necessary before drawing final conclusions. Some misclassification of exposure may have occurred, since pharmacy records, which provide information that the drug was dispensed but not if the patient actually took it, were used for identification of drug exposure. However, this misclassification is expected to be limited[16] and was assumed to be evenly distributed over cases and controls. Furthermore, non-differential misclassification may systematically lead to underestimation of the investigated effects.[26] Finally, it cannot be ruled out that potential residual confounding can explain part of the associations found.

Database systems comprising administrative healthcare data have proven to be useful for detection, verification and quantification of the risk for adverse drug

reactions in the general population.[27] Considering the design of the current study we believe the results contribute to the knowledge on drug-induced thrombocytopenia. Nevertheless, we have discussed sample size and the use of hospitalization data that limit the risk estimation and the identification of risk factors for drug-induced thrombocytopenia. Potentially, the use of laboratory data, i.e. platelet count, in future pharmacoepidemiological studies aimed at quantifying the risk for drug-induced thrombocytopenia and identification of potential risk factors, will overcome these issues partially. Furthermore, the use of laboratory data will enable us to study the severity and potentially the time of onset of the thrombocytopenia in more detail. In the current study, it was unclear what platelet count threshold was used in diagnosing the patient with thrombocytopenia. We would expect the platelet count in all cases to be $\leq 100 \times 10^9$ platelets/L; however, we could not verify this because of the lack of laboratory data.

CONCLUSION

This study provided more evidence on the increased risk for thrombocytopenia in current exposure to β-lactam antibacterials in the general population. The expected increased risk for thrombocytopenia could not be confirmed and quantified for the other drugs investigated. Therefore, future studies including more patients are necessary to confirm our findings. The potential for large retrospective studies within administrative databases investigating adverse drug reactions, such as drug-induced thrombocytopenia, might be enhanced if cases were sampled from routine laboratory data that were gathered during daily practice.

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REFERENCES

1. Handin RI, Lux SE, Stossel TP. Blood principles and practice of hematology. 2nd ed. Philadelphia (PA): Lippincott Williams and Wilkins; 2003.
2. Van den Bemt PMLA, Meyboom RH, Egberts ACG. Drug-induced immune thrombocytopenia. Drug Saf 2004;27:1243-52.

3. Carey PJ. Drug-induced myelosuppression: diagnosis and management. Drug Saf 2003;26:691-706.
4. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. Blood 2005;106:2710-5.
5. Prandoni P, Siragusa S, Girolami B, Fabris F. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. Blood 2005;106:3049-54.
6. Li X, Hunt L, Vesely SK. Drug-induced thrombocytopenia: an updated systematic review. Ann Intern Med 2005;142:474-5.
7. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998;129:886-90.
8. Rizvi MA, Kojouri K, George JN. Drug-induced thrombocytopenia: an updated systematic review. Ann Intern Med 2001;134:346.
9. Hibbard AB, Medina PJ, Vesely SK. Reports of drug-induced thrombocytopenia. Ann Intern Med 2003;138:239.
10. Pedersen-Bjergaard U, Andersen M, Hansen PB. Thrombocytopenia induced by noncytotoxic drugs in Denmark 1968-91. J Intern Med 1996;239:509-15.
11. Danielson DA, Douglas SW, Herzog P, Jick H, Porter JB, et al. Drug-induced blood disorders. JAMA 1984;252:3257-60.
12. Bottiger LE, Westerholm B. Thrombocytopenia: II. Drug-induced thrombocytopenia. Acta Med Scand 1972;191:541-8.
13. Strom BL. Pharmacoepidemiology. 3rd ed. Chichester, UK: John Wiley & Sons Ltd; 2000.
14. Kaufman DW, Kelly JP, Johannes CB, Sandler A, Harmon D, et al. Acute thrombocytopenic purpura in relation to the use of drugs. Blood 1993;82:2714-8.
15. Herings RMC. PHARMO: a record linkage system for postmarketing surveillance of prescription drugs in the Netherlands [dissertation]. Utrecht: Utrecht University; 1993.
16. Lau HS, de Boer A, Beuning KS, Porsius A. Validation of pharmacy records in drug exposure assessment. J Clin Epidemiol 1997;50:619-25.
17. CDC National Center for Health Statistics. International Classification of Diseases, 9th Revision. Clinical Modification (ICD-9-CM) [online]. Available from: http://www.cdc.gov/nchs/about/otheract/icd9/abticd9.html [Accessed 2006 Jun 27].
18. Dupont WD, Plummer WD. Power and sample size calculations for studies involving linear regression. Control Clin Trials 1998;19:589-601.
19. Greenland S. Modeling and variable selection in epidemiologic analysis. Am J Public Health 1989;79:340-9.
20. Patnode NM, Gandhi PJ. Drug-induced thrombocytopenia in the coronary care unit. J Thromb Thrombolysis 2000;10:155-67.
21. Kumar A, Choudhuri G, Aggarwal R. Piperacillin induced bone marrow suppression: a case report. BMC Clin Pharmacol 2003;3:2.
22. Reichardt P, Handrick W, Linke A, Schille R, Kiess W. Leukocytopenia, thrombocytopenia and fever related to piperacillin/tazobactam treatment: a retrospective analysis in 38 children with cystic fibrosis. Infection 1999;27:355-6.

23. Huerta C, Garcia Rodriguez LA. Risk of clinical blood dyscrasia in a cohort of antibiotic users. Pharmacotherapy 2002;22:630-6.

24. 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.

25. 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.

26. Hofler M. The effect of misclassification on the estimation of association: a review. Int J Methods Psychiatr Res 2005;14:92-101.

27. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004;329:44-7.

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Platelet measurements versus discharge diagnoses for identification of patients with potential drug-induced thrombocytopenia: a cross-sectional study in The Netherlands

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ABSTRACT

Background

In pharmacoepidemiological studies on the risk for drug-induced blood dyscrasias, including drug-induced thrombocytopenia (DIT), hospital discharge diagnoses have been used to identify potential cases. One of the possible limitations of discharge diagnoses is that due to incomplete registration not all potential cases are identified, which may limit statistical power. Clinical laboratory data have been suggested as a data type that is potentially more sensitive for identifying potential cases of adverse drug reactions than discharge diagnoses.

Objective

To compare the number of patients with potential DIT that could be identified by using platelet measurements with the number of patients with potential DIT that could be identified by using discharge diagnoses for thrombocytopenia within a population of hospitalized patients.

Methods

The study population of this cross-sectional study comprised all patients admitted to the University Medical Center Utrecht in 2004 and 2005, as captured within the Utrecht Patient Oriented Database (UPOD). The ratio of the number of patients with potential DIT based on platelet measurements (≥1 platelet count below 100×10^9/L without alternative diagnoses for DIT) to the number of patients with potential DIT based on discharge diagnoses for thrombocytopenia (International Classification of Diseases, 9th Revision [ICD-9-CM] codes 287.3-5 without alternative diagnoses for DIT) was determined.

Results

Within the study period there were 56 411 hospitalizations. 2817 patients (5.0%) had ≥1 platelet count below 100×10^9/L. In 96.3% of these patients alternative diagnoses for DIT were present, resulting in 103 (0.2%) patients with potential DIT based on platelet measurements. There were 74 patients (0.1%) with a discharge diagnosis for thrombocytopenia. In 81.1% of these patients alternative diagnoses for DIT were present, resulting in 14 (0.02%) patients with potential DIT based on discharge diagnoses. This resulted in a ratio of the number of patients with potential DIT based on platelet measurements to the number of patients with potential DIT based on discharge diagnoses for thrombocytopenia of seven.

Conclusion
This study showed that the use of platelet measurements is a more sensitive approach to identify patients with potential DIT compared to the use of discharge diagnoses for thrombocytopenia.

BACKGROUND

Drug-induced blood dyscrasias such as agranulocytosis, aplastic anemia and thrombocytopenia are among the most frequently reported fatal adverse drug reactions,[1] and have been a major reason for drug withdrawal during the past 50 years.[2] Several epidemiological studies have been conducted following up important signals on drug-induced hematological toxicity,[3-8] of which the International Agranulocytosis and Aplastic Anemia Study (IAAAS) is probably the best-known example.[9] We have previously investigated the risk for drug-induced thrombocytopenia (DIT) following exposure to non-cytotoxic drugs that are most often reported to cause thrombocytopenia in the general population.[7]
The majority of the observational studies on drug-induced blood dyscrasias have been conducted within large population-based administrative databases, using coded (e.g. International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM])[10] hospital discharge diagnoses as identifiers for patients with a potential drug-induced blood dyscrasia.[3-8] However, the validity of using discharge diagnoses for case-finding of drug-induced blood dyscrasias could be threatened by the nature of the registration of discharge diagnoses. Firstly, the registration of discharge diagnoses is primarily driven by reimbursement purposes and not by clinical care needs, and therefore discharge diagnoses are not necessarily registered for all present conditions,[11] thereby potentially limiting sensitivity. Secondly, coding mistakes by administrative personnel could occur,[11] potentially limiting both sensitivity and specificity. These two limitations could lead to incomplete case-finding, thereby introducing the potential for selection bias as well as limiting statistical power.
An alternative approach for identifying patients with potential drug-induced blood dyscrasias for pharmacoepidemiological research is the use of clinical laboratory data (i.e. blood cell counts) as an identifier. Clinical laboratory data are gathered for patient care purposes, measured using validated instruments and procedures, and the results of the measurements are increasingly automatically (i.e. without human data entry) stored in hospital information systems including the electronic medical record. Laboratory data are therefore expected to be less prone to selective

registration and coding mistakes than discharge diagnoses. In contrast to discharge diagnoses, which have been used successfully in pharmacoepidemiological research since the beginning of the 1990s,[12] clinical laboratory data have become widely available for this type of research only recently.[13] The objective of the current study was to compare the number of patients with potential DIT that could be identified within a population of hospitalized patients by using platelet measurements with the number of patients with potential DIT that could be identified by using discharge diagnoses for thrombocytopenia.

METHODS

Design, data source, setting, and study population

This retrospective cross-sectional study with prospectively collected data was conducted using the Utrecht Patient Oriented Database (UPOD). UPOD is a platform for clinical epidemiological research, the structure and content of which have been described in more detail elsewhere.[13] In brief, UPOD is an infrastructure of relational databases comprising data on patient characteristics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the University Medical Center Utrecht (UMC Utrecht) since 2004. The UMC Utrecht is a 1042-bed academic teaching hospital in the center of the Netherlands, with about 28 000 clinical and 15 000 day-care hospitalizations and 334 000 outpatient visits annually.[13] UPOD data acquisition and data management is in accordance with current Dutch privacy and ethical regulations.

The study population included all patients who were clinically admitted to the UMC Utrecht during the 2-year period of 1 January 2004 and 3l December 2005. Patients could be hospitalized more than once in the study period.

Drug-induced thrombocytopenia (DIT)

Drug-induced thrombocytopenia (DIT) is defined as thrombocytopenia due to a decreased platelet production, an increased platelet destruction or an increased platelet consumption, following an immune response to a drug or a direct toxic effect of a drug on the megakaryocytopoiesis in the bone marrow.[14] The diagnosis of DIT in clinical practice is usually the outcome of exclusion of all other possible explanations for a thrombocytopenia. DIT is commonly defined as a platelet count below 100×10^9/L without alternative diagnoses.[14-16]

Potential DIT

In this study, two different approaches for the identification of patients with potential DIT - defined as patients with thrombocytopenia without alternative diagnoses for DIT - were compared. The first approach was based on using platelet measurements as the identifier for patients with potential DIT, and the second approach was based on using discharge diagnoses for thrombocytopenia. Patients with potential DIT based on platelet measurements were defined as patients with at least one platelet count below 100×10^9/L during hospitalization, without the presence of alternative diagnoses for DIT.[15] Patients with potential DIT based on discharge diagnosis of thrombocytopenia were defined as patients with an in-patient discharge diagnosis of primary (ICD-9-CM code 287.3), secondary (287.4) or unspecified thrombocytopenia (287.5), without the presence of alternative diagnoses for DIT. The discharge diagnosis for secondary thrombocytopenia (ICD-9-CM code 287.4) codes for DIT, among other types of secondary thrombocytopenia. However, in this study, all three discharge diagnoses that code for thrombocytopenia according the ICD-9-CM classification (Table 1) were taken into account in defining potential

Table 1 Thrombocytopenia coded according to the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)10

Code	Description
287.3	Primary thrombocytopenia
	287.30: primary thrombocytopenia, unspecified
	287.31: idiopathic thrombocytopenic purpura (ITP), tidal platelet dysgenesis
	287.32: Evans' syndrome
	287.33: congenital and hereditary thrombocytopenia, thrombocytopenia with absent radii (TAR)
	287.39: other primary thrombocytopenia
287.4	Secondary thrombocytopenia
	Posttransfusion purpura;
	Thrombocytopenia due to dilution, drugs, extracorporeal circulation of blood, massive blood transfusion, platelet alloimmunization
287.5	Thrombocytopenia, unspecified

DIT based on discharge diagnoses for thrombocytopenia. This was done to anticipate potential misclassification of patients with DIT as primary or unspecified thrombocytopenia.

Alternative diagnoses for DIT were defined as diseases or therapeutic procedures that could explain the thrombocytopenia. The presence of alternative diagnoses for DIT was investigated using automated data on discharge diagnoses (coded according the ICD-9-CM),[10] medical procedures (coded according the Classification of Procedures by Medical Specialists, published by the Dutch CBV Foundation)[17] and hematological laboratory parameters, as captured within UPOD.[13] Alternative explanations for DIT were based on causes of thrombocytopenia reported in different textbooks on hematology.[18-21] Treatment with chemotherapy was taken into account as alternative diagnosis, since the study concerned potential immune-mediated DIT and not DIT due to myelotoxicity that is caused by chemotherapy. The alternative diagnoses for DIT were grouped into (1) underlying hematologic disease, (2) congenital causes not included in ICD-9-CM code 287.33, (3) acquired immune causes, and (4) acquired nonimmune causes (Table 2 and Appendix I).

Table 2 Categories and most prevalent alternative diagnoses for drug-induced thrombocytopenia (DIT) in patients with thrombocytopenia according to platelet measurements and discharge diagnoses for thrombocytopenia

Alternative diagnosis	≥1 Platelet count below 100×10^9/L	Discharge diagnoses for thrombocytopenia
	n=2 817 (100%)	n=74 (100%)
Hospitalizations with one or more alternative diagnoses	2 714 (96.3%)	60 (81.1%)
Underlying hematologic disease	2 310 (82.0%)	45 (60.8%)
Anemia based on hemoglobin measurement	2 034 (72.2%)	36 (48.6%)
Blood transfusion (proxy for hematological instability)	1 791 (63.6%)	30 (40.5%)
Leucopenia based on white blood cell measurement	903 (32.1%)	15 (20.3%)
Neutropenia based on neutrophil measurement	827 (29.4%)	12 (16.2%)
Congenital causes not included in ICD-9-CM code 287.33	10 (0.3%)	0 (0.0%)
Acquired immune causes	125 (4.4%)	5 (6.8%)
Acquired nonimmune causes	2 612 (92.7%)	50 (67.6%)
Bleeding	298 (10.6%)	7 (9.5%)
Cardiac surgery with cardiopulmonary bypass	477 (16.9%)	7 (9.5%)
Chemotherapy	372 (13.2%)	4 (5.4%)
Hematologic malignancy	628 (22.3%)	6 (8.1%)
Pregnancy [a]	415 (14.7%)	6 (8.1%)
Surgery	1 515 (53.8%)	17 (23.0%)

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification
a) Proxy for gestational (incidental) thrombocytopenia.

Outcomes

The ratio of the number of patients with potential DIT based on platelet measurements to the number of patients with potential DIT based on discharge diagnoses for thrombocytopenia was determined. In addition, it was investigated whether patients that were identified as patients with potential DIT based on platelet measurements were also identified as patients with potential DIT based on discharge diagnoses for thrombocytopenia, and vice versa.

Data handling

Data selection, transformation and analysis was performed using SAS Software, version 9.0 of the SAS System for Windows (© 2004, SAS Institute Inc., Cary, NC, USA) under Windows XP.

RESULTS

Within the study period there were 56 411 clinical hospitalizations for 41 112 unique patients. In 27 984 patients (49.6%) at least one platelet count was measured at any time during hospitalization. In 2817 (5.0%) patients there was at least one platelet count below 100×10^9/L during hospitalization. In 2714 (96.3%) of the patients there was at least one alternative diagnosis for DIT present during hospitalization (Table 2 and Appendix I), resulting in 103 (0.2%) patients with potential DIT based on platelet measurements. A discharge diagnosis for thrombocytopenia was registered for 74 (0.1%) patients, mostly concerning unspecified thrombocytopenia, followed by primary and secondary thrombocytopenia (Table 3). In 60 of these patients (81.1%) there was at least one alternative diagnosis for DIT present during

Table 3 Potential drug-induced thrombocytopenia based on a discharge diagnosis of thrombocytopenia

Discharge diagnosis for thrombocytopenia	Hospitalizations with a discharge diagnosis for thrombocytopenia	Hospitalization with a discharge diagnosis for thrombocytopenia without alternative diagnoses
	n	n (%)
Any	74	14 (18.9%)
Primary	29	9 (31.0%)
Secondary	11	1 (9.1%)
Unspecified	34	4 (11.8%)

hospitalization (Table 2 and Appendix I), resulting in 14 (0.02%) patients with potential DIT based on a discharge diagnosis for thrombocytopenia. Comparison of the number of patients with potential DIT based on platelet measurements and based on discharge diagnoses for thrombocytopenia resulted in a ratio of seven (103 vs. 14).

In both patients with at least one platelet below 100×10^9/L and patients with a discharge diagnosis for thrombocytopenia, underlying hematologic diseases (severe anemia, severe leukopenia/neutropenia, blood transfusion) and acquired nonimmune causes (surgery [mostly cardiac], pregnancy, and hematologic malignancy) were the most prevalent alternative diagnoses for DIT present (Table 2 and Appendix I).

There were twelve patients who were identified as having potential DIT using both platelet measurements and discharge diagnoses for thrombocytopenia (Figure 1).

Figure 1 **Patients identified as having potential drug-induced thrombocytopenia (DIT) based on platelet measurements compared with patients identified as having potential DIT based on discharge diagnoses for thrombocytopenia.**

		Potential DIT based on platelet measurement		
		Yes	**No**	**Total**
Potential DIT based on discharge diagnoses for thrombocytopenia	**Yes**	12	2 [a]	14
	No	91	12 913	13 004
	Total	103	12 915	13 018 [b]

a) In one patient no platelet count was performed, in the other patient the platelet count did not drop below 100×10^9/L during admission.
b) There were 13 018 patients without alternative diagnoses for DIT.

This corresponds with 11.6% of the patients with potential DIT based on platelet measurements and 85.7% of the patients with potential DIT based on discharge diagnoses for thrombocytopenia. For one patient with potential DIT based on a discharge diagnosis for thrombocytopenia who was not identified with platelet measurements no platelet measurements was performed; for another patient with potential DIT based on a discharge diagnosis for thrombocytopenia who was not identified with platelet measurements the platelet count did not drop below 100×10^9/L during admission (Figure 1).

DISCUSSION

In this study the use of platelet measurements was found to result in the identification of seven times more patients with potential DIT than the use of discharge diagnoses for thrombocytopenia, suggesting that platelet measurements are a more sensitive identifier for DIT than ICD-coded discharge diagnoses for thrombocytopenia. In this study the identification of patients with potential and not actual DIT was investigated, because such case-finding would be the first step in an epidemiological investigation of DIT. Patients with potential DIT are cases that need further detailed medical chart review to determine whether DIT actually occured. Studying methods for case-finding is important because a more complete identification of patients with potential DIT could lead to a more complete identification of patients with actual DIT, and therefore to more statistical power and less bias in pharmacoepidemiological studies on DIT. A potential increase in statistical power is relevant, since our recent population-based study on the relative risk for DIT, using a source population of >2 million patients during 13 years, and discharge diagnoses for thrombocytopenia as case identifier, lacked sufficient power to evaluate the risk of DIT in patients using drugs with lower exposure frequency.[7]
The strength of this study lies in the use of complete and validated automated data available within UPOD.[13] However, this study is potentially limited because UPOD comprises data from only one hospital. Because differences in characteristics of patient populations may exist, as well as differences between hospitals regarding the process of registration of discharge diagnoses or in the practice of requesting platelet measurements, we have to be careful in extrapolating our findings to other settings.
In this study, potential DIT based on platelet measurements was defined by a commonly used definition of DIT: a platelet count below 100×10^9 platelets/L without alternative diagnoses.[15,16] When a lower cutoff for the platelet count was used, the ratio of the number of patients with potential DIT based on platelet measurements to the number of patients with potential DIT based on discharge diagnoses for thrombocytopenia decreased. For example, considering a platelet count of 50×10^9 platelets/L as cutoff value in defining potential DIT would have resulted in 28 patients with potential DIT based on platelet measurements, and, consequently in a ratio of 2.0 between both case-finding approaches (i.e. 28 vs. 14 patients with potential DIT based on discharge diagnoses for thrombocytopenia). This suggests that a discharge diagnosis for thrombocytopenia is more likely to be registered in case of severe thrombocytopenia. Comparable findings were made for the registration of a discharge diagnosis for hyponatremia in patients with low serum sodium levels.[22]

In addition to the sensitivity of discharge diagnoses and platelet measurements for identifying patients with DIT it is also important to consider the specificity of these identifiers for this purpose. Both platelet measurements and discharge diagnoses for thrombocytopenia can be considered as nonspecific identifiers for DIT, since there are many causes of thrombocytopenia, and no specific ICD code for DIT exists (Table 1). The finding that alternative explanations for DIT were present in 96.3% of the patients with a platelet count below 100×10^9/L, and in 81.1% of the patients with a discharge diagnosis for thrombocytopenia illustrates the nonspecificity of both identifiers for DIT. In case-finding of potential DIT with either identifier it is necessary to deal with the nonspecificity in order to limit an elaborative and time-consuming process of medical chart review. A way of dealing with the nonspecificity is excluding patients with all other causes for thrombocytopenia, as we did in the current study and in our previous study on the risk for DIT using discharge diagnoses for thrombocytopenia as the case identifier.[7] A potential limitation of this approach is that patients who experienced DIT in the presence of an alternative diagnosis for DIT are excluded, which reduces sensitivity.

From the current study it cannot be concluded whether the use of platelet measurements will result in the identification of more patients with actual DIT compared to the use of discharge diagnosis for thrombocytopenia. Future studies should look into the validation of these case-finding strategies by using detailed medical chart review. Such studies should also focus on the drugs associated with these validated cases, taking into account diagnostic criteria for DIT like exposure to drugs reported to cause thrombocytopenia, the time of onset of the thrombocytopenia in relation to the start of drug exposure, and improvement of the platelet count after drug withdrawal.

It has been reported that about 60-65% of the adverse drug reactions can be detected with a laboratory test;[23-25] for example drug-induced blood dyscrasias like anemia, neutropenia and thrombocytopenia, and drug-induced hyponatriemia or hyperkalemia. Laboratory data can be considered as identifier for patients potentially experiencing these adverse drug reactions. The relative sensitivity of platelet measurements compared to discharge diagnoses for thrombocytopenia found in the current study is illustrative for the potential value of using laboratory measurements for case-finding for pharmacoepidemiological research.[13] Two other population-based studies compared the presence of severe neutropenia and hyponatriemia based on discharge diagnoses with the presence of these conditions based on laboratory measurements, and found that discharge diagnoses could lead to an incomplete identification of patients.[22,26] Although we have to be cautious in generalizing the results from the current study, it is to be expected that the availability

of clinical laboratory data within database systems fit for pharmacoepidemiological research will increase the possibilities for conducting drug safety studies.

CONCLUSION

This study compared the identification of patients with potential DIT based on platelet measurements and based on discharge diagnoses. The use of platelet measurements was found to be a more sensitive approach to the identification of patients with potential DIT using discharge diagnoses for thrombocytopenia. The results of this study illustrate the potential value of clinical laboratory data for case-finding for pharmacoepidemiological research.

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REFERENCES

1. Kelly WN. Potential risks and prevention, Part 1: Fatal adverse drug events. Am J Health Syst Pharm 2001;58:1317-24.
2. Fung M, Thornton A, Mybeck K, Hsiao-Hui Wu J, Hornbuckle K, et el. Evaluation of the characteristics of safety withdrawals of prescription drugs from worldwide pharmaceutical markets-1960 to 1999. Drug Inf J 2001;35:293-317.
3. 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.
4. Van der Klauw MM, Goudsmit R, Halie MR, van't Veer MB, Herings RM, et al. A population-based case-cohort study of drug-associated agranulocytosis. Arch Intern Med 1999;159:369-74.
5. Huerta C, Garcia Rodriguez LA. Risk of clinical blood dyscrasia in a cohort of antibiotic users. Pharmacotherapy 2002;22:630-6.
6. Van Staa TP, Boulton F, Cooper C, Hagenbeek A, Inskip H, et el. Neutropenia and agranulocytosis in England and Wales: incidence and risk factors. Am J Hematol 2003;72:248-54.
7. Ten Berg MJ, Huisman A, Souverein PC, Schobben AF, Egberts AC, et al. Drug-induced thrombocytopenia: a population study. Drug Saf 2006;29:713-21.

8. Handoko KB, Souverein PC, van Staa TP, Meyboom RH, Leufkens HG, et al. Risk of aplastic anemia in patients using antiepileptic drugs. Epilepsia 2006;47:1232-6.
9. Risks of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special reference to analgesics. The International Agranulocytosis and Aplastic Anemia Study. JAMA 1986;256:1749-57.
10. CDC National Center for Health Statistics. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) [online]. Available from: http://www.cdc.gov/nchs/about/otheract/icd9/abticd9.htm. [Accessed 2008 Jul 10].
11. Strom BL. Overview of automated databases in pharmacoepidemiology. In: Strom BL, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd.; 2005. p. 219-22.
12. 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.
13. Ten Berg MJ, Huisman A, van den Bemt PM, Schobben AF, Egberts AC, et al. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. Clin Chem Lab Med 2007;45:13-9.
14. Van den Bemt PM, Meyboom RH, Egberts AC. Drug-induced immune thrombocytopenia. Drug Saf 2004;27:1243-52.
15. Standardization of definitions and criteria of causality assessment of adverse drug reactions. Drug-induced cytopenia. Int J Clin Pharmacol Ther Toxicol 1991;29:75-81.
16. George JN, Raskob GE, Shah SR, Rizvi MA, Hamilton SA, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998;129:886-90.
17. CBV Foundation. About the Classification of Medical Specialist Procedures (CMSV) [in Dutch: online]. Available from: http://www.cbv.nl.html. [Accessed 2008 Jul 10 2008].
18. McCrae KR. Thrombocytopenia. New York: Taylor and Francis; 2006.
19. Liles DK, Knupp CL. Disorders of primary hemostasis, quantitative and qualitative platelet disorders and vascular disorders. In: Harmening DM, editor. Clinical hematology and fundamentals of hemostasis. 4th ed. Philadelphia (PA): F.A. Davis Company; 2002. p. 471-94.
20. Gresele P, Page C, Fuster V, Vermylen J. Platelets in thrombotic and non-thromboctic disorders pathophysiology, pharmacology and therapeutics. Cambridge: Cambridge University Press; 2002.
21. Benichou C. Abnormal hematologic value. In: Benichou C, editor. Adverse drug reactions: a practical guide to diagnosis and management. Chichester: John Wiley & Sons; 1994.
22. 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.
23. Azaz-Livshits T, Levy M, Sadan B, Shalit M, Geisslinger G, et al. Computerized surveillance of adverse drug reactions in hospital: pilot study. Br J Clin Pharmacol 1998;45:309-14.
24. Levy M, Azaz-Livshits T, Sadan B, Shalit M, Geisslinger G, et al. Computerized surveillance of adverse drug reactions in hospital: implementation. Eur J Clin Pharmacol 1999;54:887-92.
25. Tegeder I, Levy M, Muth-Selbach U, Oelkers R, Neumann F, et al. Retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. Br J Clin Pharmacol 1999;47:557-64.

26. Petitti DB, Contreras R, Glowalla M, Miday R. Most severe neutropenia in individuals with no chronic condition did not result in a specific diagnosis. J Clin Epidemiol 2004;57:1182-7.

Appendix I Alternative diagnoses for DIT in patients with thrombocytopenia according to platelet measurements and discharge diagnoses for thrombocytopenia		
Alternative diagnosis [a]	**≥1 Platelet count below 100×10^9/L**	**Discharge diagnoses for trombocytopenia**
	n=2 817 (100%) [b]	**n=74 (100%)** [b]
Hospitalizations with ≥1 alternative diagnosis	2 714 (96.3%)	60 (81.1%)
Underlying hematologic disease	2 310 (82.0%)	45 (60.8%)
Agranulocytosis/neutropenia based on discharge diagnosis	44 (1.6%)	5 (6.8%)
Anemia based on discharge diagnosis	136 (4.8%)	6 (8.1%)
Anemia based on hemoglobin measurement	2 034 (72.2%)	36 (48.6%)
Blood transfusion (proxy for hematological instability)	1 791 (63.6%)	30 (40.5%)
Leucopenia based on white blood cell measurement	903 (32.1%)	15 (20.3%)
Neutropenia based on neutrophil measurement	827 (29.4%)	12 (16.2%)
Congenital causes not included in ICD-9-CM code 287.33	10 (0.3%)	0 (0.0%)
Bernard-Soulier syndrome	1 (0.0%)	0 (0.0%)
DiGeorge syndrome	1 (0.0%)	0 (0.0%)
Fanconi's anemia	7 (0.2%)	0 (0.0%)
Wiskott-Aldrich syndrome	1 (0.0%)	0 (0.0%)
Acquired immune causes	125 (4.4%)	5 (6.8%)
Collagen vascular diseases(polyarteritis nodosa, systemic lupus erythematosus)	19 (0.7%)	2 (2.7%)
Infections with HIV, varicella, measles, rubella, dengue, viral hepatitis, mumps, Epstein-Barr virus (infectious mononucleosis), cytomegalovirus, influenza	96 (3.4%)	2 (2.7%)
Neonatal isoimmune purpura	10 (0.3%)	1 (1.3%)
Acquired nonimmune causes	2 612 (92.7%)	50 (67.6%)
Aortic valve stenosis (proxy for turbulent circulation)	112 (4.0%)	1 (1.3%)
Aplastic anemia	69 (2.4%)	2 (2.7%)
Bacteremia / bacterial sepsis	156 (5.5%)	2 (2.7%)
Bleeding	298 (10.6%)	7 (9.5%)
Bone marrow metastases	31 (1.1%)	0 (0.0%)
Bone marrow or stem cell transplantation	225 (8.0%)	1 (1.3%)
Carcinoma	280 (9.9%)	7 (9.5%)
Cardiac surgery with cardiopulmonary bypass	477 (16.9%)	7 (9.5%)
Chemotherapy	372 (13.2%)	4 (5.4%)
Chronic alcoholism	15 (0.5%)	1 (1.3%)
Cyanotic heart disease	44 (1.6%)	0 (0.0%)
Diffuse intravascular coagulation (incl. neonatal)	6 (0.2%)	1 (1.3%)
Dys- or premature birth	171 (6.1%)	4 (5.4%)

Extra corporeal circulation	100 (3.5%)	4 (5.4%)
Graft versus host disease	65 (2.3%)	1 (1.3%)
Hemangiomas	3 (0.1%)	0 (0.0%)
Hematologic malignancy	628 (22.3%)	6 (8.1%)
Hemodialysis	41 (1.5%)	1 (1.3%)
Hemolytic uremic syndrome	4 (0.1%)	0 (0.0%)
Hypersplenism/splenomegaly (incl. secondary forms: sarcoidosis, polycythemia vera, Gaucher disease, amyloidosis, hereditary spherocytosis, hereditary elliptocytosis, thalassemia, sickle cell anemia, warm autoimmune hemolytic anemia, splenic sequestration, splenic tumour or cyst, subacute bacterial endocarditis, congestive heart failure, portal vein thrombosis, hepatic vein thrombosis, Felty's syndrome)	112 (4.0%)	5 (6.8%)
Intra-aortic balloon pumps	30 (1.1%)	3 (4.0%)
Iron deficiency	5 (0.2%)	1 (1.3%)
Large aortic aneurysm	73 (2.6%)	1 (1.3%)
Liver cirrhosis	54 (1.9%)	0 (0.0%)
Malaria	3 (0.1%)	0 (0.0%)
Meningitis	14 (0.5%)	0 (0.0%)
Metastatic carcinomas	125 (4.4%)	4 (5.4%)
Multiple organ failure and systemic inflammatory response syndrome (SIRS)	53 (1.9%)	2 (2.7%)
Myelodysplastic syndrome	27 (1.0%)	0 (0.0%)
Myelofibrosis	4 (0.1%)	0 (0.0%)
Paroxysmal Nocturnal Hemoglobinuria	3 (0.1%)	0 (0.0%)
Preeclampsia-eclampsia (incl. HELLP syndrome)	64 (2.3%)	0 (0.0%)
Pregnancy (proxy for gestational (incidental) thrombocytopenia)	415 (14.7%)	6 (8.1%)
Pregnancy-thrombosis	2 (0.1%)	0 (0.0%)
Prematurity-new born hypoxia	82 (2.9%)	3 (4.0%)
Radiation therapy	123 (4.4%)	0 (0.0%)
Septic shock	8 (0.3%)	0 (0.0%)
Solid organ transplantation	60 (2.1%)	1 (1.3%)
Surgery	1 515 (53.8%)	17 (23.0%)
Thrombotic Thrombocytopenic Purpura (TTP)	3 (0.1%)	0 (0.0%)
Tuberculosis	3 (0.1%)	0 (0.0%)

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; HELLP = Hemolysis Elevated Liver Enzymes and Low Platelets

a) May-Hegglin anomaly, Von Willebrand Disease, acute fatty liver of pregnancy, antiphospholipid syndrome, babesiosis, burns, cobalamin deficiency, ehrlichiosis, spirochetal infections, folic acid and vitamin B12 deficiency were also considered but found not to be present in any of the patients with thrombocytopenia.

b) Numbers do not add up to 100% because patients could have more than one alternative diagnosis.

4

STUDIES ON DRUG-INDUCED THROMBOCYTOPENIA USING CLINICAL LABORATORY AND MEDICATION DATA

4.)

CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

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Thrombocytopenia in adult oncology patients receiving cytostatic drug treatment: incidence and relative risk estimates from a retrospective hospital-based cohort using laboratory data

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ABSTRACT

Objective

To estimate the incidence and relative risk of thrombocytopenia in adult oncology patients treated with different cytostatic agents in clinical practice.

Methods

Single-center retrospective cohort study using data from the Utrecht Patient Oriented Database (UPOD) and the Regional Cancer Registry Middle Netherlands. Oncology patients receiving non-experimental chemotherapy regimens at the in- and outpatient clinical of University Medical Center Utrecht in the period 2004-2006 were included. First, the incidence of thrombocytopenia, considering four grades of severity, was determined, as well as the incidence of isolated thrombocytopenia (defined as a platelet count less than 100×10^9/L without concurrent anemia, leukopenia or neutropenia). Second, the incidence and relative risk of thrombocytopenia for different cytostatic agents, either used in monotherapy or in combination therapy, was estimated.

Results

614 patients receiving 19 different cytostatic agents in 39 different regimens were included. The incidence of grade 1-4 thrombocytopenia was 21.8%. The incidence of isolated thrombocytopenia was 6.2%. The highest incidences of thrombocytopenia were observed in carboplatin monotherapy (81.8%), carboplatin combination therapy (58.2%), gemcitabine combination therapy (64.4%) and paclitaxel combination therapy (59.3%). The highest relative risk of thrombocytopenia was observed for combination therapy of gemcitabine and carboplatin (relative risk [RR] 10.1; 95% confidence intervals [95%CI] 5.5–18.5) and for combination therapy of paclitaxel, carboplatin and etoposide (RR 11.8; 95%CI 6.7–20.8). The highest incidences of isolated thrombocytopenia were observed in combination therapies including oxaliplatin (28.6%) and gemcitabine (28.9%).

Conclusion

The results of this study indicate that thrombocytopenia occurs in about one out of five oncology patients treated with chemotherapy. Regimens including carboplatin, gemcitabine and paclitaxel carry the highest risk of thrombocytopenia. High incidences of isolated thrombocytopenia, possibly representing immune-mediated thrombocytopenia, were observed in patients receiving oxaliplatin and gemcitabine. Further research should focus on the incidence of immune-mediated

chemotherapy-induced thrombocytopenia and on risk factors and early warning markers of chemotherapy-induced thrombocytopenia.

INTRODUCTION

Many cytostatic agents are known to cause thrombocytopenia in normal doses,[1] most frequently by inducing aplasia or hypoplasia of the megakaryocytic cells of the bone marrow.[1,2] The interference of cytostatic agents with blood cell replication in the bone marrow is the same mechanism that is intended in the treatment of cancer. Cytostatic agents can also cause thrombocytopenia, though far less frequently, by immune-mediated mechanisms.[1] Data on the incidence and relative risk of thrombocytopenia in cytostatic drug treatment are scarce. Most data on the incidence of thrombocytopenia originate from phase II and phase III clinical trials. However, these data may be unrepresentative for clinical practice due to strict inclusion criteria in clinical trials. In addition, the limited sample size of clinical trials prohibits the detection of rare adverse events like immune-mediated thrombocytopenia.[3] Results from a recent study concerning breast cancer patients suggest that the incidence of chemotherapy-related serious adverse events, including hematotoxicity, may be higher in clinical practice than reported in large clinical trials.[4] Three large population-based studies performed in the 1980s and 1990s showed incidences of thrombocytopenia (defined as a platelet count < 100×10^9/L) of 36.3% in patients with gynaecologic cancer and of 19–24% in patients with a solid tumor (thrombocytopenia defined as a platelet count < 50×10^9/L).[5-7] Whether these data are still valid for cytostatic therapies used in current clinical practice is unknown. To our knowledge no data are available on the relative risk of thrombocytopenia for different regimens used in clinical practice. In this manuscript we report the results of a single-center retrospective cohort study aimed at determining the incidence and relative risk of thrombocytopenia in a population of adult oncology patients receiving non-experimental chemotherapy treatment for solid tumors in the in- and out patient setting.

PATIENTS AND METHODS

Data sources and setting

Data from the Utrecht Patient Oriented Database (UPOD) and the Regional Cancer Registry (RCR) Middle Netherlands were used. UPOD is a data platform for clinical

epidemiological research encompassing administrative and clinical data collected during clinical care for all patients treated at the University Medical Center Utrecht (UMC Utrecht). The UMC Utrecht is a 1042-bed academic teaching hospital in the center of The Netherlands. The structure and content of UPOD have been described in detail elsewhere.[8] UPOD data acquisition and data management is in line with current Dutch regulations concerning privacy and ethics and is approved by the institution's medical ethics committee. The RCR is a patient registry of disease- and treatment-related information of all new cancer patients in the central part of The Netherlands and is imbedded in the Comprehensive Cancer Center Middle Netherlands (CCCMN). The CCCMN does not treat patients, but fosters expertise and multidisciplinary cohesion in (regional) cancer care. PALGA, the Dutch network and registry of histo- and cytopathology, notifies the CCCMN of all newly diagnosed malignancies. Following this notification, trained registry personnel from the CCCMN collect data on diagnosis, staging and treatment from hospital records, including pathology and surgery reports. Case ascertainment is provided by the national hospital discharge database, which receives discharge diagnoses of patients admitted from all hospitals in The Netherlands. For the current study we obtained data on the tumor diagnosis from the RCR for patients receiving chemotherapy treatment at the UMC Utrecht. The design and data abstraction process of the current study have been approved by the supervisory committee of the RCR.

Study population

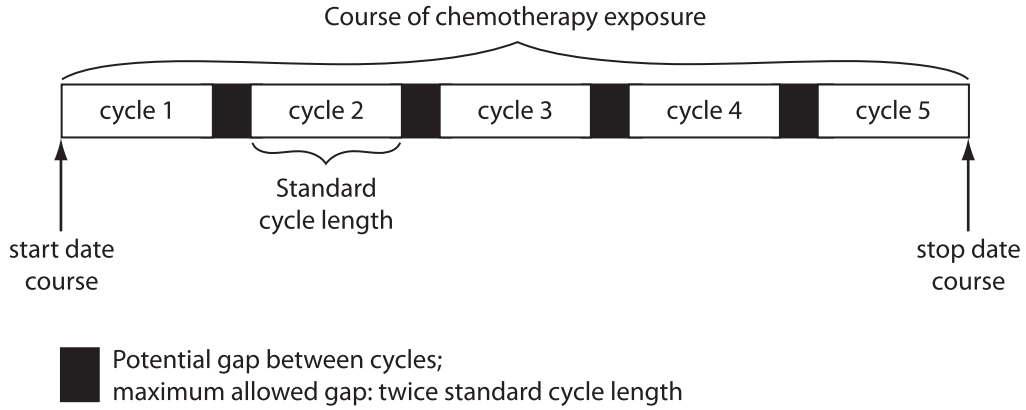
The study population comprised adult oncology patients who received their first course of non-experimental chemotherapy for any type of solid tumor at the in- or outpatient clinic of the UMC Utrecht in the period of 1 January 2004 to 31 December 2006. The selection of the study population followed several consecutive steps. Initially, patients who received a non-experimental chemotherapy regimen that was indicated for the treatment of a solid tumor (based on information from the electronic chemotherapy order entry system) within the study period at the UMC Utrecht were identified from UPOD. Per patient the first course of cytostatic drug therapy in the study period was identified. The patient was excluded if this first course was not the first course ever at the UMC Utrecht. In addition, patients whose course continued after the end of the study period were excluded in order to exclusively include patients with complete cytostatic exposure data. Furthermore, patients without a baseline platelet count (i.e. within 30 days before the start of the course, including the start date) or without a follow-up platelet count during the course were excluded. Finally, patients with thrombocytopenia at baseline

(i.e. baseline platelet count less than 100×10^9 platelets/L) were excluded. Data on solid tumor diagnoses for the included patients were obtained from the RCR. We selected solid tumors coded with the topography codes C00-C41 and C44-C80 and the morphology codes 800-958 according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3).[9] Patients without diagnostic tumor information within the RCR were excluded, as were patients with a registry of a hematological malignancy within the RCR.

Chemotherapy exposure

Per patient one period of consecutive exposure to a specific chemotherapy regimen was studied. This period was called a *course* of chemotherapy treatment. The course was constructed from consecutive automated medications orders for *cycles* of chemotherapy (i.e. one round of chemotherapy), as illustrated in Figure 1. Cycles

Figure 1 Definition of a cycle and a course of chemotherapy treatment



of chemotherapy that did not immediately follow each other in time were still considered consecutive when the gap between the cycles did not exceed twice the standard cycle length (Figure 1). The start date of the first cycle was considered the start date of the course. The theoretical end date of the last cycle, calculated as the start date of the last cycle plus the standard length of the cycle, was considered as the end date of the course. The duration of the course was determined by substracting the end and the start date of the course. Per course the individual cytostatic agents that were part of the regimen were identified.

Thrombocytopenia

The occurence of thrombocytopenia within the course of chemotherapy exposure was determined by using data on platelet count measurements from the laboratory information system. Thrombocytopenia was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events as a platelet count less than the local lower limit of normal,[10] i.e. 100×10^9 platelets/L. In addition, grades of severity of thrombocytopenia were defined according to these criteria: grade 1 ($75–100\times10^9$/L), grade 2 ($50–74\times10^9$/L), grade 3 ($25–49\times10^9$/L) and grade 4 ($< 25\times10^9$/L).[10] Grade 1 thrombocytopenia is considered to have no clinical relevance, but with grade 2-4 thrombocytopenia the risk of bleeding is increased and clinical observation of the patient is required.[1] For patients with thrombocytopenia the date and value of the first platelet count less than 100×10^9/L was identified, as well as for the lowest platelet count within the course. The lowest platelet count was considered as the platelet count nadir. Furthermore, the occurence of isolated thrombocytopenia within the course of chemotherapy exposure was determined. Isolated thrombocytopenia was considered as a proxy for immune-mediated thrombocytopenia and was defined as a platelet count less than 100×10^9/L without anemia (hemoglobin > 9.7 g/dL), leukopenia (leucocyte count > 4.0×10^9/L) and neutropenia (neutrophil granulocyte count > 1.5×10^9/L).

Data analysis

The incidence of thrombocytopenia, defined as the percentage of patients who developed thrombocytopenia during the course of chemotherapy exposure, was determined. The incidence of thrombocytopenia was stratified by grades of severity considering the platelet count nadir. Additionally, the incidence of isolated thrombocytopenia, defined as the percentage of patients who developed isolated thrombocytopenia during a course of chemotherapy exposure, was determined. The median number of days to the first occurrence of thrombocytopenia since the start date of the course and the median number of days to the platelet count nadir were determined for patients with thrombocytopenia. In addition, the mean value of the first platelet count below 100×10^9/L and the mean value of the platelet count nadir were calculated.

The incidences of both thrombocytopenia and isolated thrombocytopenia were stratified by exposure to specific cytostatic agents. When a cytostatic agent was used both as monotherapy and as combination therapy separate frequency estimates for mono and combination therapy were determined. Finally, the association between exposure to a cytostatic agent and thrombocytopenia was assessed and expressed as relative risk with 95% confidence interval (95%CI). Exposure to cisplatin

monotherapy was chosen as reference category, because of the large number of patients exposed. For cytostatic agents that were used in mono and combination therapy separate relative risk estimates were obtained. For cytostatic agents for which a high incidence of thrombocytopenia was observed, the most frequently used regimens containing these agents were identified. For these regimens the incidence and relative risk of thrombocytopenia were estimated.

RESULTS

We initially identified 676 adult patients who received their first course of a non-experimental chemotherapy regimen at the UMC Utrecht in the period 2004–2006. For 62 patients reasons for exclusion were present: 36 patients could not be found in the RCR. In the RCR data 7 patients were reported to have a lymphoma based on tumor morphology data. For 8 patients no baseline platelet count was available in UPOD and for another 5 patients no follow-up platelet count was available. Finally, 6 patients had thrombocytopenia at baseline. This led to the inclusion of 614 patients in the study. The patient characteristics, the tumor diagnosis and the hematological parameters at the start of the course for the included patients are presented in Table 1. Female and male patients were equally included. On average patients were 54 years old at the start of the course. Patients were diagnosed with 14 different types of malignancies based on the major ICD-O-3 categories. Six types of malignancies were most frequent: lip, oral cavity and pharynx cancer, digestive organ cancer (incl. colon), respiratory system and intrathoracic organs (incl. small cell and non small cell lung cancer), breast, female genital organs (incl. cervix, endometrium and ovarium) and male genital organs (incl. prostate). The median number of days between the date of tumor diagnosis and the date of start of the first course of chemotherapy treatment was 73 days (interquartile range 39–331). The patients were treated with 39 different regimens, including 19 different cytostatic agents. Details on the regimens and the frequency in which they were present in the study are presented in Appendix 1. The regimens concerned monotherapy and combination therapy. The cytostatics dacarbazine, mitoxantrone and temozolomide were only given as monotherapy. Cyclophosphamide, ifosfamide, gemcitabine, etoposide, paclitaxel, epirubicine, bleomycine and mitomycine were only used in combination with other cytostatic agents. Methotrexate, fluorouracil, docetaxel, doxorubicine, cisplatin, carboplatin and oxaliplatin were used in both mono- and combination therapy. The median length of a course was 65 days (range 43–105). Thrombocytopenia at any moment during the course occurred in 134 patients,

Table 1 Characteristics of the study population	
Patient demographics	**n=614 (100%)**
Female	312 (50.8%)
Average age at start of first chemotherapy treatment within the study period (sd)	54 (13)
age 18–39 years	87 (14.2%)
age 40–59 years	278 (45.3%)
age ≥ 60 years	249 (40.6%)
Primary tumor site (ICD-0-3 major categories)	
Lip, oral cavity and pharynx	90 (14.7%)
Digestive organs	72 (11.7%)
Respiratory system and intrathoracic organs	86 (14.0%)
Skin	23 (3.7%)
Peripheral nerves and autonomic nervous system	2 (0.3%)
Retroperitoneum and peritoneum	9 (1.5%)
Connnective, subcutaneous and other soft tissue	7 (1.1%)
Breast	109 (17.8%)
Female genital organs	78 (12.7%)
Male genital organs	84 (13.7%)
Urinary tract	20 (3.3%)
Eye, brain and other parts of the central nervous system	14 (2.3%)
Thyroid and other endocrine glands	2 (0.3%)
Unknown primary site	18 (2.9%)
Blood cell counts at baseline	
Mean platelet count $\times 10^9$/L (sd)	324 (126)
Mean hemoglobin in g/dL (sd)[a]	12.9 (1.7)
Hemoglobin ≤ 6.0 g/dL	16 (2.6%)
Mean leucocyte count $\times 10^9$/L (sd)[a]	9.1 (5.0)
Leucocyte count ≤ 4.0×10^9/L	12 (2.0%)
Mean neutrophil granulocyte count $\times 10^9$/L (sd)[b]	6.3 (3.2)
Neutrophil granulocyte count ≤ 1.6×10^9/L	3 (0.5%)

a) Mean value calculated for part of the study population; n=602.
b) Mean value calculated for part of the study population; n=427.

resulting in an incidence of 21.8%. In Table 2 the severity of the thrombocytopenia based on the platelet count nadir is presented.

Based on this severity classification the incidence of grade 2-4 thrombocytopenia was 11.9% (n=73), the incidence of grade 3-4 thrombocytopenia 6.8% (n=42) and the incidence of grade 4 thrombocytopenia 3.3% (n=20). Isolated thrombocytopenia occurred in 38 patients, resulting in an incidence of 6.2%.

Table 2	Incidence of thrombocytopenia based on the platelet count nadir classified by grades of severity
Grade [a]	**n=614 (100%)**
1	61 (9.9%)
2	31 (5.0%)
3	22 (3.6%)
4	20 (3.3%)

a) Grade 1: 75–100×10^9; the lower limit of normal (LLN) was defined as 100×10^9/L; grade 2: 50–74×10^9 platelets/L; grade 3: 25–49×10^9 platelets/L ; grade 4: < 25×10^9 platelets/L

Thrombocytopenia was detected for the first time after a median number of 35 days (range 14–57) following the start date of the course. The platelet count nadir in patients with thrombocytopenia, mean value 62 (sd 28), was measured after a median number of 43 days (range 15–67).

The incidence of thrombocytopenia stratified by cytostatic agent is presented in the third column of Table 3. The highest incidences of thrombocytopenia were observed in carboplatin monotherapy (81.8%), combination therapies including carboplatin (58.2%), combination therapies including gemcitabine (64.4%) and combination therapies with paclitaxel (59.3%). In the last column of Table 3 the incidence of isolated thrombocytopenia stratified by cytostatic agent is presented. The incidence of isolated thrombocytopenia was highest in patients treated with combination therapies including oxaliplatin (28.6%) and in patients treated with combination therapies including gemcitabine (28.9%).

The relative risk of thrombocytopenia per cytostatic agent, either in mono- or combination therapy, compared to receiving cisplatin monotherapy is presented in the fourth column of Table 3. The highest relative risks were found for carboplatin monotherapy (relative risk [RR] 9.7; 95%CI 5.1–18.2) and gemcitabine in combination therapy (RR 7.6; 95%CI 4.2-14.0). Carboplatin, gemcitabine and paclitaxel were identified as the cytostatic agents with the highest incidence of thrombocytopenia. In Figure 2 the severity of thrombocytopenia based on the platelet count nadir is presented for patients with any chemotherapy regimen including carboplatin, gemcitabine or paclitaxel. The vertical lines represent the categories of severity of thrombocytopenia. The figure shows that thrombocytopenia with carboplatin, gemcitabine and paclitaxel exposure is relatively high for all grades of severity of thrombocytopenia. On the bottom rows of Table 3 the incidence and relative risk of thrombocytopenia for the most frequently used regimens including gemcitabine, carboplatin or paclitaxel are presented. The highest relative risk was observed for combination therapy with gemcitabine and carboplatin

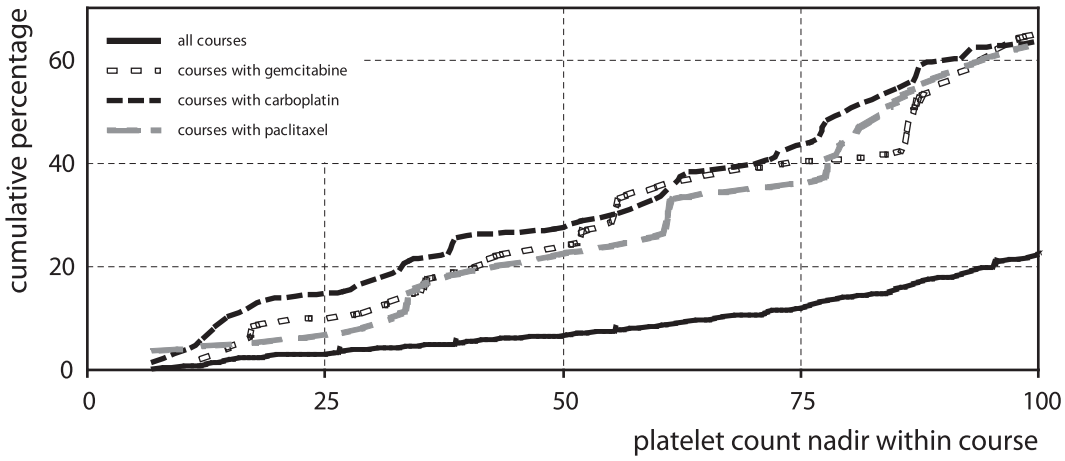
Table 3	Incidence and relative risk of thrombocytopenia				
Type of cytostatic drug	**Mono or combination therapy**	**n**	**Incidence of thrombocytopenia**	**RR of thrombo-cytopenia compared to cisplatin monotherapy**	**Incidence of isolated thrombocytopenia**
			n (%)	**RR (95%CI)**	**n (%)**
Alkylating agents					
cyclophosphamide	combination	131	17 (13.0%)	1.5 (0.7-3.1)	3 (2.3%)
ifosfamide	combination	14	5 (35.7%)	4.2 (1.7-10.4)	0 (0.0%)
dacarbazine	mono	21	2 (9.5%)	1.1 (0.3-4.7)	0 (0.0%)
temozolomide	mono	13	3 (23.1%)	2.7 (0.9-8.5)	1 (7.7%)
Antimetabolites					
methotrexate	mono	22	2 (9.1%)	1.1 (0.2-4.5)	1 (4.5%)
	combination	1	0 (0.0%)	NA	0 (0.0%)
fluorouracil	mono	5	0 (0.0%)	NA	0 (0.0%)
	combination	114	20 (17.5%)	2.1 (1.0-4.1)	11 (9.6%)
gemcitabine	combination	45	29 (64.4%)	7.6 (4.2-14.0)	13 (28.9%)
capecitabine	mono	5	0 (0.0%)	NA	0 (0.0%)
	combination	17	5 (29.4%)	3.5 (1.4-8.8)	3 (17.6%)
Plant alkaloids and other natural products					
etoposide	combination	84	31 (36.9%)	4.4 (2.3-8.2)	3 (3.6%)
paclitaxel	combination	27	16 (59.3%)	7.0 (3.7-13.4)	3 (11.1%)
docetaxel	mono	30	2 (6.7%)	0.8 (0.2-3.4)	0 (0.0%)
	combination	8	0 (0.0%)	NA	0 (0.0%)

Cytostatic antibiotics and related substances					
doxorubicine	mono	11	0 (0.0%)	NA	0 (0.0%)
	combination	67	13 (19.4%)	2.3 (1.1-4.8)	1 (1.5%)
epirubicine	combination	84	10 (11.9%)	1.4 (0.6-3.2)	5 (5.9%)
mitoxantrone	mono	11	0 (0.0%)	NA	0 (0.0%)
bleomycine	combination	37	6 (16.2%)	1.9 (0.8-4.8)	2 (5.4%)
mitomycine	combination	25	7 (28.0%)	3.3 (1.4-7.7)	1 (4.0%)
Platinum compounds					
cisplatin	mono	130	11 (8.5%)	1.0 (reference)	2 (1.5%)
	combination	131	44 (33.6%)	4.0 (2.1-7.3)	14 (10.7%)
carboplatin	mono	11	9 (81.8%)	9.7 (5.1-18.2)	0 (0.0%)
	combination	55	32 (58.2%)	6.9 (3.7-12.6)	9 (16.4%)
oxaliplatin	mono	2	1 (50.0%)	5.9 (1.3-26.4)	0 (0.0%)
	combination	28	10 (35.7%)	4.2 (2.0-9.0)	8 (28.6%)
Combination therapies including cytostatic agents most frequently associated with high risk of thrombocytopenia					
gemcitabine + carboplatin		14	12 (85.7%)	10.1 (5.5-18.5)	5 (35.7%)
gemcitabine + cisplatin		31	17 (54.8%)	6.5 (3.4-12.4)	8 (25.8%)
paclitaxel + carboplatin		19	9 (47.4%)	5.6 (2.7-11.7)	3 (15.8%)
paclitaxel + carboplatin + etoposide		7	7 (100%)	11.8 (6.7-20.8)	0 (0.0%)
carboplatin + docetaxel		8	0 (0.0%)	NA	0 (0.0%)

RR = relative risk; NA = not applicable

(RR 10.1; 95%CI 5.5-18.5) and combination therapy with paclitaxel, carboplatin and etoposide (RR 11.8; 95%CI 6.7–20.8).

Figure 2 **Cumulative incidence of the platelet count nadir per course of chemotherapy treatment**



DISCUSSION

This study primarily aimed to quantify the incidence of thrombocytopenia in oncology patients treated with non-experimental regimens of chemotherapy in the clinical care setting and to compare the risk between different cytostatic agents. Thrombocytopenia was found to occur in about one in five patients. In 55% of these patients the thrombocytopenia was of a severity that can be considered as clinically relevant (grade 2-4). Regimens including carboplatin, gemcitabine and paclitaxel were found to carry the highest risk of thrombocytopenia. In addition, the incidence of isolated thrombocytopenia was investigated. The highest incidences of isolated thrombocytopenia were found for patients receiving regimens including oxaliplatin and gemcitabine.

Few population-based data are available to compare our findings with. Data from two large retrospective studies, published in 1984 and 1990, indicated that grade 3-4 thrombocytopenia occurs in about 19–24% of patients receiving dose-intensive myelosuppression chemotherapy for solid tumors or lymphoma.[5,7] In the current study, including patients with solid tumors and all types of chemotherapy, we

observed an incidence of 6.8% of grade 3-4 thrombocytopenia. A retrospective analysis of patients with gynaecological cancer, published in 1994, showed an incidence of thrombocytopenia (platelet count < 100×10^9/L) of 36.3%.[6] In the current study we observed a platelet count < 100×10^9/L in 20.5% of patients with gynaecological cancer (ICD-0-3 category female genital organs, C51-C58). To our knowledge more recent population-based data on the incidence of thrombocytopenia in oncology patients can not be found in the literature, except from data of a large prospective study that was presented at the ASCO annual meeting in 2006. In that study thrombocytopenia, defined as a platelet count less than 150×10^9/L, occurred in 47% of the patients and grade 2-4 thrombocytopenia (platelet count < 75×10^9/L) was found in 12.4%. The latter estimate is comparable to our observation of 11.9%.[11]

We stratified the incidence of thrombocytopenia by cytostatic agent. Many cytostatic agents included in this study were used in combination therapy. In interpreting the presented incidence estimates for these agents the fact that other drugs in the regimen may have been responsible for the observed thrombocytopenia needs to be considered. Detailed investigation into the causal agent was not performed and may in most cases be inconclusive since agents are often administered on the same day or on consecutive days. In addition, from a clinical perspective knowledge on the risk of thrombocytopenia associated with the regimen seems more relevant, since most regimens concern combination therapy. We observed the highest incidence of thrombocytopenia in patients treated with carboplatin, either in monotherapy or in combination therapy. Organoplatinum agents, especially carboplatin, are well-known for causing dose-limiting thrombocytopenia.[1] The area under the curve (AUC) that is targeted in dosing carboplatin is correlated with the platelet count nadir, often resulting in platelet counts below 100×10^9 platelets/L.[12] The observed incidence of thrombocytopenia in cisplatin monotherapy was much lower than for carboplatin. Noteworthy, however, is the difference in incidence of thrombocytopenia in patients with cisplatin in combination therapy compared to patients treated with cisplatin monotherapy. This observation gives rise to the questions whether the other drug(s) in the regimen cause thrombocytopenia or whether the combination of cisplatin and other drugs leads to thrombocytopenia. We were not able to unravel this question, but cisplatin is frequently administered in combination regimens with gemcitabine. Gemcitabine was identified as having a clearly increased relative risk of thrombocytopenia, so this may explain the high incidence for cisplatin combination therapies. Besides for organoplatinum agents, dose-limiting thrombocytopenia has been reported to be common in treatment with nitrosoureas, anthracyclines, podophyllotoxin, most

alkylating agents and anthraquinones.[1] We could not estimate the incidence of thrombocytopenia in nitrosurea treatment, because these cytostatic agents were not used in the study population. The results of our study indicate that the incidence of thrombocytopenia is relative high for the anthracycline-drug doxorubicine, the podophyllotoxin etoposide, and the alkylating agent ifosfamide. For the anthraquinone mitoxantrone a low incidence of thrombocytopenia was found. Thrombocytopenia has been reported to be infrequent in treatment with vinca-alkaloids and some antimetabolites, like fluorouracil.[1] We could not estimate the incidence of thrombocytopenia in vinca-alkaloid treatment, because these drugs were not used in the study population. In patients exposed to antimetabolites we observed diverse frequencies: a low incidence for methotrexate, fluorouracil and capecitabine monotherapy, a higher incidence for capecitabine in combination therapy and a high incidence for exposure to gemcitabine in combination therapy.
To our knowledge, the incidence of isolated thrombocytopenia has never been investigated as such before. Because of the low incidence, immune-mediated adverse drug reactions are often not detected in clinical trials, but they can be clinically relevant when the drug is used in large populations of patients.[13] We considered isolated thrombocytopenia as a proxy for thrombocytopenia caused by an immune-mediated mechanism, although we acknowledge that isolated thrombocytopenia can also be the consequence of selective suppression of the megakaryocytopoiesis.[14] The highest incidence of isolated thrombocytopenia was observed in patients treated with combination therapies including oxaliplatin and gemcitabine. We did not further investigate which drug of the regimen was most likely to be the causal agent of the isolated thrombocytopenia. In addition, it was not possible to determine whether immune-mediated thrombocytopenia was truly present, because this can only be confirmed by determination of the presence of drug-related antibodies, for which no tests were performed. However, we believe that the observation of the high incidence of isolated thrombocytopenia in patients receiving oxaliplatin is of special interest, because recently several case reports for thrombocytopenia due to hypersensitivity reactions to oxaliplatin have been published.[15-17] For decision making in clinical practice knowledge on the mechanism by which cytostatic agents cause thrombocytopenia is important. When the thrombocytopenia is immune-mediated renewed exposure to the suspected agent should be avoided, whereas myelosuppression-related thrombocytopenia may be prevented in subsequent cycles by dose adjustment. We propose further research, including testing for drug-related antibodies, to determine the incidence of immune-mediated thrombocytopenia in patients treated with chemotherapy.

For this study a patient-oriented automated database with data collected in patient care was used. Such databases are widely used in pharmacoepidemiological research and provide opportunities for estimating the risk of adverse effects of cytostatic drugs on a population level, including hematotoxicity. In two recent database studies incidences of thrombocytopenia of 0.6% and 5.5% (in combination with neutropenia) were found.[4,18] In these studies hospital discharge diagnoses were used to identify patients with thrombocytopenia. It has been suggested that hospital diagnoses might lead to underidentification of patients with thrombocytopenia,[19] and that platelet measurements are a more sensitive case-finder for drug-induced thrombocytopenia.[20] In the current study we used platelet measurements to identify thrombocytopenia and for breast cancer patients we found an incidence of 6.4%.

A number of potential limitations of this study need to be addressed. First, UPOD currently comprises data of only one institution. As a consequence, exposure data are limited in numbers, possibly limiting the power of the study. In addition, because of possible differences in patient population or treatment practice we have to be careful in extrapolating the results from the current study to different settings. Second, in clinical practice platelet counts are obtained on fixed points in time, i.e. when the patients comes for evaluation during the cycle or for a new round of chemotherapy. The day the blood count is checked may not necessarily be the day that the platelet count nadir for a specific cytostatic agent is expected. For that reason platelet count nadirs below 100×10^9/L may have remained undetected, resulting in an underestimation of the true incidence. However, it seems unlikely that these potentially missed thrombocytopenias were clinically relevant. Despite these limitations, this study contributes to the knowledge on the incidence of thrombocytopenia and isolated thrombocytopenia in oncology patients treated with chemotherapy in clinical practice. Severe thrombocytopenia can be a life-threatening complication and it may be useful for prevention of thrombocytopenia to identify patients at high risk of thrombocytopenia. The identification of potential patient and treatment related risk factors and potential biomarkers ('early warning markers') for thrombocytopenia should be subject of further research.

CONCLUSION

This study contributes to better knowledge on the incidence and relative risk of thrombocytopenia in adult oncology patients treated with current chemotherapy regimens in clinical practice. We found an incidence of thrombocytopenia of 21.8% and an incidence of isolated thrombocytopenia of 6.2%. In 55% of the patients with

thrombocytopenia the severity could be considered clinically relevant. Regimens including carboplatin, gemcitabine and paclitaxel were found to carry the highest risk of thrombocytopenia. High incidences of isolated thrombocytopenia, possibly representing immune-mediated thrombocytopenia, were observed in patients receiving oxaliplatin and gemcitabine. Because the underlying mechanism of thrombocytopenia is clinically relevant, further research is needed to determine the risk of immune-mediated thrombocytopenia for different cytostatic agents. Finally, future research should focus on identifying risk factors and early warning markers for thrombocytopenia.

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REFERENCES

1. Jelic S, Radulovic S. Chemotherapy-associated thrombocytopenia: Current and emerging management strategies. Am J Cancer 2006;5:371-82.
2. Zeuner A, Signore M, Martinetti D, Bartucci M, Peschle C, et al. Chemotherapy-induced thrombocytopenia derives from the selective death of megakaryocyte progenitors and can be rescued by stem cell factor. Cancer Res 2007;67:4767-73.
3. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004;329:44-7.
4. Hassett MJ, O'Malley AJ, Pakes JR, Newhouse JP, Earle CC. Frequency and cost of chemotherapy-related serious adverse effects in a population sample of women with breast cancer. J Natl Cancer Inst 2006;98:1108-17.
5. Dutcher JP, Schiffer CA, Aisner J, O'Connell BA, Levy C, et al. Incidence of thrombocytopenia and serious hemorrhage among patients with solid tumors. Cancer 1984;53:557-62.

6. Goldberg GL, Gibbon DG, Smith HO, DeVictoria C, Runowicz CD, et al. Clinical impact of chemotherapy-induced thrombocytopenia in patients with gynecologic cancer. J Clin Oncol 1994;12:2317-20.
7. Elting LS, Rubenstein EB, Loewy J, Beach K. Incidence and Outcomes of Chemotherapy-Induced Thrombocytopenia in Patients with Solid Tumors (abstract). Support Care Cancer 1996;4:238.
8. Ten Berg MJ, Huisman A, van den Bemt PMLA, Schobben AF, Egberts AC, et al. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. Clin Chem Lab Med 2007;45:13-9.
9. Fritz, A, Percy C, Jack A, Shanmugaratnam K, Sobin L, et al., editors. International Classification of Diseases for Oncology (ICD-O). 3rd ed. Geneva: World Health Organization; 2001.
10. Cancer Therapy Evaluation Program, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events, version 3.0. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf [Accessed 2009 Mar 6].
11. Kuderer NM, Francis CW, Crawford J, Dale DC, Wolff DA, et al. A prediction model for chemotherapy-associated thrombocytopenia in cancer patients (abstract). J Clin Oncol 2006;24:8616.
12. Alberts DS, Dorr RT. New Perspectives on an Old friend: Optimizing carboplatin for the treatment of solid tumors. Oncologist 1998;3:15-34.
13. Meyboom RH, Lindquist M, Egberts AC. An ABC of drug-related problems. Drug Saf 2000;22:415-23.
14. Wazny LD, Ariano RE. Evaluation and management of drug-induced thrombocytopenia in the acutely ill patient. Pharmacotherapy 2000;20:292-307.
15. Beg MS, Komrokji RS, Ahmed K, Safa MM. Oxaliplatin-induced immune mediated thrombocytopenia. Cancer Chemother Pharmacol 2008;62:925-7.
16. Curtis BR, Kaliszewski J, Marques MB, Saif MW, Nabelle L, et al. Immune-mediated thrombocytopenia resulting from sensitivity to oxaliplatin. Am J Hematol 2006;81:193-8.
17. Pavic M, Moncharmont P, Seve P, Rigal D, Broussolle C. Oxaliplatin-induced immune thrombocytopenia. Gastroenterol Clin Biol 2006;30:797-8.
18. Du XL, Osborne C, Goodwin JS. Population-based assessment of hospitalizations for toxicity from chemotherapy in older women with breast cancer. J Clin Oncol 2002;20:4636-42.
19. Happe LE, Farrelly EM, Stanford RH, Sarnes MW. Cost and occurrence of thrombocytopenia in patients receiving venous thromboembolism prophylaxis following major orthopaedic surgeries. J Thromb Thrombolysis 2008;26:125-31.
20. Ten Berg MJ, van Solinge WW, van den Bemt PMLA, Huisman A, Schobben AF, et al. Platelet measurements versus discharge diagnoses for identification of patients with potential drug-induced thrombocytopenia: A cross-sectional study in the Netherlands. Drug Saf 2009;32:69-76.

Appendix I Non-experimental chemotherapy regimens included in this study

Cytostatic drug(s)	Type of cancer(s)[a] the regimen was used in	Number of courses of the regimen included in the study
		n=614 (100%)
cisplatin	lip, oral cavity and pharynx; digestive organs; respiratory system and intrathoracic organs; female genital organs; male genital organs; urinary tract; unknown primary site	130 (21.2%)
cyclophosphamide; fluorouracil; epirubicine	breast	68 (11.1%)
cyclophosphamide; doxorubicine	skin; connnective, subcutaneous and other soft tissue; breast	40 (6.5%)
etoposide; bleomycine; cisplatin	respiratory system and intrathoracic organs; retroperitoneum and peritoneum; female genital organs; male genital organs	39 (6.4%)
gemcitabine; cisplatin	respiratory system and intrathoracic organs; male genital organs; urinary tract	31 (5.0%)
docetaxel	female genital organs; male genital organs; urinary tract	30 (4.9%)
fluorouracil; oxaliplatin	digestive organs	22 (3.6%)
methotrexate	lip, oral cavity and pharynx; digestive organs; respiratory system and intrathoracic organs; connnective, subcutaneous and other soft tissue; female genital organs; male genital organs; urinary tract	22 (3.6%)
dacarbazine	skin; eye, brain and other parts of the central nervous system; thyroid and other endocrine glands; unknown primary site	21 (3.4%)
etoposide; cisplatin	respiratory system and intrathoracic organs; retroperitoneum and peritoneum; male genital organs; urinary tract; thyroid and other endocrine glands; unknown primary site	19 (3.1%)
paclitaxel; carboplatin	retroperitoneum and peritoneum; female genital organs	19 (3.1%)
cyclophosphamide; etoposide; doxorubicine	respiratory system and intrathoracic organs	18 (2.9%)
ifosfamide; mitomycine; cisplatin	lip, oral cavity and pharynx; digestive organs; respiratory system and intrathoracic organs	14 (2.3%)
temozolamide	eye, brain and other parts of the central nervous system	13 (2.1%)
capecitabine; epirubicine; cisplatin	digestive organs; respiratory system and intrathoracic organs	11 (1.8%)
carboplatin	lip, oral cavity and pharynx; respiratory system and intrathoracic organs; female genital organs; male genital organs	11 (1.8%)

Cytostatic drug(s)	Type of cancer(s)[a] the regimen was used in	Number of courses of the regimen included in the study
		n=614 (100%)
doxorubicine	peripheral nerves and autonomic nervous system; connnective, subcutaneous and other soft tissue; breast; female genital organs; unknown primary site	11 (1.8%)
fluorouracil; mitomycine	digestive organs; skin; female genital organs	11 (1.8%)
mitoxantrone	digestive organs; breast; male genital organs	11 (1.8%)
carboplatin; gemcitabine	urinary tract	8 (1.3%)
docetaxel; carboplatin	respiratory system and intrathoracic organs	8 (1.3%)
etoposide; paclitaxel; carboplatin	unknown primary site	7 (1.1%)
capecitabine; oxaliplatin	digestive organs	6 (1.0%)
gemcitabine; carboplatin	respiratory system and intrathoracic organs; unknown primary site	6 (1.0%)
capecitabine	digestive organs; breast; unknown primary site	5 (0.8%)
cisplatin; fluorouracil	digestive organs; respiratory system and intrathoracic organs; skin	5 (0.8%)
fluorouracil	digestive organs	5 (0.8%)
cyclophosphamide; doxorubicine; cisplatin	lip, oral cavity and pharynx; respiratory system and intrathoracic organs	4 (0.7%)
fluorouracil; epirubicine; cisplatin	digestive organs; respiratory system and intrathoracic organs	4 (0.7%)
doxorubicine; cisplatin	female genital organs	3 (0.5%)
carboplatin; etoposide	male genital organs	2 (0.3%)
carboplatin; fluorouracil	lip, oral cavity and pharynx; respiratory system and intrathoracic organs	2 (0.3%)
oxaliplatin	digestive organs	2 (0.3%)
carboplatin; epirubicine; paclitaxel	retroperitoneum and peritoneum	1 (0.2%)
cyclophosphamide; carboplatin	female genital organs	1 (0.2%)
cyclophosphamide; doxorubicine; carboplatin	lip, oral cavity and pharynx	1 (0.2%)
cyclophosphamide; doxorubicine; fluorouracil	connnective, subcutaneous and other soft tissue	1 (0.2%)
cyclophosphamide; methotrexate; fluorouracil	breast	1 (0.2%)
fluorouracil; cisplatin	respiratory system and intrathoracic organs	1 (0.2%)

a) Major categories of the Third Edition of the International Classification of Diseases for Oncology (ICD-O-3).

4.1.2

Discriminative value of platelet size indices for the identification of the mechanisms of chemotherapy-induced thrombocytopenia

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ABSTRACT

Introduction

Immune-mediated and bone marrow suppression-related thrombocytopenia due to chemotherapy require different follow-up. A simple parameter discriminating between these mechanism of chemotherapy-induced thrombocytopenia (CIT) could be valuable in clinical practice. Indices related to platelet size, including mean platelet volume (MPV) and platelet distribution width (PDW), may be useful for this purpose.

Objective

To explore the discriminative value of MPV and PDW for immune-mediated and bone marrow-suppression related CIT in oncology patients.

Methods

Data from the Utrecht Patient Oriented Database (UPOD) were used for this retrospective study. Within a cohort of oncology patients who received their first course of non-experimental chemotherapy in the period 2005-2006 three groups of patients were identified. First, patients were identified who had isolated thrombocytopenia, defined as a platelet count $< 100\times10^9$/L without concurrent anemia, leukopenia and neutropenia. These patients were considered to have immune-mediated thrombocytopenia. The second group consisted of patients with non-isolated thrombocytopenia. These patients were considered to have bone marrow suppression-related thrombocytopenia. The third group contained patients without thrombocytopenia. For the first two groups the complete blood count at the first event of (non-)isolated thrombocytopenia within the course was identified. For the third group the complete blood count for the lowest platelet count in the course was identified. For each group mean MPV, mean PDW and the percentage of patients with an abnormally high MPV (> 9.5 femtoliter [fL]) was determined. Between-group differences in mean MPV, mean PDW and percentages of patients with an abnormally high MPV were tested for statistical significance with appropriate tests.

Results

Isolated thrombocytopenia was determined in 34 patients, non-isolated thrombocytopenia in 63 patients and 305 patients did not have thrombocytopenia. Mean MPV and mean PDW were not different for patients with isolated and non-isolated thrombocytopenia (MPV 9.0 vs. 8.7, p=0.381; PDW 16.5 vs. 15.8, p=0.248), nor were the percentages of patients with an abnormally high MPV

(29.4% vs. 27.0%, p=0.799). Mean MPV and the percentage of patients with an abnormally high MPV for patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia were significantly different ($p<0.05$) from patients without thrombocytopenia (MPV 7.6; high MPV 4.6%). Mean PDW for patients without thrombocytopenia (16.0) did not differ from mean PDW of the other groups.

Discussion

The results of this study suggest that MPV and PDW are not useful to discriminate between immune-mediated and bone marrow suppression-related CIT. However, other biomarkers, e.g. reticulated platelet count or immature platelet fraction, may have the potential to do so. Further research should determine the usefulness of these biomarkers for this purpose.

INTRODUCTION

Thrombocytopenia is a common and well-known adverse effect of cytostatic agents. Most frequently, chemotherapy-induced thrombocytopenia (CIT) is the consequence of bone marrow hypoplasia or aplasia due to a toxic effect of the cytostatic agent on the megakaryocytic cell line in bone marrow.[1] Though far less frequently, cytostatic agents may also induce thrombocytopenia by causing increased consumption or destruction of platelets in the peripheral circulation involving immune antibodies.[1] When a patient develops severe hematotoxicity during cytostatic drug treatment clinical oncologists evaluate whether treatment can be continued, whether treatment should be discontinued or whether dose delay or dose reduction is warranted. Knowledge on the underlying mechanism of thrombocytopenia in patients treated with cytostatic drugs is relevant in making decisions in this situation. Renewed exposure to the suspected agent should be avoided in case of immune-mediated thrombocytopenia, whereas in case of bone marrow suppression-related thrombocytopenia dose adjustment in subsequent cycles may be effective for prevention of thrombocytopenia. Antibody testing and bone marrow investigation could provide information on the underlying mechanism, but cytostatic drug-related antibody tests are not widely available and bone marrow investigation is a burden for the patient. Therefore, a simple parameter (i.e. a non-invasive, fast and inexpensive measurement) that could provide information about the mechanism underlying the thrombocytopenia in chemotherapy treatment would be useful in clinical practice. Indices related to

platelet size which can be measured with modern hematology analyzers, including mean platelet volume (MPV), platelet distribution width (PDW) and platelet large cell ratio (P-LCR), may be useful for this purpose. In general, in immune-mediated thrombocytopenia the normal bone marrow will release younger, larger, platelets to keep up with ongoing losses, resulting in an increase in platelet size indices.[2,3] In bone marrow suppression-related thrombocytopenia these platelet size indices are considered to be normal or even smaller.[2,3] Recent studies have shown that MPV, PDW and P-LCR have sufficient validity and accuracy in discriminating thrombocytopenia resulting from an increased consumption or destruction of platelets in the peripheral circulation involving antibodies (e.g. idiopathic thrombocytopenic purpura [ITP]) and thrombocytopenia resulting from a decreased production of platelets due to myelosuppression (e.g. aplastic anemia, high-dose chemotherapy in hematologic cancer patients).[4-6] We hypothesize that these platelet indices also have discriminative value for immune-mediated and bone marrow suppression-related thrombocytopenia caused by cytostatic agents. Although the MPV is considered to provide valuable information on the presence of immune-mediated drug-induced thrombocytopenia[3] its discriminative value for this purpose has not been investigated before. We conducted a retrospective study within a cohort of oncology patients treated with chemotherapy to test the hypothesis that MPV and PDW have discriminative value for immune-mediated and bone marrow suppression-related CIT.

METHODS

Setting

For this study, data from a cohort of oncology patients treated with non-experimental chemotherapy regimens were used. The cohort, recently described in more detail,[7] concerns patients with solid tumors who received their first course of chemotherapy treatment at the University Medical Center Utrecht (UMC Utrecht) in the three-year period of 2004-2006. The cohort was drawn based upon data on chemotherapy exposure from the Utrecht Patient Oriented Database (UPOD). UPOD has been described in detail elsewhere.[8] In brief, UPOD is a data platform encompassing automated data collected during clinical care on patient demographics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the UMC Utrecht. In addition to these data UPOD comprises a database with hematological data obtained with Cell-Dyn 4000 and Cell-Dyn Sapphire hematology analyzers (Abbott Diagnostics,

Santa Clara, CA, USA) used in routine blood cell analysis at the UMC Utrecht since January 2005. Per blood sample measured, all blood cell parameters the analyzer is capable of measuring[9] are collected within the database, providing complete and validated automated hematological data, including absolute cell counts, cell volume indices and morphological data.[8]

Patients

Patients who were treated with chemotherapy in 2005-2006 were selected from the UPOD-oncology cohort. Per patient the first period of consecutive exposure to a specific chemotherapy regimen was studied. This period was called a course of chemotherapy treatment. The course was constructed from consecutive automated medications orders for cycles of chemotherapy (i.e. one round of chemotherapy). For each patient the last complete blood count obtained before the start of the course of chemotherapy treatment was identified within the UPOD hematology database. This blood count was considered the baseline measurement. In addition, all complete blood cells counts within the course of chemotherapy exposure were selected. Based on these data three selective groups of patients were identified:

1) *isolated thrombocytopenia*: defined as patients with an event of isolated thrombocytopenia at least once. An event of isolated thrombocytopenia was defined as the presence of a platelet count less than 100×10^9/L without anemia (hemoglobin > 9.7 g/dL), leukopenia (leucocyte count > 4.0×10^9/L) and neutropenia (neutrophil granulocyte count > 1.6×10^9/L) based on the same complete blood count. The complete blood count of the first event in time within the course was identified per patient and considered as the event measurement. Isolated thrombocytopenia was considered as a proxy for immune-mediated CIT.[3]
2) *non-isolated thrombocytopenia only*: defined as patients with only events of non-isolated thrombocytopenia. An event of non isolated thrombocytopenia was defined as a platelet count less than 100×10^9/L with concurrent anemia (hemoglobin ≤ 9.7 g/dL) and/or leukopenia (leucocyte count ≤ 4.0×10^9/L) and/or neutropenia (neutrophil granulocyte count ≤ 1.6×10^9/L) based on the same complete blood count. The complete blood for the first event in time within the course was identified per patient and considered as the event measurement. Non-isolated thrombocytopenia was considered to be a proxy for bone marrow suppression-related CIT.
3) *no thrombocytopenia:* defined as patients with only platelet measurements equal or greater than 100×10^9/L during the course of chemotherapy treatment. The

complete blood count with the lowest platelet count within the course was identified per patient and considered as the event measurement.

Platelet size indices

For all patients the values of MPV and PDW for the baseline measurement and the event measurement were identified. MPV was calculated by the hematology analyzer as the arithmetic mean from the impedance platelet histogram (Figure 1) and was reported in femtoliter (fL). Per patient it was determined whether the MPV was abnormally high, defined as > 9.5 fL based on the upper limit of the reference range used at the UMC Utrecht. PDW was calculated by the hematology analyzer from the impedance platelet histogram (Figure 1) and was reported in ten times the geometric standard deviation.

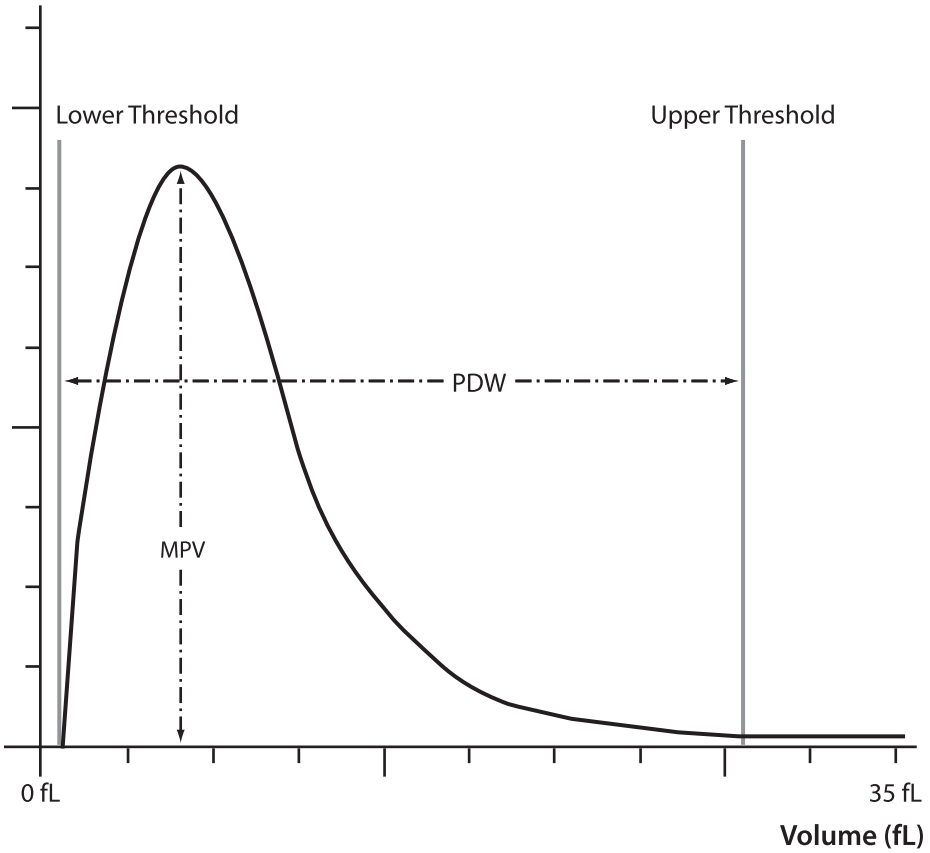
Data analysis

Per group the MPV and PDW values of the baseline and event measurement were checked for normality by comparison of the mean and median, by comparison of the mean and the standard deviation and by visual inspection of the distribution histogram. After confirming normality mean MPV and PDW were calculated per group for the baseline and event measurement. Between-group differences in mean MPV and mean PDW were tested for statistical significance using a students t-test considering a p-value smaller than 0.05 statistically significant. Per group the percentage of patients with an abnormally high MPV at baseline and event measurement was determined. Between-group differences in percentage of patients with an abnormally high MPV were tested for statistical significance using a chi-square test considering a p-value smaller than 0.05 as statistical significant. Data analysis was performed using SPSS 16.0 (SPSS Inc. Chicago, Ill., USA).

RESULTS

We included 402 patients in the study. Isolated thrombocytopenia occurred in 34 patients (8.6%), non-isolated thrombocytopenia occurred in 63 patients (15.7%) and 305 patients (75.7%) did not develop thrombocytopenia. Patient characteristics and mean baseline values for platelet indices per group are presented in Table 1. Patients with isolated thrombocytopenia were more frequently male compared to patients with non-isolated thrombocytopenia and patients without thrombocytopenia. On average patients with isolated thrombocytopenia were older than patients with non-

Figure 1 **Histogram of platelet volume distribution and the definition of mean platelet volume (MPV) and platelet distribution width (PDW) as determined by Abbott Cell-Dyn hematology analyzer**



Under normal circumstance: lower threshold 2 fl, upper threshold 20 fl.

isolated thrombocytopenia and patients without thrombocytopenia. Platelet count, MPV and PDW were not significantly different for the three groups at baseline.
Mean MPV and mean PDW for the event measurement per group are presented in Table 2. Mean MPV of the event measurement was 0.3 fL higher for patients with isolated thrombocytopenia compared to patients with non-isolated thrombocytopenia (p=0.381). Mean MPV of the event measurement was 1.5 fL higher for patients with isolated thrombocytopenia compared to patients without thrombocytopenia, which was significantly different. Mean PDW of the event measurement was 0.7 fL higher for patients with isolated thrombocytopenia compared to patients with non-isolated thrombocytopenia (p=0.248). Mean PDW of the event measurement was 0.5 fL higher for patients with isolated thrombocytopenia compared to patients without thrombocytopenia (p<0.001).

Table 1 Comparison of demographic characteristics and platelet indices at baseline patients with isolated thrombocytopenia, non-isolated thrombocytopenia and without thrombocytopenia

		Isolated thrombocytopenia (n=34)	Non-isolated thrombocytopenia only (n=63)	No thrombocytopenia (n=305)	p-value isolated vs. non-isolated	p-value isolated vs. no thrombocytopenia	p-value non-isolated vs. no thrombocytopenia
Female	number (%)	11 (32.3%)	29 (46.0%)	154 (50.5%)	0.192	0.045	0.519
Age (yrs)	mean (sd)	57.9 (11.2)	56.0 (12.4)	53.5 (13.0)	0.446	0.036	0.142
Platelet count ($\times 10^9$/L)	mean (sd)	311 (120)	300 (106)	316 (122)	0.657	0.861	0.325
MPV (fL)	mean (sd)	7.4 (1.0)	7.3 (1.0)	7.4 (1.0)	0.928	0.633	0.437
	median (range)	7.1 (5.9-10.3)	7.3 (5.1-10.1)	7.4 (5.6-12.6)			
MPV > 9.5 fL	number (%)	2 (5.9%)	2 (3.2%)	11 (3.6%)	0.522	0.512	0.866
PDW (10GSD)	mean (sd)	16.3 (0.6)	16.2 (0.6)	16.1 (1.4)	0.299	0.203	0.785
	median (range)	16.4 (15.3-18.0)	16.0 (14.8-17.5)	16.0 (14.5-38.1)			

sd = standard deviation; MPV = mean platelet volume; fL = femtoliter; PDW = platelet distribution width; 10GSD = 10 times the geometric standard deviation

Table 2	Comparison of platelet indices at event date between patients with isolated thrombocytopenia, non-isolated thrombocytopenia and with thrombocytopenia						
		Isolated thrombo-cytopenia (n=34)	Non-isolated thrombocytopenia only (n=63)	No thrombo-cytopenia (n=305)	p-value isolated vs. non-isolated	p-value isolated vs. no thrombo-cytopenia	p-value non-isolated vs. no thrombo-cytopenia
Platelet count ($\times 10^9$/L)	mean (sd)	81 (18)	75 (23)	201 (91)	0.220	<0.001	<0.001
MPV (fL)	mean (sd)	9.0 (2.1)	8.7 (1.2)	7.6 (1.0)	0.381	<0.001	<0.001
	median (range)	8.8 (5.8-17.1)	8.6 (6.2-11.4)	7.5 (5.0-12.9)			
MPV > 9.5 fL	number (%)	10 (29.4%)	17 (27.0%)	14 (4.6%)	0.799	<0.001	<0.001
PDW (10GSD)	mean (sd)	16.5 (2.8)	15.8 (1.2)	16.0 (1.3)	0.248	0.368	0.388
	median (range)	15.9 (10.3-28.1)	15.9 (10.4-18.1)	16.0 (10.1-35.2)			

sd = standard deviation; MPV = mean platelet volume; fL = femtoliter; PDW = platelet distribution width; 10GSD = 10 times the geometric standard deviation

The percentages of patients with an abnormally high MPV per group are presented in Table 2. An abnormally high MPV was observed in 2.4% more patients with isolated trombocytopenia compared to patients with non isolated trombocytopenia ($p=0.799$). Percentages of patients with an abnormally high MPV were different for patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia compared to patients with no thrombocytopenia ($p<0.001$).

DISCUSSION

We observed no differences in mean MPV, mean PDW and the percentage of patients with an abnormally high MPV between patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia. These results suggest that MPV and PDW have no discriminate value for immune-mediated thrombocytopenia and bone marrow suppression-related CIT.

Our hypothesis was based on recent studies in which MPV, PDW and P-LCR were found to be useful to discriminate immune-mediated thrombocytopenia from thrombocytopenia due to bone marrow suppression.[4-6] In these studies large significant differences in mean MPV were observed between patients with these two types of thrombocytopenia. Kaito et al.[5] compared patients with ITP and aplastic anemia and found a difference of 2.0 fL in MPV (12.2 vs. 10.2 fL). Bowles et al.[4] compared patients with bone marrow disease and patients without bone marrow disease and found a difference of 1.9 fL in MPV (9.8 vs. 8.1 fL). Ntaios et al.[6] compared patients with ITP and myelosuppression following chemotherapy for hematological malignancy and found a difference of 4.21 (11.38 vs. 7.17). In the current study we only observed a non-significant difference of 0.3 fL in mean MPV between patients with isolated thrombocytopenia versus patients with non-isolated thrombocytopenia. Kaito et al.[5] also considered PDW and found a difference of 5.2 fL between patients with ITP and patients with aplastic anemia (16.8 vs. 11.6). In contrast to the results reported by Kaito et al.[5], we did not find any significant difference in mean PDW between patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia. Finally, Kaito et al.[5] compared P-LCR and found a difference of 16.5 between patients with ITP and patient with aplastic anemia (42.2 vs. 25.7). In the current study P-LCR was not investigated because the Abbott Cell-Dyn hematology analyzer does not report this parameter. Compared to these previous studies we observed a relatively low MPV for patients with immune-mediated thrombocytopenia. Immune mediated CIT is considered as an acute event. In this group of patients MPV and PDW may be not as high as

in patients with ITP, because here the increase in MPV and PDW following the occurrence of trombocytopenia develops over time. The observation of the relatively high mean MPV in patients with non-isolated thrombocytopenia was unexpected. This may suggest that in CIT due to bone marrow suppression the MPV increases and partly affected bone marrow may be able to respond to thrombocytopenia by increasing the megakaryocytic activity. MPV is considered to be influenced by several conditions. Increased platelet size has been shown in for example ITP, diabetes, obesity, sepsis, DIC and myocardial infarction.[10,11] Recently, a lower MPV was also reported to be associated with the presence of bone marrow metastasis in patients with solid tumors.[12] Information on co-morbidity and presence of bone marrow metastasis at time of chemotherapy treatment was not available for our study population and therefore we could not investigate whether differences in presence of such conditions contributed to our findings. The finding that MPV was different between patients with thrombocytopenia, either isolated or non-isolated and patients without thrombocytopenia suggests that increased MPV is associated with thrombocytopenia. An inverse relation between platelet count and MPV has been described.[13-16] Our observation of a relatively high mean MPV in patients with either isolated or non-isolated thrombocytopenia could simply be explained by the presence of thrombocytopenia. To our knowledge such a relation has not been described for PDW.

Some potential limitations of our study need to be addressed, that may explain to some extent why we did not observe a difference in MPV and PDW between patients with isolated thrombocytopenia and patients with non-isolated thrombocytopenia. First, the proxies we used for immune-mediated thrombocytopenia and bone marrow suppression-related thrombocytopenia may have had limited sensitivity and specificity for these conditions. We had to use proxies for these conditions because no antibody tests and bone marrow biopsies or aspirations were performed in these patients. We considered isolated thrombocytopenia as a proxy for immune-mediated thrombocytopenia, because immune-mediated drug-induced thrombocytopenia in general presents as isolated thrombocytopenia.[3] However, we acknowledge that isolated thrombocytopenia can also be the result of selective bone marrow suppression on the level of the megakaryocyte cell line in the bone marrow. Second, our study may have lacked power to detect a difference between patients with isolated and patients with non-isolated thrombocytopenia. We compared groups of 34 patients with isolated thrombocytopenia with 63 patients with non-isolated thrombocytopenia. With these numbers only a difference of at least 0.7 fL in MPV between these groups could been detected with statistical significance. However, the differences identified in earlier studies were larger than 0.7, so power

should not have been a problem. Despite these limitations we believe our study shows that MPV and PDW have little value as biomarkers for the identification of the mechanism of CIT. However, other biomarkers, e.g. reticulated platelet count or immature platelet fraction, may have the potential to do so. These platelet indices reflect thrombopoiesis activity in the bone marrow.[17,18] The reticulated platelet count has been reported to provide similar information as MPV about the underlying mechanism of thrombocytopenia, as the reticulated platelet count tends to vary proportionately with bone marrow function and very high counts can be seen in the setting of peripheral platelet destruction.[2] The immature platelet fraction has been reported to a marker for bone marrow recovery after chemotherapy.[17] The reticulated platelet count and immature platelet fraction may have additional value to discriminate bone marrow suppression-related and immune-mediated chemotherapy-related thrombocytopenia.

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REFERENCES

1. Jelic S, Radulovic S. Chemotherapy-associated thrombocytopenia: Current and emerging management strategies. Am J Cancer 2006;5:371-82.
2. Kenney B, Stack G. Drug-induced thrombocytopenia. Arch Pathol Lab Med 2009;133:309-14.
3. Wazny LD, Ariano RE. Evaluation and management of drug-induced thrombocytopenia in the acutely ill patient. Pharmacotherapy 2000;20:292-307.
4. Bowles KM, Cooke LJ, Richards EM, Baglin TP. Platelet size has diagnostic predictive value in patients with thrombocytopenia. Clin Lab Haematol 2005;27:370-3.
5. Kaito K, Otsubo H, Usui N, Yoshida M, Tanno J, et al. Platelet size deviation width, platelet large cell ratio, and mean platelet volume have sufficient sensitivity and specificity in the diagnosis of immune thrombocytopenia. Br J Haematol 2005;128:698-702.
6. Ntaios G, Papadopoulos A, Chatzinikolaou A, Saouli Z, Karalazou P, et al. Increased values of mean platelet volume and platelet size deviation width may provide a safe positive diagnosis of idiopathic thrombocytopenic purpura. Acta Haematol 2008;119:173-7.
7. Ten Berg MJ, van den Bemt PMLA, Shantakumar S, Bennett D, Voest EE, et al. Thrombocytopenia in adult oncology patients receiving chemotherapy: incidence and relative

risk estimates from a retrospective hospital-based cohort study using laboratory data. In preparation.

8. Ten Berg MJ, Huisman A, van den Bemt PMLA, Schobben AF, Egberts AC, et al. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. Clin Chem Lab Med 2007;45:13-9.
9. Muller R, Mellors I, Johannessen B, Aarsand AK, Kiefer P, et al. European multi-center evaluation of the abbott cell-dyn sapphire hematology analyzer. Lab Hematol 2006;12:15-31.
10. Kim KY, Kim KE, Kim KH. Mean platelet volume in the normal state and in various clinical disorders. Yonsei Med J 1986;27:219-26.
11. Yetkin E. Mean platelet volume not so far from being a routine diagnostic and prognostic measurement. Thromb Haemost 2008;100:3-4.
12. Aksoy S, Kilickap S, Hayran M, Harputluoglu H, Koca E, et al. Platelet size has diagnostic predictive value for bone marrow metastasis in patients with solid tumors. Int J Lab Hematol 2008;30:214-9.
13. Bessman JD, Williams LJ, Gilmer PR, Jr. Mean platelet volume. The inverse relation of platelet size and count in normal subjects, and an artifact of other particles. Am J Clin Pathol 1981;76:289-93.
14. Levin J, Bessman JD. The inverse relation between platelet volume and platelet number. Abnormalities in hematologic disease and evidence that platelet size does not correlate with platelet age. J Lab Clin Med 1983;101:295-307.
15. Bain BJ. Platelet count and platelet size in males and females. Scand J Haematol 1985;35:77-9.
16. Buckley MF, James JW, Brown DE, Whyte GS, Dean MG, et al. A novel approach to the assessment of variations in the human platelet count. Thromb Haemost 2000;83:480-4.
17. Abe Y, Wada H, Tomatsu H, Sakaguchi A, Nishioka J, et al. A simple technique to determine thrombopoiesis level using immature platelet fraction (IPF). Thromb Res 2006;118:463-9.
18. Briggs C, Kunka S, Hart D, Oguni S, Machin SJ. Assessment of an immature platelet fraction (IPF) in peripheral thrombocytopenia. Br J Haematol 2004;126:93-9.

4.2

HEPARIN-INDUCED THROMBOCYTOPENIA

Compliance with recommendations for platelet count monitoring and management of possible heparin-induced thrombocytopenia in hospitalized patients receiving low molecular weight heparin

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ABSTRACT

Background

Summaries of product characteristics (SPCs) and clinical guidelines recommend to monitor the platelet count for heparin-induced thrombocytopenia (HIT) in patients receiving low molecular weight heparin (LMWH). Testing for the presence of heparin platelet factor-4 antibodies (HPF4-Ab) and starting alternative anticoagulation is recommended when HIT is suspected.

Objective

To investigate the frequency of compliance with recommendations for platelet count monitoring and management of possible HIT in hospitalized patients receiving prophylaxis and treatment dosing of LMWH for at least five consecutive days.

Methods

Retrospective cohort study within the Utrecht Patient Oriented Database (UPOD). For all inpatients all episodes of exposure to dalteparin or nadroparin for at least five consecutive days in 2004-2005 were selected. In four different non-exclusive groups of patients (all patients receiving dalteparin, all patients receiving nadroparin, surgical patients with a prophylactic dose of either dalteparin or nadroparin, and patients exposed to unfractionated heparin (UFH) within 100 days before receiving either dalteparin or nadroparin) it was studied whether recommendations for platelet count monitoring from SPCs and a clinical guideline were abided by. The frequency of compliance to these recommendations was determined. In addition, it was determined whether patient and treatment characteristics were associated with regular platelet count monitoring. Finally, the frequency of testing for HPF4-Ab and initiation of danaparoid treatment in patients with a drop of at least 50% in platelet count was investigated.

Results

6804 patients with 7770 episodes of LMWH treatment were included. The frequency of compliance with platelet count monitoring recommendations was 26.3% for all patients receiving dalteparin, 35.6% for all patients receiving nadroparin, 23.0% for surgical patients receiving prophylactic dosing of either dalteparin or nadroparin and 41.8% for patients exposed to UFH in 100 days before the start of either dalteparin or nadroparin treatment. Regular platelet count monitoring was strongly positively associated with medical patients (relative risk [RR] 2.33), surgical patients (RR 2.03), critically ill patients (RR 2.80) and recent exposure to UFH (RR 2.19). The frequency of testing for HPF4-Ab and starting alternative

anticoagulation with danaparoid in patients with a 50%-drop in platelet count was 5.4% and 0% respectively.

Conclusions

The results suggest that compliance with recommendations for platelet count monitoring and management of possible HIT is low at our institution. Policies and tools to improve compliance with recommended laboratory monitoring should be developed to secure the safe use of LMWH and other medications.

INTRODUCTION

For many medications laboratory monitoring is recommended for early detection of adverse drug reactions.[1] Such recommendations are laid down in clinical guidelines and in Summaries of Product Characteristics (SPCs) of medications. A SPC is composed by a drug manufacturer and contains information for health professionals on how to use the product; package leaflets are drawn up in accordance with the SPC.[2] Heparin-induced thrombocytopenia (HIT) is a well-known and potentially severe adverse drug reaction for which laboratory monitoring is recommended for early-detection. HIT is considered to occur in up to 5% of patients receiving unfractionated heparin (UFH) and in up to 0.9% of patients receiving low molecular weight heparin (LMWH).[3] HIT is associated with a high risk for thrombosis and death.[4] The SPCs of UFH and LMWHs recommend to regularly obtain a platelet count during treatment.[5-7] More detailed recommendations on the frequency of platelet count monitoring, distinguishing patient populations at different risk for HIT, are made in clinical guidelines.[8-11] HIT should be suspected when the platelet count drops without an obvious explanation in patients receiving heparin. In this case testing for the presence of heparin-platelet factor 4 antibodies (HPF4-Ab) is recommended as well as discontinuation of heparin treatment and start of alternative anticoagulation.[5,7,8] Because of the widespread use of heparin and the potential severe consequences of HIT, knowledge on the compliance with these recommendations is important from a patient safety perspective. The single center retrospective cohort study presented in this manuscript was aimed at determining the compliance with recommendations for platelet count monitoring and management of possible HIT for inpatients receiving prophylaxis and treatment dosing of LMWH for at least five consecutive days.

METHODS

Data source, and setting

For this study, data from the Utrecht Patient Oriented Database (UPOD) were used. UPOD is an infrastructure of relational databases comprising coded electronic data on patient demographics, hospital discharge diagnoses, medical procedures, medication orders and laboratory tests for all patients treated at the University Medical Center Utrecht (UMC Utrecht) since 2004. The content of UPOD and its setting have been described in detail elsewhere.[12]

Study population

The study population comprised all patients (including surgical, medical, obstetrical and critically ill patients) exposed to prophylaxis or treatment dosing of the LMWHs dalteparin (Fragmin®)[6] and nadroparin (Fraxiparin®)[7] for at least five consecutive days in the period of 1 January 2004 till 31 December 31 2005. Dalteparin and nadroparin were the only two LMWHs used at our institution during the study period. All types of patients were included because the SPCs of dalteparin and nadroparin recommend platelet count monitoring in all types of patients receiving these medications.[6,7] All episodes of LMWH treatment for these patients within the study period were selected. Episodes were constructed from automated medication order data from the computerized physician order entry system (CPOE). Consecutive medication orders, allowing one day difference between the stop date of the first order and the start date of the second order, were considered as one treatment episode. The reason for selecting episodes of LMWH treatment of at least five consecutive days is that we were interested in platelet count monitoring and follow-up to a large drop in platelet count in the time period HIT type II typically occurs, i.e. day 5-10 following the start of treatment.[13,14] To prohibit the inclusion of patients in whom the platelet count was likely to be monitored for other reasons than LMWH exposure episodes for patients with 'thrombocytopenia-related conditions' on admission were excluded. The following thrombocytopenia-related conditions (based on International Classification of Diseases, 9th Revision [ICD-9-CM]-coded hospital discharge diagnosis data) were considered: idiopathic thrombocytopenic purpura, cancer, aplastic anemia, vitamin B12 deficiency, folate deficiency, alcohol abuse, hypersplenism/splenomegaly incl. secondary forms, collagen vascular diseases, HIV infection, measles, mononucleosis infectiosa, malaria, thrombotic thrombocytopenia purpura, and hemolytic uremic syndrome. In addition, patients receiving chemotherapy (based on drug exposure data) or radiotherapy (based on billing data) during hospital admission or within 30 days before admission were excluded.

For dalteparin a dosage equal or smaller than 5000 E/day was considered prophylactic and a dosage greater than 5000 IE/day therapeutic.[6] For nadroparin a dosage less than or equal to 5700 IE/day was considered prophylactic, and a dosage greater than 5700 IE/day therapeutic.[7] Surgical patients were defined as patients who underwent a surgical procedure requiring an operating room (based on billing data). Obstetrical patients were defined as patients who were admitted to the department of obstetrics (based on billing data).
Patients who were non-surgical and non-obstetrical were considered to be medical patients. Critically ill patients were defined as patients whose course of LMWH was begun in the intensive care unit (ICU).

Compliance with recommendations for platelet count monitoring and management of possible HIT

Using data on platelet count measurements from the laboratory information system compliance with different recommendations for platelet count monitoring from the SPC of dalteparin, the SPC of nadroparin and a clinical guideline were investigated.[5,7,8] The recommendations applied to four different non-exclusive groups of patients: 1) patients receiving nadroparin, 2) patients receiving dalteparin, 3) surgical patients receiving prophylactic doses of either dalteparin or nadroparin, and 4) patients exposed to UFH within 100 days before the start of treatment with either dalteparin or nadroparin. The SPC of nadroparin recommends to obtain a platelet count regularly during treatment in all patients treated with the drug.[7] Compliance with this recommendation was defined as performance of a platelet count on at least two different days during nadroparin treatment. The SPC of dalteparin recommends to obtain a platelet count at start of treatment and to regularly obtain a platelet count during treatment in all patients treated with the drug.[6] Compliance with this recommendation was defined as performance of at least one platelet count at the day of start of treatment and performance of platelet counts on at least two different following days during dalteparin treatment. The clinical guideline does not recommend platelet count monitoring in all patients receiving LMWH, but only in patients who are considered to be at increased risk for HIT when receiving LMWH, i.e. patients who were exposed to UFH within 100 days before LMWH treatment, and post-operative patients treated with prophylactic dose LMWH. For patients exposed to UFH within 100 days before receiving LMWH treatment the clinical guideline recommends to monitor the platelet count during the first 24 hours of LMWH treatment.[8] Compliance with this recommendation was defined as performance of at least one platelet count at the day of start of treatment and performance of at least one platelet count at the second

day of treatment in patients receiving dalteparin or nadroparin who had received UFH within 100 days before the start of the LMWH episode (based on CPOE data). For postoperative patients receiving prophylactic dosing of LMWH the clinical guideline recommends to obtain a platelet count two or three times from day 4 to day 10, when practical, in postoperative patients receiving prophylactic dosing of LMWH.[8] Compliance with this recommendation was defined as performance of at least one platelet count within day 4 to the stop date for episodes with a duration of 5-9 days in surgical patients receiving prophylactic doses of either dalteparin or nadroparin. For these patients receiving episodes of at least 10 days compliance was defined as the performance of at least two platelet counts on at least two different days within days 4-10 of treatment.

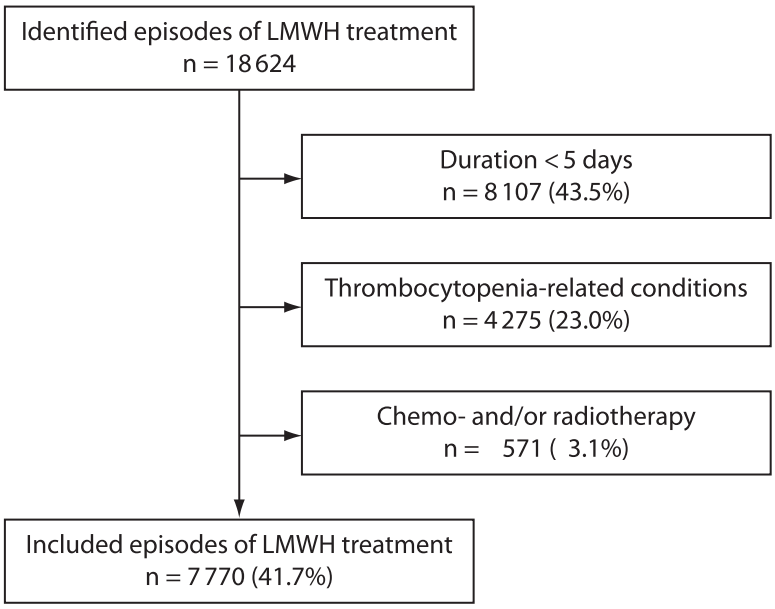
In addition to the investigation of compliance with these specific recommendations for platelet count monitoring from the SPCs and the clinical guideline we investigated whether the platelet count was monitored regularly in all types patients receiving LMWH for at least 5 days, as well as in patients with specific patient and treatment characteristics. Regular platelet count monitoring was defined as the performance of platelet counts on at least two different days during LMWH exposure. The specific patients characteristics that were selected *a priori* were: surgical, medical, obstetrical and critically ill. The treatment characteristics that were selected *a priori* were: receiving dalteparin, nadroparin, prophylactic dosing, therapeutic dosing, (non-)exposure to UFH in the past 100 days, and receiving LWMH for 5-9 days or for 10 days or more.

Finally, compliance with recommendations for managing possible HIT was investigated. Possible HIT was defined as drop in platelet count typical for HIT, i.e. a drop of at least 50% in platelet count within day 5 to stop date up to day 10, compared to highest platelet count within days 1 to 4. The SPCs of dalteparin and nadroparin and the clinical guideline recommend to test for the presence of HPF4-Ab in patients when HIT is suspected.[5,7,8] Compliance with this recommendation was defined as performance of an HPF4-Ab test within two days of the first occurrence of a drop of at least 50% in platelet count. During the whole study period the ID-HPF4 Particle Gel Immuno Assay (PaGIA; Diamed, Cressier sur Morat, Switserland) [15] was the only test used to screen for HPF4-Ab at our institution. In addition, the clinical guideline recommends to initiate alternative anticoagulation when HIT is suspected.[8] Compliance with this recommendation was defined as initiation of treatment with danaparoid (Orgaran®) [16] within two days of the first occurrence of a drop of at least 50% in platelet count. During the study period danaparoid was the only drug used at our institution in patients for alternative anticoagulation in case of suspected or diagnosed HIT.

Data analysis

First, the frequency of compliance with the specific recommendations for platelet count monitoring from the SPCs and the clinical guideline was determined and expressed as the percentage of episodes in which the recommendations were followed over the episodes the recommendations applied to. Second, the frequency of regular platelet count monitoring was determined and expressed as the percentage of episodes in which regular platelet count monitoring was present over all episodes. Stratified analyses were performed for the specified patient and treatment characteristics. In addition, the association between patient and treatment characteristics and regular platelet count monitoring was assessed and expressed as relative risk with 95% confidence interval. For this analysis only the first episode of LMWH exposure per patient in time in the study period was included. A chi-square test was used to determine the statistical significance for the relative risk estimates. A p-value of 0.05 or less was considered statistically significant. Finally, the frequency of compliance with recommendations for managing possible HIT was determined and expressed as the percentage of episodes in which the recommendations were followed over all episodes with a drop in platelet count typical for HIT. Data analysis was performed using SAS 9.0 (SAS Institute, Care, NC, USA).

Figure 1 Selection of the study population



LMWH = low molecular weight heparin

RESULTS

In the study period 15 001 unique patients received 18 624 episodes of dalteparin and nadroparin treatment. In 10 854 episodes at least one reason for exclusion was present: 8107 episodes (43.5%) had a duration shorter than five days, in 4275 episodes (23.0%) patients had thrombocytopenia-related conditions, and in 571 episodes (3.1%) patients were receiving chemo- and/or radiotherapy during admission or within 30 days before admission (Figure 1). This led to the inclusion of 7770 episodes (41.7%) of LMWH exposure for 6804 unique patients (Figure 1). The median hospital duration of included patients was 10 days. Table 1 presents the patient and treatment characteristics of the included episodes. The majority of the episodes concerned surgical patients receiving prophylactic dosing with dalteparin.

Table 1 Patient and treatment characteristics of included episodes

Characteristic	n=7 770 (100%)
Male	3 864 (49.7%)
Average age at time of LMWH initiation (sd)	55.9 (19.1)
Surgical	6 041 (77.7%)
Obstetrical	375 (4.8%)
Medical	1 354 (17.4%)
Critically ill	1 035 (13.3%)
Dalteparin	6 572 (84.6%)
Exposure to UFH with 100 days before start	1 432 (18.4%)
Median duration in days (range)	8 (5-306)
Duration of at least ten days	2 833 (36.5%)
Prophylactic dosage	6 621 (85.2%)
Therapeutic dosage	769 (9.9%)
Dosage unknown	380 (4.9%)

LMWH = low molecular weight heparin; sd = standard deviation; UFH = unfractionated heparin

Medical patients mainly had neurologic (21%), cardiovascular (15%) or pulmonary disease (11%). The frequencies of compliance with the recommendations for platelet count monitoring from the SPCs and the clinical guideline are presented in Table 2.

Regular platelet count monitoring was performed in 3184 of all episodes (41.0%). Stratified analyses of the frequency of regular platelet count monitoring by patient and treatment characteristics, including only the 6804 first episodes per patient, are

Table 2 Compliance with recommendations for platelet count monitoring

Patient population	Definition of compliance	N	Episodes with compliance with recommendations (%)
All patients receiving nadroparin (SPC nadroparin)	Platelet counts on at least 2 different days	1 198	427 (35.6%)
All patients receiving dalteparin (SPC dalteparin)	Platelet counts on the day of start and on at least 2 different days	6 572	1 732 (26.4%)
All patients exposed to UFH within 100 days (clinical guideline)	Platelet counts on the day of start and on the second day	1 432	594 (41.5%)
Surgical patients receiving prophylactic-dose LMWH (clinical guideline)	Platelet counts within day 4 to stopdate episodes with a duration of 5-9 days, and at least 2 on at least 2 different days within days 4-10 of treatment for episodes of at least 10 days	5 063	1 164 (23.0%)
Critically ill (no recommendation)	Platelet count on least two different days	987	980 (99.3%)
Therapeutic dosage (no recommendation)	Platelet count on at least two different days	680	465 (68.4%)

SPC = summary of product characteristics; UFH = unfractionated heparin; LMWH = low molecular weight heparin

presented in Table 3. Regular platelet count monitoring was found to be strongly positively associated (relative risk [RR]>2.0) with medical and surgical patients compared to obstetrical patients, critically ill-patients compared to non-critically ill patients and exposure to UFH within the past 100 days before the start of LMWH exposure compared to non-exposure. There were 74 episodes in which a drop of at least 50% in platelet count occurred. The frequency of compliance with recommendations for managing possible HIT in these patients was 5.4% (4 patients) regarding the performance of a HPF4-Ab test, and 0% for initiating treatment with danaparoid.

DISCUSSION

Our results suggest that compliance with recommendations for platelet count monitoring and management of possible HIT in patients receiving prophylaxis and treatment dosing of LMWH for at least five days was low at our institution over the period 2004-2005. This study is illustrative for the value of linking pharmacy and

Table 3	Association between patient and treatment characteristics and regular platelet count monitoring		
Type of patient population	**N**	**Episodes with regular platelet count monitoring (%)**	**RR (95%CI)** [a]
Total	6 804	2 817 (41.4%)	
Type of patient:			
- obstetrical	372	76 (20.4%)	1.00 (reference)
- medical	1 165	555 (47.6%)	2.33 (1.89-2.87)
- surgical	5 267	2 186 (41.5%)	2.03 (1.66-2.49)
Critically ill:			
- no	5 272	1 828 (34.7%)	1.00 (reference)
- yes	987	980 (99.3%)	2.80 (2.70-2.91)
Type of LMWH:			
- nadroparin	1 082	360 (33.3%)	1.00 (reference)
- dalteparin	5 722	2 457 (42.9%)	1.29 (1.18-1.41)
Type of dosing:			
- prophylactic	5 769	2 031 (35.2%)	1.00 (reference)
- therapeutic	680	465 (68.4%)	1.94 (1.83-2.07)
Exposure to UFH within past 100 days:			
- no	5 504	1 857 (33.7%)	1.00 (reference)
- yes	1 300	960 (73.8%)	2.19 (2.09-2.30)
Duration of LMWH exposure:			
- 5–9 days	4 447	1 585 (35.6%)	1.00 (reference)
- 10 days or more	2 357	1 232 (52.3%)	1.47 (1.39-1.55)

RR = relative risk; LMWH = low molecular weight heparin; UFH = unfractionated heparin
a) All p-values <0.0001.

laboratory data within a research database for identifying potential drug-related safety issues.[12,17] We are not aware of any other study reporting on compliance with recommendations for platelet count monitoring and management of possible HIT in patients receiving LMWH. However, compliance with recommendations for drug-laboratory monitoring has been investigated for other medications.[18-24] These studies showed that compliance with recommendations for laboratory monitoring in drug treatment is low in general.[18-24]

The relatively high frequencies for regular platelet count monitoring that were found in critically ill patients, patients exposed to UFH, patients receiving therapeutic dosing, and patients treated for 10 days or more may suggest that compliance with recommendations for platelet count monitoring for HIT is relatively good in these patients. However, the findings may also reflect the disease status of these patients,

in which platelet count monitoring is required for other reasons than HIT. With regard to the estimate for critically ill patients it should be mentioned that the definition of critically ill patients may be imperfect, because we did not take into account the possibility that patients who started LMWH treatment at a non-ICU ward could be transferred to the ICU during treatment because of critical illness.
We observed a higher frequency of compliance with recommendations for platelet count monitoring in patients receiving nadroparin than in patients receiving dalteparin. However, the frequency of regular platelet count monitoring for patients receiving dalteparin was found to be higher than in patients receiving nadroparin. The observed difference was due to the different definitions we used for compliance and regular monitoring. The increased risk estimate for regular platelet count monitoring in patients receiving dalteparin compared to patients receiving nadroparin may have been caused by a low frequency of regular monitoring in nadroparin. Further analyses (data not shown) showed that patients exposed to nadroparin were mainly obstetrical patients, suggesting that the relatively low frequency of regular platelet count monitoring in patients exposed to nadroparin can be explained largely by the low platelet count monitoring in obstetrical patients.
The strengths of this study are the complete and validated automated data that are available in UPOD, allowing accurate retrospective assessment of drug-exposure and laboratory testing.[12] However, some potential limitations need to be addressed. First, the retrospective design limited the investigation of the reason for lack of performing a platelet count. To increase the likelihood that platelet counts were obtained for platelet count monitoring for HIT we excluded patients in whom 'thrombocytopenia-related conditions' were present. However potential incompleteness of administrative data that were used to identify thrombocytopenia-related conditions may have limited our ability to control for all thrombocytopenia-related conditions.[25] Therefore, the actual compliance to recommendations for platelet count monitoring for HIT might be different than reported. Second, we lacked information on clinical judgment other than data on thrombocytopenia-related conditions in assessing whether the 50%-drop in platelet count could be considered possible HIT. Therefore, we may have overestimated the number of patients with possible HIT, and underestimated the frequency of compliance with recommendations for managing possible HIT. Finally, the representativeness of the results may be limited, because UPOD currently comprises data from one hospital. Future studies in other settings must demonstrate whether the findings can be generalized.

In this study we considered recommendations for platelet count monitoring that involved multiple platelet measurements during treatment. However, a single platelet count measurement within days 5 to 10, when the risk for HIT is highest, could also be considered as awareness of recommendations for platelet count monitoring for HIT. We found that in only 17.7% of surgical patients with prophylactic dosing of LMWH for at least 10 days in which compliance to recommendations for platelet count monitoring were not followed, one platelet count was obtained. This also suggests that the awareness for recommendations for platelet count monitoring with LMWH is low.

To investigate compliance to recommendations for managing possible HIT we had to define thrombocytopenia typical for HIT. No single definition exists for thrombocytopenia that is appropriate for all clinical appearances of HIT. However a drop of at least 50% in platelet count within days 5-10 is considered to be typical for HIT.[11] In the recommendations for platelet count monitoring published by the College of American Pathologists in 2002 the highest platelet count from day 4 onward was indicated as the baseline value for monitoring for typical onset HIT. Although we investigated recommendations for platelet count monitoring presented in this guideline, we choose to use to use the highest platelet count within days 1-4 of treatment as baseline value for possible HIT. This was done because we reasoned that physicians might consider platelet counts within the first days of treatment as baseline value. It is possible that in postoperative patients the drop in platelet count represents normalization of the platelet count after a transient postoperative increase. However, it has been reported that a fall in platelet count of at least 50% following the postoperative peak is considered a sensitive definition of HIT in postoperative patients.[14]

A key recommendation for practitioners when suspecting HIT is to immediately discontinue LMWH treatment.[8] In this study we did not consider 'discontinuing LMWH treatment' alone, i.e. without the performance of a HPF4-Ab test and/or the initiation of danaparoid treatment, as a valid outcome for following up on possible HIT, because we believe performing an HPF4-Ab test is essential to rule out HIT.

We investigated compliance with recommendations that were the most current at the time our retrospective patient population was receiving LMWH. Since then some changes in the clinical guidelines for platelet count monitoring with LMWH were made. First, the time window in which platelet count monitoring is recommended has been widened to 4 to 14 days.[10,11] Second, medical and obstetrical patients receiving LMWH after first receiving UFH are now specifically mentioned. The frequency of HIT in these groups of patients is still debated. In follow-up on the findings that the frequency of HIT in medical patients receiving LMWH is not

as low as was previously expected,[26] the Haemostasis and Thrombosis Task Force of the British Committee for Standards in Haematology included a recommendation on platelet count monitoring in these patients,[10] however the American College of Chest Physicians did not.[9,11]

Low compliance with monitoring recommendations may put patients at higher risk for adverse drug reactions. In the current study we did not investigated the association between compliance to platelet count monitoring, this is subject of further research. In addition to potential harm to the patient in case of undetected adverse drug reactions, non-compliance with recommendations for drug-laboratory monitoring may also negatively influence a drug's life cycle. Lack of recommended drug-laboratory monitoring played a role in several recent withdrawals of drugs from the market.[20,27] We believe that appropriate actions are needed to improve laboratory monitoring for adverse drug reactions like HIT, and we agree with the Joint Commission's statement that hospital organizations should have a policy that addresses baseline and ongoing laboratory tests that are required for UFH and LMWH therapies.[28] In addition, we believe that educating physicians about the benefits of early detection of adverse drug reactions and the development of reminder and alert tools are potentially valuable actions. Regarding the latter, real-time linkage of medication and laboratory data with clinical decision support, enabling the generation of automated alerts and reminders, promises to be a valuable method for improving clinical risk management in drug treatment and patient safety.[17,29] With ICT solutions for linking medication and laboratory data becoming available increasing opportunities emerge for improving the safe use of medications.[30,31]

CONCLUSION

In conclusion, the results of this study suggest that compliance with recommendations for platelet count monitoring and management of possible HIT in patients receiving LMWH for at least five days is incomplete at our institution. Further research should elucidate the reasons for non-compliance. To secure the safe use of LMWH and other medications policies and tools to improve compliance with recommendations for laboratory monitoring for adverse drug reactions like HIT need to be developed.

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REFERENCES

1. Pirmohamed M, Ferner RE. Monitoring drug treatment. BMJ 2003;327:1179-81.
2. European Commission Enterprise and Industry Directorate-General. A guideline on Summary of Product Characteristics. October 2005. Available from: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/spcguidrev1-oct2005.pdf [Accessed 2008 Dec 23].
3. Arepally GM, Ortel TL. Clinical practice. Heparin-induced thrombocytopenia. N Engl J Med 2006;355:809-17.
4. Warkentin TE. Clinical presentation of heparin-induced thrombocytopenia. Semin Hematol 1998;35:9-16, discussion 35-6.
5. Leo Pharma B.V. Heparine Leo Summary of Product Characteristics. Breda, The Netherlands, April 2008.
6. Pharmacia. Dalteparin (Fragmin) Summary of Product Characteristics. Woerden, The Netherlands, May 2002.
7. GlaxoSmithKline. Nadroparine (Fraxiparine) Summary of Product Characteristics. Zeist, The Netherlands, March 2003.
8. Warkentin TE. Platelet count monitoring and laboratory testing for heparin-induced thrombocytopenia. Arch Pathol Lab Med 2002;126:1415-23.
9. Warkentin TE, Greinacher A. Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004;126:311S-37S.
10. Keeling D, Davidson S, Watson H. The management of heparin-induced thrombocytopenia. Br J Haematol 2006;133:259-69.
11. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:340S-80S.
12. Ten Berg MJ, Huisman A, van den Bemt PM, Schobben AF, Egberts AC, et al. Linking laboratory and medication data: new opportunities for pharmacoepidemiological research. Clin Chem Lab Med 2007;45:13-9.
13. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, et al. Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thromb Haemost 2005;94:132-5.
14. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. An improved definition of immune heparin-induced thrombocytopenia in postoperative orthopedic patients. Arch Intern Med 2003;163:2518-24.
15. Meyer O, Salama A, Pittet N, Schwind P. Rapid detection of heparin-induced platelet antibodies with particle gel immunoassay (ID-HPF4). Lancet 1999;354:1525-6.

16. Organon. Danaparoid (Orgaran) Summary of Product Characteristics. Oss, The Netherlands, February 2006.
17. Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. Arch Intern Med 2003;163:893-900.
18. Wagner AK, Chan KA, Dashevsky I, Raebel MA, Andrade SE, et al. FDA drug prescribing warnings: is the black box half empty or half full? Pharmacoepidemiol Drug Saf 2006;15:369-86.
19. Lasser KE, Seger DL, Yu DT, Karson AS, Fiskio JM, et al. Adherence to black box warnings for prescription medications in outpatients. Arch Intern Med 2006;166:338-44.
20. Derijks HJ, De Koning GH, Mantel-Teeuwisse AK, Egberts AC. Limited adherence to safety instructions in drug leaflets. Br J Clin Pharmacol 2002;54:678-9.
21. Calabrese AT, Coley KC, DaPos SV, Swanson D, Rao RH. Evaluation of prescribing practices: risk of lactic acidosis with metformin therapy. Arch Intern Med 2002;162:434-7.
22. Abookire SA, Karson AS, Fiskio J, Bates DW. Use and monitoring of "statin" lipid-lowering drugs compared with guidelines. Arch Intern Med 2001;161:53-8.
23. Raebel MA, McClure DL, Simon SR, Chan KA, Feldstein A, et al. Laboratory monitoring of potassium and creatinine in ambulatory patients receiving angiotensin converting enzyme inhibitors and angiotensin receptor blockers. Pharmacoepidemiol Drug Saf 2006;16:55-64.
24. Raebel MA, Lyons EE, Andrade SE, Chan KA, Chester EA, et al. Laboratory monitoring of drugs at initiation of therapy in ambulatory care. J Gen Intern Med 2005;20:1120-6.
25. Iezzoni LI. Using administrative diagnostic data to assess the quality of hospital care. Pitfalls and potential of ICD-9-CM. Int J Technol Assess Health Care 1990;6:272-81.
26. Prandoni P, Siragusa S, Girolami B, Fabris F. The incidence of heparin-induced thrombocytopenia in medical patients treated with low-molecular-weight heparin: a prospective cohort study. Blood 2005;106:3049-54.
27. Seligman PJ. Thinking outside the (black) box: a new research agenda. Pharmacoepidemiol Drug Saf 2006;15:387-9.
28. The Joint Commission. 2009 National Patient Safety Goals Hospital Program. Available from: http://www.jointcommission.org/NR/rdonlyres/31666E86-E7F4-423E-9BE8-F05BD1CB0AA8/0/HAP_NPSG.pdf [Accessed 2008 Dec 23].
29. Degnan D, Merryfield D, Hultgren S. Reaching out to clinicians: implementation of a computerized alert system. J Healthc Qual 2004;26:26-30.
30. De Clercq PA, Blom JA, Hasman A, Korsten HHM. GASTON: an architecture for the acquisition and execution of clinical guideline-application tasks. Med Inform 2000;25:247-63.
31. Jha AK, Laguette J, Seger A, Bates DW. Can surveillance systems identify and avert adverse drug events? A prospective evaluation of a commercial application. J Am Med Inform Assoc 2008;15:647-53.

5

GENERAL DISCUSSION, CONCLUSIONS, AND FUTURE RESEARCH PERSPECTIVES

INTRODUCTION

Major safety issues during the past years have led to an intense discussion on the need to improve the process of assessing and managing the safety of a drug in the different phases of a drug's life cycle. Regarding the postmarketing phase the prevailing opinion is that better and more integrated methods and tools are needed for earlier detection, quantification, mechanistic unravelling and managing of associations between drug exposure and adverse health outcomes.[1-3] As discussed in the introductory chapter of this thesis, patient-oriented data on medication exposure linked to laboratory data may be one of the valuable, still underutilized, tools for this purpose. The overall aim of the studies presented in this thesis was to investigate the value of laboratory markers in drug safety research, using the recently established Utrecht Patient Oriented Database (UPOD) as the data source. UPOD is a hospital-based data platform encompassing automated patient-oriented data on laboratory tests, medication exposure, hospital discharge diagnoses, medical procedures and patient demographics for the patients treated at the University Medical Center Utrecht, and has been described in more detail in Chapter 2. The purpose of this final chapter is to put the use of laboratory markers into the broader perspective of the current needs of drug safety research and the current needs of patients treated in clinical care and to make recommendations for further research. Three themes will be discussed:

- laboratory markers as outcome measure in risk assessment of adverse drug reactions;
- laboratory markers as biomarkers of adverse drug reactions;
- laboratory markers and medication safety in patient care.

LABORATORY MARKERS AS OUTCOME MEASURE IN RISK ASSESSMENT OF ADVERSE DRUG REACTIONS

Population-based databases containing data on both medication exposure (e.g. physician prescriptions and pharmacy dispensings) and health outcomes (e.g. hospital discharge diagnoses or general practitioner's diagnoses) have shown to be of substantial value for the detection and quantification of associations between drug exposure and patient outcomes.[4] Despite the value of such healthcare databases for pharmacoepidemiological research in general and drug safety research in specific, these databases have some drawbacks concerning the validity and accuracy of outcome data for adverse drug reactions. The major drawbacks of hospital discharge diagnoses and to a lesser extent diagnostic information

from general practitioners are misclassification, lack of clinical detail and the encapturing of only a fraction of most outcomes within such databases, i.e. low sensitivity.[5,6] Laboratory data gathered in clinical practice may be considered as an additional data source of health outcomes for the risk assessment of adverse drug reactions. The degree of misclassification of laboratory data is considered to be low since most laboratory tests are performed with automated techniques following high quality standardized procedures. Laboratory data may provide more clinical detail, for example on the severity, underlying mechanisms and the time of onset of disease. For several adverse drug reactions laboratory data can be considered to be more sensitive identifiers than hospital discharge diagnoses, for example for drug-induced thrombocytopenia.

In this thesis we have given examples of the value of laboratory data for both improvement of sensitivity and insight into the underlying mechanisms of drug-induced thrombocytopenia.

In the study presented in Chapter 3.2 we found that, based on platelet measurements, seven times more patients could be considered as patients with possible drug-induced thrombocytopenia than based on hospital discharge diagnoses for thrombocytopenia. The results of our study are comparable to findings of previous studies in which the registration of hospital discharge diagnoses for neutropenia and hyponatriemia was compared with the presence of these conditions based on laboratory measurements.[7,8] These findings suggest that laboratory parameters can be used as outcome measures for adverse drug reactions such as blood disorders and electrolyte disorders instead of hospital discharge diagnoses for these conditions. The use of laboratory parameters to identify patients with adverse drug reactions may therefore provide more statistical power to pharmacoepidemiological studies than hospital discharge diagnoses do, which is important for the assessment of the association between drug exposure and adverse events. The population-based case control study presented in Chapter 3.1 illustrates the consequences of the lack of sensitivity of hospital discharge diagnoses. In this study we assessed the association between exposure to medicines that are most frequently reported in the literature to cause thrombocytopenia. By using hospital discharge diagnoses for thrombocytopenia as outcome for possible drug-induced thrombocytopenia we found that only exposure to beta-lactam antibiotics was associated with hospitalization for thrombocytopenia. For the other medicines investigated we could not confirm associations with thrombocytopenia, which suggests a limited sensitivity.

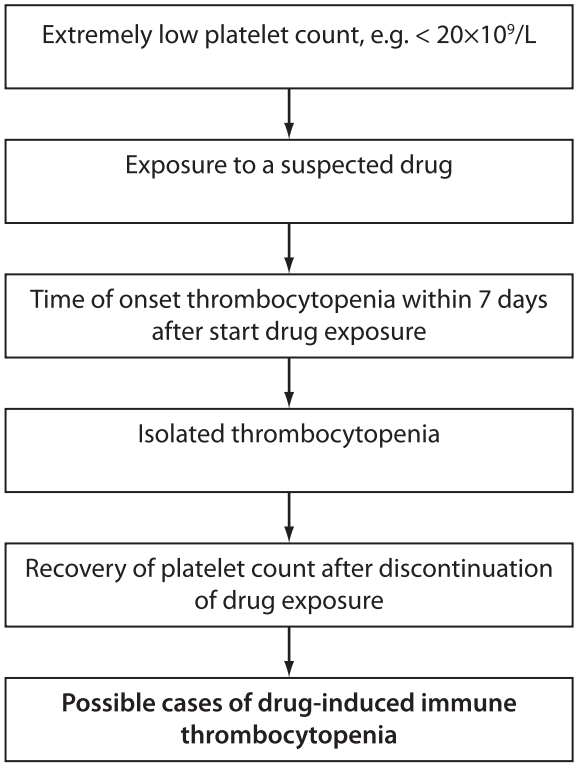
The value of laboratory data for gaining insight into the underlying mechanism of adverse drug reactions is illustrated in the study presented in Chapter 4.1.1.

Although chemotherapy-induced thrombocytopenia is generally believed to be caused by bone marrow depression, immune-mediated mechanisms may also play a role. By using laboratory data we were able to identify patients who developed isolated thrombocytopenia characteristic for an immune mediated mechanism of drug-induced thrombocytopenia.[9] Insight in the underlying mechanism is important for risk assessment of adverse drug reactions, because the implications for treatment of an immune-mediated mechanism differ from the implications of bone marrow depression. The first mechanism is an example of a type B reaction [10] and thus implies that the medication should be stopped. The second mechanism, however, is an example of a dose dependent type A reaction [10] which implies that the dosage of the cytostatic therapy should be reduced.

Despite the value of laboratory markers in the assessment of associations between drug exposure and adverse drug reactions, potential limitations to laboratory data collected during clinical practice need to be considered. First, a laboratory test that can be used as outcome measure, does not exist for all adverse drug reactions. However, in the majority of serious adverse drug reactions laboratory data could be used to identify patients with a potential drug toxicity, including hepato-, nephro- and hematotoxicity. Second, one must be aware of potential selection bias that could be introduced by selective measurement of laboratory tests in clinical practice. Laboratory tests are known to be performed more frequently in patients perceived by physicians to be at greater risk of complications.[11] In the study presented in Chapter 4.2.1 we observed that platelet measurements are obtained more frequently in patients who are severely ill. Third, it is important to be aware of the potential unspecificity of laboratory parameters for adverse drug reactions. Most abnormal laboratory results can reflect several pathological conditions. For example, over 60 diseases and medical interventions other than medication can cause thrombocytopenia (see Appendix Chapter 3.2). In the study presented in Chapter 3.2 we found that in 96.3% of patients with thrombocytopenia, based on a platelet count less than 100×10^9/L, one or more of these conditions were present. When a patient is exposed to a medicine suspected to cause thrombocytopenia, but also suffers from a condition known to be associated with thrombocytopenia, the question arises whether the medicine or the disease caused the thrombocytopenia. Therefore, it is important to take the presence of diseases that could explain the thrombocytopenia into account in designing studies aimed at assessing the association between drug exposure and thrombocytopenia. Restriction, stratification and modelling techniques could be used to unravel the question whether the medicine or the disease is responsible for the observed association between drug exposure and thrombocytopenia in patient populations. An additional approach

to deal with the potentially limited specificity of a low platelet count for drug-induced thrombocytopenia could be the use of a more specific definition of the drug-induced thrombocytopenia under investigation, reflected in a case-finding algorithm (Figure 1). For immune-mediated drug-induced thrombocytopenia characteristics that could be incorporated in such an algorithm include the time of onset, the underlying mechanism, the severity of the thrombocytopenia and recovery of the platelet count after discontinuation of the medication. Further research is needed to investigate the usefulness in terms of validity and accuracy of such an algorithm for identifying cases of drug-induced thrombocytopenia within population-based healthcare databases.

Figure 1 **Conceptual algorithm for identification of cases of drug-induced immune thrombocytopenia from automated health care data based on specific characteristics of drug-induced immune thrombocytopenia**



LABORATORY MARKERS AS BIOMARKERS OF ADVERSE DRUG REACTIONS

Tools that enable the identification of patients at high risk of adverse drug reactions can be valuable in preventing or minimizing the patient harm caused by these adverse drug reactions. Biomarkers, defined by the Biomarkers Definitions Working Group [12] as characteristics that can be objectively measured and evaluated as indicators of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention, may be such tools. Dedicated to develop safer drugs and to improve safer use of drugs, research into biomarkers of adverse drug reactions has expanded in recent years.[13-15] Three general applications of biomarkers of adverse drug reactions are identified: biomarkers for the identification of patients at high risk of drug-related toxicity at the start of treatment, biomarkers for the detection of early toxicity that would indicate further progression to severe toxicity and biomarkers for discriminating between underlying mechanisms of an adverse drug reaction.

In this thesis we have looked into an example of a mechanistic biomarker for an adverse drug reaction. In the study presented in Chapter 4.1.2 we tested the hypothesis that mean platelet volume and platelet distribution width have discriminative value for immune-mediated and myelosuppression-related chemotherapy-induced thrombocytopenia. Such a biomarker could be valuable in clinical practice because these types of chemotherapy-induced thrombocytopenia require different follow-up to prevent more severe thrombocytopenia in recurrent exposure to the cytostatic drug. The results of our study suggest that the investigated platelet indices are not useful for this purpose. However, as discussed in Chapter 4.1.2 other biomarkers such as reticulated platelets and immature platelet fraction may be useful for discriminating immune-mediated and myelosuppression related chemotherapy-induced thrombocytopenia. Further research with UPOD will be conducted to test this hypothesis.

Data platforms comprising patient-oriented data on laboratory markers, medication exposure and health outcomes collected from patient care, such as UPOD, provide unique opportunities for the identification of currently unknown potential biomarkers of adverse drug reactions. Such data platforms allow the conduct of large scale biomarker studies in a clinically representative population in a relatively short time and against low costs, which is difficult to realize in prospective studies. In addition, such data platforms allow to investigate potential multimarker panels, i.e. combination of individual biomarkers. This is relevant with regard to adverse drug reactions because these may arise from multiple interacting factors and

therefore multimarker panels may be more informative for adverse drug reactions than individual biomarkers.

UPOD provides specific opportunities for identifying new biomarkers of drug-induced blood disorders. In addition to standard reported cell count parameters like hemoglobin, differential leucocyte count and platelet count, this database also contains parameters on young blood cell counts and cell morphology parameters measured by flow cytometry techniques with automated hematology analysers during patient care. In addition to being potential mechanistic biomarkers of chemotherapy-induced blood disorders, as described above, hematological parameters on young blood cells and cell morphology are also of interest as potential biomarkers for early detection of different types of drug induced blood disorders. For example, decreases in parameters reflecting bone marrow activity like reticulocyt count and reticulated platelet count may be early signals of the occurrence of myelosuppression due to chemotherapy. The association between changes in these parameters and the occurrence of drug-induced myelosuppression has not been investigated before and will be subject of research with data from UPOD. Another example of a drug-induced blood disorders for which early detection with hematology parameters may be possible is heparin-induced thrombocytopenia (HIT). Platelet activation, which is a component of the underlying mechanism of HIT [16] results in a change of the shape of platelets.[17] Platelet shape change may be detectable with hematology parameters reflecting platelet size [18] and platelet morphology. Currently we are investigating whether such parameters have sufficient prognostic value to be useful as early warning biomarkers of HIT.

LABORATORY MARKERS AND MEDICATION SAFETY IN PATIENT CARE

Laboratory test results are often important for appropriate selection, dosing and monitoring of drug therapy. This creates an important role for clinical chemists and pharmacists in optimizing the benefits of drug therapy. On average, drug package inserts contain 6.6 laboratory-related issues per medicine, including indications, contraindications, dose adjustments, toxicity indicators, baseline monitoring, follow-up monitoring and medicine-test interference.[19] In Table 1 several examples of such issues are presented. With regard to drug-drug interactions a recent study showed that laboratory information is required to interpret the clinical relevance of a third of all signaled drug-drug interactions in the community pharmacy setting.[20]

Table 1 Ten ways laboratory-pharmacy linkage can help in patient care [a]

Category	Concept	Special role for the computer/linkage	Example		
			lab [b]	–	**drug**
Drug selection	Lab contraindicates drug	prevents prescription writing or dispensing	+ pregnancy test	–	ACE inhibitor
			↑ SUN/Cr	–	metformin
	Lab suggests indication for drug	generate timely reminders, tracking interventions	↑ TSH	–	levothyroxine sodium
			↑ cholesterol	–	lipid-lowering treatment
Dosing	Lab affecting drug dose	performs dose calculations based on age, sex, lab value and weight	↑ creatinine	–	digoxin, vancomycine hydrochloride
	Drug requiring lab for titration	statistical process control dosing adjustment charts	PT/INR	–	warfarin sodium
			drug levels	–	anticonvulsant
Monitoring	Abnormal lab signaling toxicity	triggers alert, assesses likelihood	liver enzymes	–	isoniazid, glitazones
			↓ HCT, WBC	–	chloramphenicol
			↓ platelets	–	LMWH (**Ch. 4.2.1**)
	Drug warranting lab monitoring for toxicity	oversees scheduling of both baseline and serial monitoring tests	WBC	–	clozapine
			creatinine	–	amphotericin B
			platelet count	–	heparin (**Ch. 4.2.1**)
Lab interpretation	Drug influencing or interfering with lab	warns against/interprets false-positives and false-negatives	free thyroxine	–	carbamazepine
			false + urine opiates	–	quinolones
	Drug impacting on response to lab finding	resets alarm threshold for treated patients	↓ or ↑ glucose	–	insulin
			+ RPR	–	penicillin
Improvement	Drug toxicity/Effects surveillance	data mining of lab and drug data to generate new hypotheses of drug effects	▪ detects signals of previously undocumented reaction (e.g. hepatotoxicity) ▪ Isolated thrombocytopenia in cytostatic drug treatment (**Ch. 4.1.1**)		
	Quality oversight	monitors time interval between lab testing and prescription change, adequacy/appropriateness of lab monitoring	▪ treatment delay after abnormal results (↑ TSH, ↑ K^+, + blood culture) and initiation of appropriate treatment ▪ ↓ platelet count in heparin treatment and testing for antibodies and starting alternative anticoagulation (**Ch. 4.2.1**)		

lab = laboratory; ACE = angiotensin; SUN = serum urea nitrogen; Cr = creatinine; TSH = thyrotropin; PT = prothrombin time; INR = international normalized ratio; HCT = hematocrit; WBC = white blood cell count; RPR = rapid plasma regain; K^+ = potassium

a) Adapted from Schiff et al.[19] by permission of the American Medical Association.

b) Plus sign indicates positive.

The laboratory and medication data in UPOD have value for analyzing the use of laboratory information in monitoring pharmacotherapy and thereby for identifying potential threats to the safety of patients.[19] The application of UPOD for this purpose is illustrated by the study presented in Chapter 4.2.1 in which we found that compliance with recommendations for platelet count monitoring for heparin-induced thrombocytopenia in patients treated with low molecular weight heparin at our institution is low. In addition, the results of the study suggest that recommendations for management of possible heparin-induced thrombocytopenia in these patients are not abided by. Suboptimal use of laboratory information in pharmacotherapy, as illustrated in our study, may put patients at higher risk of adverse drug reactions than necessary. This could be a motive for licensing authorities to demand withdrawal of a drug from the market. For example, lack of compliance with recommendations for liver enzyme monitoring, despite recurrent notification of physicians, played an important role in the withdrawal of troglitazone from the market.[21] The rationale behind recommendations for laboratory monitoring during treatment is the premise that monitoring is useful for preventing harm due to adverse drug reactions. However, for most recommendations on monitoring no evidence exists on the prevention of actual harm. In order to prevent harm the monitoring procedures must be designed in such a way that the adverse drug reaction can be detected, i.e. is sensitive for the adverse drug reactions. However, the underlying mechanism of an adverse drug reaction may prohibit it from being detected by regular monitoring, for instance in case of idiosyncratic acute toxicity. For example, in the case of troglitazone it is still unclear whether the recommended regular monitoring of liver enzymes would have prevented liver toxicity.[22] An example of drug-laboratory monitoring that has been shown to be effective in preventing severe patient outcomes is close leukocyte monitoring for severe agranulocytosis in patients treated with clozapine.[23] In addition to the sensitivity of a laboratory test to detect the adverse drug reactions, several other criteria have to be met to make laboratory monitoring for the adverse drug reaction useful, including the severity of the adverse drug reaction, the availability of an effective strategy following a critical test result, the availability of a valid test,[24,25] and the specificity of the test for the adverse drug reactions compared to other conditions with symptoms similar to the adverse drug reactions. Non-specificity of laboratory test results for an adverse drug reaction may lead to alert fatigue and consequently to overriding of alerts by physicians.[25] For platelet count monitoring in heparin-induced thrombocytopenia, which we investigated in Chapter 4.2.1, most criteria seem to be met, but whether close monitoring of the platelet count truly prevents the severe outcomes of heparin-induced thrombocytopenia has never been investigated.

Drug-laboratory monitoring procedures which have been shown to be useful for lowering the risk of adverse drug reactions should be actively used in clinical practice. A tool that is considered to be valuable for this purpose is guidance for medication-associated laboratory testing by clinical decision support by which physicians are supported in ordering and interpreting laboratory test at initiating and follow-up drug treatment.[19,26-28] For this purpose electronic clinical laboratory and medication information systems should be linked 'real-time'. This linkage may lead to a reduction in medication errors [29] and drug-related hospitalizations. Regarding the latter, impaired renal function was recently reported to be a determinant for medication-related hospitalizations.[30] The potential for improving patient care by linking laboratory and medication information systems has also recently been acknowledged by professional organizations representing community pharmacists, hospital pharmacists and clinical chemists in the Netherlands.[31] In this perspective the recent initiatives of Dutch community pharmacists to take the patient's renal function and genetic profile into account in checking the prescribed medication when appropriate at the time of dispensing are noteworthy.[32,33] The effectiveness and cost-effectiveness for improving patient outcome of such approaches have not been investigated. Although more research is needed into the usefulness of laboratory monitoring of pharmacotherapy we believe that better integration of laboratory and medication data has great potential for improving patient care and safety.

CONCLUSIONS AND FUTURE RESEARCH PERSPECTIVES

The findings from the studies presented in this thesis justify the conclusion that automated laboratory data collected in patient care have substantial value for different aspects of drug safety research. Laboratory parameters can be considered as more sensitive identifiers of patients with adverse drug reactions which can be detected with a laboratory test, such as thrombocytopenia, compared to hospital discharge diagnoses. When the potential non-specificity of laboratory tests for adverse drug reactions can be dealt with appropriately, laboratory data provide better opportunities for assessing and quantifying the risk of such adverse drug reactions. In addition, laboratory parameters can be useful in elucidating the mechanism of newly detected adverse drug reactions and as biomarkers in determination and management of the risk of adverse drug reactions. Finally, retrospective linkage of laboratory and medication data allows the identification of potential hazardous situations in which recommended laboratory tests are not performed in patients at risk of adverse drug reactions. Integration of laboratory

and medication information systems in clinical care has potential for improving the safe use of medication and thereby improving patient care. Data platforms comprising patient-oriented data on laboratory markers, medication exposure and patient outcomes collected during patient care, such as UPOD, can be used for all these purposes.

With new drugs coming to the market the need for good methods and tools to determine the risk of adverse drug reactions is evident. Data platforms like UPOD are a unique resource to learn about the positive and negative effects of medicines and how these need to be used in clinical practice in order to obtain maximum benefit for the patient. Perspectives for future research with such data platforms concerning drug-induced blood disorders include the detection and quantification of signals for drug-induced blood disorders, the elucidation of the underlying mechanisms, the identification of potential biomarkers for early detection of drug-induced blood disorders and the investigation of the usefulness of laboratory monitoring for early detection of drug-induced blood disorders.

REFERENCES

1. Hampton T. Postmarket "pharmacovigilance" program on alert for adverse events from drugs. JAMA 2007;298:851-2.
2. Solomon DH, Avorn J. Coxibs, science, and the public trust. Arch Intern Med 2005;165:158-60.
3. Weaver J, Willy M, Avigan M. Informatic tools and approaches in postmarketing pharmacovigilance used by FDA. AAPS J 2008;10:35-41.
4. Stricker BH, Psaty BM. Detection, verification, and quantification of adverse drug reactions. BMJ 2004;329:44-7.
5. Iezzoni LI. Using administrative diagnostic data to assess the quality of hospital care. Pitfalls and potential of ICD-9-CM. Int J Technol Assess Health Care 1990;6:272-81.
6. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. J Clin Epidemiol 2005;58:323-37.
7. 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.
8. Petitti DB, Contreras R, Glowalla M, Miday R. Most severe neutropenia in individuals with no chronic condition did not result in a specific diagnosis. J Clin Epidemiol 2004;57:1182-7.
9. Wazny LD, Ariano RE. Evaluation and management of drug-induced thrombocytopenia in the acutely ill patient. Pharmacotherapy 2000;20:292-307.
10. Meyboom RH, Lindquist M, Egberts AC. An ABC of drug-related problems. Drug Saf 2000;22:415-23.

11. Selby JV, Smith DH, Johnson ES, Raebel MA, Friedman GD, et al. Kaiser Permanente Medical Care Program. In: Strom B, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd.; 2005. p. 241-59.
12. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89-95.
13. Woodcock J, Woosley R. The FDA critical path initiative and its influence on new drug development. Annu Rev Med 2008;59:1-12.
14. Altar CA. The Biomarkers Consortium: on the critical path of drug discovery. Clin Pharmacol Ther 2008;83:361-4.
15. Lesko LJ, Atkinson AJ, Jr. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. Annu Rev Pharmacol Toxicol 2001;41:347-66.
16. Warkentin TE. Heparin-induced thrombocytopenia: pathogenesis and management. Br J Haematol 2003;121:535-55.
17. Storey RF. Biology and pharmacology of the platelet P2Y12 receptor. Curr Pharm Des 2006;12:1255-9.
18. Tomer A. Platelet activation as a marker for in vivo prothrombotic activity: detection by flow cytometry. J Biol Regul Homeost Agents 2004;18:172-7.
19. Schiff GD, Klass D, Peterson J, Shah G, Bates DW. Linking laboratory and pharmacy: opportunities for reducing errors and improving care. Arch Intern Med 2003;163:893-900.
20. Geerts AFJ, de Koning GHP, de Smet PAGM, van Solinge WW, Egberts ACG. Laboratory tests in the clinical risk management of potential drug-drug interactions. Submitted for publication.
21. Graham DJ, Mosholder AD, Gelperin K, Avigan MI. Pharmacoepidemiology and Risk Management. In: Strom B, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd.; 2005. p. 515-30.
22. Senior JR. Monitoring for hepatotoxicity: what is the predictive value of liver "function" tests? Clin Pharmacol Ther 2009;85:331-4.
23. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry 1998;59 Suppl 3:3-7.
24. Pirmohamed M, Ferner RE. Monitoring drug treatment. BMJ 2003;327:1179-81.
25. Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. J Am Med Inform Assoc 2006;13:138-47.
26. Derijks HJ, Oosterhuis WP, de Koning GHP, Egberts ACG. Geneesmiddelgebruik gekoppeld aan klinisch-chemische parameters. Een nieuwe dimensie in medicatiebegeleiding. Pharm Weekbl 2002;19:691-96.
27. Kuperman GJ, Bobb A, Payne TH, Avery AJ, Gandhi TK, et al. Medication-related clinical decision support in computerized provider order entry systems: a review. J Am Med Inform Assoc 2007;14:29-40.
28. Rommers MK, Teepe-Twiss IM, Guchelaar HJ. Preventing adverse drug events in hospital practice: an overview. Pharmacoepidemiol Drug Saf 2007;16:1129-35.
29. Kaushal R, Bates DW. The use of pharmacoepidemiology to study medication errors. In: Strom B, editor. Pharmacoepidemiology. 4th ed. Chichester: John Wiley & Sons Ltd.; 2005.

30. Leendertse AJ, Egberts AC, Stoker LJ, van den Bemt PM. Frequency of and risk factors for preventable medication-related hospital admissions in the Netherlands. Arch Intern Med 2008;168:1890-6.
31. Netherlands Society for Clinical Chemistry and Laboratory Medicine (NVKC). Apothekers en klinisch chemici reduceren medische missers [Persbericht]. Available from: http://www.nvkc.nl/organisatie/documents/persbericht-28-11-2007.pdf (in Dutch) (Accessed March 5, 2009).
32. Royal Dutch Society for the advancement of Pharmacy (KNMP). Farmacogenetica. Available from: http://www.knmp.nl/vakinhoud/farmacotherapie/g-standaard/G-standaard/farmaceutische-en-medicatiebewakingsgegevens/farmacogenetica (in Dutch) (Accessed March 5, 2009).
33. Royal Dutch Society for the advancement of Pharmacy (KNMP). Verminderde nierfunctie. Available from: http://www.knmp.nl/vakinhoud/farmacotherapie/g-standaard/G-standaard/farmaceutische-en-medicatiebewakingsgegevens/verminderde-nierfunctie (in Dutch) (Accessed March 5, 2009).

SUMMARY

SUMMARY

CHAPTER 1

Recent major safety issues have led to an intense discussion on the need to improve the process of assessing and managing the safety of a drug in the different phases of a drug's life cycle. Regarding the postmarketing phase the prevailing opinion is that better and more integrated methods and tools are needed for earlier detection, quantification and mechanistic unraveling of associations between drug exposure and adverse health outcomes. One of the tools that is considered to be valuable for this purpose is a database with patient-oriented data on medication exposure and laboratory test results collected in clinical care. Linkage of such data on a patient-level provides the opportunity to investigate the association between medication exposure and adverse reactions, which can be detected with laboratory tests that are used in routine clinical practice. There are many adverse drug reactions that can be detected with laboratory test results, for example drug-induced blood disorders. Blood disorders, including conditions like aplastic anemia, neutropenia and thrombocytopenia are among the most reported severe adverse drug reactions. Several drugs have been withdrawn from the market because of their potential to cause severe hematological effects. The majority of drug-induced blood disorders are considered to be type B (hypersensitivity) adverse drug reactions. Despite the high report rates and the potential severity, knowledge on causality, incidence, risk factors, biomarkers, underlying mechanisms and clinical management of drug-induced blood disorders in patient populations is currently still very limited. A database with linked data on medication exposure and laboratory test results may be a valuable instrument for learning more about these issues. The objective of this thesis was to investigate the additional value of laboratory data collected in patient care for drug safety research. We focused on drug-induced thrombocytopenia as an example.

CHAPTER 2

In four of the studies presented in this thesis we used data from the Utrecht Patient Oriented Database (UPOD), a recently established hospital-based database for (pharmaco-)epidemiological research, which is presented in **Chapter 2**. UPOD encompasses automated patient-oriented data on laboratory test results, medication exposure, hospital discharge diagnoses, medical procedures and patient demographics for all patients who were treated at the University Medical Center Utrecht (UMC Utrecht). We present the contents of UPOD in detail and we discuss the potential aspects of drug safety that could be investigated with such databases.

These aspects include the quantification of the risk and risk factors of adverse drug reactions, investigating drug-test interference, determining appropriate prescribing and identification of predictive or prognostic markers for adverse drug reactions. UPOD could specifically be of value for epidemiological investigations on drug-induced blood disorders, because it comprises a unique database with complete automated hematological data, including absolute cell counts and morphological cell characteristics, which are collected in patient care with modern automated hematology analysers.

CHAPTER 3

Chapter 3 of this thesis concerns the quantification of the association between exposure to drugs reported to cause thrombocytopenia and the occurrence of thrombocytopenia in the general population by conducting pharmacoepidemiological studies within population-based automated health care databases. In *Chapter 3.1* we present a population-based retrospective case-control study aimed at quantifying the risk for thrombocytopenia following exposure to drugs that are most often reported in the literature to cause thrombocytopenia in the general population. For this study data from the Dutch PHARMO Record Linkage System were used. Patients with thrombocytopenia (cases) were identified based on the registration of a hospital discharge diagnosis for thrombocytopenia. We identified 705 cases and 2658 matched controls. Within these patients we found that current exposure to β-lactam antibacterials was associated with an increased risk for thrombocytopenia (adjusted odds ratio 7.4; 95% confidence interval 1.8-29.6). Increased risk estimates, although not significant, were found for current exposure to disease modifying antirheumatic drugs and the sulfonamide antibacterial cotrimoxazole (trimethoprim/sulfamethoxazole). No increased risk was found for exposure to anticonvulsants, cinchona alkaloids, diuretics, non-steroidal antiinflammatory drugs or tuberculostatics. This study provided more evidence for an increased risk for thrombocytopenia in current use of β-lactam antibacterials in the general population. However, the expected increase in risk could not be confirmed for the other drugs investigated, which may be the result of limited statistical power.

In this study we used hospital discharge diagnoses for case-finding patients with potential drug-induced thrombocytopenia. However, hospital discharge diagnose are prone to misclassification and underregistration due to the nature of the registration

process, which may be a threat to the validity of a pharmacoepidemiological study in which hospital discharge diagnoses are used for case-finding. An alternative type of data for case-finding potential adverse drug reactions for pharmacoepidemiological research, that is expected to be less prone to misclassification and underregistration, are laboratory data. Within UPOD we conducted a cross-sectional study (*Chapter 3.2*) in which we compared the number of patients with potential drug-induced thrombocytopenia that could be identified by using hospital discharge diagnoses for thrombocytopenia with the number of patients with potential drug-induced thrombocytopenia that could be identified by using platelet measurements. Patients with potential drug-induced thrombocytopenia were defined as patients with potential drug-induced thrombocytopenia (based on discharge diagnosis or a platelet count less than 100×10^9/L) without an alternative diagnosis other than drug-induced thrombocytopenia. Within 56 411 clinical hospitalizations over the two-year period 2004-2005 we found 2817 patients with a platelet count below 100×10^9/L and 74 patients with a discharge diagnoses for treatment. Alternative diagnoses for drug-induced thrombocytopenia were present in respectively 96.3% and 81.1% of the patients, resulting in the identification of 103 patients with potential drug-induced thrombocytopenia based on platelet measurements and 14 patients with potential drug-induced thrombocytopenia based on discharge diagnoses for thrombocytopenia. From these findings we conclude that using platelet measurements data is a more sensitive approach for case-finding potential drug-induced thrombocytopenia than using hospital discharge diagnoses for thrombocytopenia. Our data also illustrated that a low platelet count is very non-specific for potential drug-induced thrombocytopenia. This non-specificity should be dealt with to prohibit extensive manual case-validation of potential cases of drug-induced thrombocytopenia based on platelet measurements. Further research is needed to investigate the best method for this purpose.

CHAPTER 4

In **Chapter 4** we present three observational studies each concerning a different drug safety aspect for which a database with linked data on medication exposure and laboratory test results could be a value tool for gaining knowledge on:

- estimating the incidence of adverse drug reactions (*Chapter 4.1.1*);
- the identification of potential biomarkers for the mechanism of adverse drug reactions (*Chapter 4.1.2*);

▹ and the compliance of physicians with recommendations for laboratory monitoring for early detection of adverse drug reactions (*Chapter 4.2.1*).

The first two studies concern chemotherapy-induced thrombocytopenia, the third study concerns heparin-induced thrombocytopenia.

Many cytostatic agents are known to cause thrombocytopenia, most frequently by inducing aplasia or hypoplasia of the megakaryocytic cells of the bone marrow. However, though far less frequently, cytostatic agents can also cause thrombocytopenia by immune-mediated mechanisms. Although the occurrence of chemotherapy-induced thrombocytopenia is well known in cancer patients receiving chemotherapy data on the incidence and relative risk in clinical practice are scarce, especially regarding immune-mediated chemotherapy-induced thrombocytopenia. We performed a retrospective cohort study (*Chapter 4.1.1*), using data from UPOD and the Regional Cancer Registry Middle Netherlands, to estimate the incidence and relative risk of thrombocytopenia in adult patients with solid tumors. The first course of cytostatic drug treatment at the UMC Utrecht after diagnosis of the tumor was selected per patient. Within a population of 614 patients an incidence of thrombocytopenia (grade 1-4) of 21.4% was observed. The highest incidences of thrombocytopenia were observed in carboplatin mono therapy (81.8%) and in combination therapies including carboplatin (58.2%), gemcitabine (64.4%) and paclitaxel (59.3%). In addition to the incidence of thrombocytopenia we estimated the incidence of isolated thrombocytopenia, which was considered to be a proxy for immune-mediated thrombocytopenia. Isolated thrombocytopenia was observed in 6.2% of all included patients, with the highest incidences of isolated thrombocytopenia observed in combination therapies including oxaliplatin (28.6%) and gemcitabine (28.9%). Further research should focus on the unraveling of the underlying mechanism and on the identification of risk factors and biomarkers of chemotherapy-induced thrombocytopenia.

Knowledge on the underlying mechanism of chemotherapy-induced thrombocytopenia, i.e. immune-mediated or myelosuppression-related, is relevant in clinical practice. In case of immune-mediated thrombocytopenia renewed exposure to the cytostatic agent that caused the thrombocytopenia should be avoided because severe thrombocytopenia and uncontrollable bleeding could occur. However, in case of bone marrow suppression-related chemotherapy-induced thrombocytopenia dose adjustment in subsequent cycles may be an effective measure to prevent further development of thrombocytopenia. A simple parameter that can be used to discriminate between these mechanisms of chemotherapy-

induced thrombocytopenia could be valuable in clinical practice. Previous research has shown that indices related to platelet size, including mean platelet volume (MPV) and platelet distribution width (PDW) have value to discriminate between immune- and myelosuppression-related causes of thrombocytopenia. We hypothesized that these platelet indices also have value for discriminating immune-mediated chemotherapy-induced thrombocytopenia from myelosuppression-related chemotherapy-induced thrombocytopenia. This hypothesis was tested in the retrospective cohort study presented in *Chapter 4.1.2*. In this study a subgroup of patients from the cohort of oncology patients receiving cytostatic drug treatment (as presented in Chapter 4.1.1) was studied. This subgroup concerned patients for which complete hematology data obtained during the course of chemotherapy treatment were available within the UPOD hematology database. We compared MPV and PDW between 34 patients with isolated thrombocytopenia (proxy for immune-mediated thrombocytopenia) and 63 patients with non-isolated thrombocytopenia (proxy for myelosuppression-related thrombocytopenia). We did not observe significant differences and concluded that our hypothesis is unlikely to be true. Further research into a mechanistic biomarker for chemotherapy-induced thrombocytopenia could focus on reticulated platelet count or immature platelet fraction, two new platelet indices that reflect the megakaryocytic function of the bone marrow.

For many medications close monitoring of laboratory parameters during treatment is recommended for detection of possible adverse drug reactions in an early phase, including monitoring of blood cell counts for detection of blood disorders. For example, for patients receiving heparin treatment it is recommended, in summaries of product characteristics and clinical guidelines, to monitor the platelet count for detection of heparin-induced thrombocytopenia (HIT), an adverse drug reaction with potentially severe consequences due to its association with thrombosis. It was unknown whether recommendations for platelet count monitoring for HIT were abided by at our institution. By conducting a retrospective cohort study (*Chapter 4.2.1*), using data from UPOD, we investigated the frequency of compliance with recommendations for platelet count monitoring in 6804 hospitalized patients who received prophylaxis and treatment dosing of the low molecular weight heparins dalteparin and nadroparin for at least five consecutive days. In addition, we investigated in this study population the frequency of compliance with recommendations, from summary of product characteristics and clinical guidelines, for testing for the presence of heparin platelet factor 4 antibodies (HPF4-Ab) and starting alternative anticoagulation when a considerable drop

in platelet count occured. The frequency of compliance with platelet count monitoring recommendations was 26.3% for all patients receiving dalteparin, 35.6% for all patients receiving nadroparin, 23.0% for surgical patients receiving prophylactic dosing of either dalteparin or nadroparin and 41.8% for patients exposed to unfractionated heparin in 100 days before the start of either dalteparin or nadroparin treatment. The frequency of testing for HPF4-Ab and starting alternative anticoagulation with danaparoid in patients with a 50%-drop in platelet count was 5.4% and 0% respectively. The results of our study suggest that compliance with recommendations for platelet count monitoring and management of possible heparin-induced thrombocytopenia is low at our institution. Further research should elucidate the reasons for non-compliance. Policies and tools to improve compliance with recommended laboratory monitoring should be developed to secure the safe use of low molecular weight heparins and other medications.

CHAPTER 5

In **Chapter 5**, the general discussion, the value of linking data on laboratory test results to data on medication exposure is put into the broader perspective of the current needs of drug safety research as well as the needs of clinical patient care and recommendations for further research are given. We believe that the findings from the studies presented in this thesis justify the conclusion that a research database with data on laboratory test results linked to data on medication exposure is a tool with substantial additional value for drug safety research. Databases like UPOD are a unique resource to learn about the positive and negative effects of medicines and how these need to be used in clinical practice in order to obtain maximum benefit for the patients.

SAMENVATTING

SAMENVATTING

HOOFDSTUK 1

Op het moment dat een nieuw geneesmiddel door de registratieautoriteit wordt toegelaten tot de markt zijn mogelijk nog niet alle effecten van het geneesmiddel bekend. Regelmatig blijkt dat een geregistreerd geneesmiddel, nadat het gedurende langere tijd door een groot aantal patiënten in de dagelijkse praktijk is gebruikt, schadelijke, soms zelfs zeer ernstige, neveneffecten (bijwerkingen) heeft, welke niet zijn ontdekt in het onderzoek dat voorafging aan het op de markt komen van het geneesmiddel. Verklaringen hiervoor zijn dat in pre-registratie onderzoeken maar een beperkt aantal en bovendien streng geselecteerde patiënten over een beperkte duur kan worden bestudeerd. De ontdekking van een aantal ernstige bijwerkingen na toelating van het geneesmiddel tot de markt, heeft in de afgelopen decennia geleid tot de ontwikkeling van farmacovigilantie (geneesmiddelenbewaking). Dit is de wetenschap die zich bezighoudt met de detectie, beoordeling en preventie van bijwerkingen van geneesmiddelen nadat deze zijn toegelaten tot de markt. Naar aanleiding van recente gevallen van ernstige bijwerkingen zijn de verschillende partijen die betrokken zijn bij de beoordeling van de veiligheid van geneesmiddelen van mening dat er behoefte is aan betere methoden en instrumenten om bijwerkingen van geneesmiddelen tijdig te ontdekken, het risico op de bijwerking met voldoende zekerheid te kwantificeren en het mechanisme van de bijwerking te duiden. Een instrument dat nog weinig wordt gebruikt, maar waarvan wordt verondersteld dat het meerwaarde heeft voor het bestuderen van bijwerkingen van geneesmiddelen, is een databank met geautomatiseerde zorggegevens over medicatieblootstelling en laboratoriumuitslagen. Een groot aantal bijwerkingen van geneesmiddelen, zoals bloedbeeldafwijkingen, leverschade en verstoringen van de elektrolytenbalans, is te detecteren met een laboratoriumtest. Door koppeling van zorggegevens over medicatieblootstelling en laboratoriumuitslagen op het niveau van de patiënt kan epidemiologisch onderzoek worden gedaan naar een verband tussen geneesmiddelgebruik en het optreden van biochemisch detecteerbare bijwerkingen. Het onderzoek beschreven in dit proefschrift heeft als doel de meerwaarde van laboratoriumuitslagen voor verschillende aspecten van het bestuderen van de veiligheid van geneesmiddelen in patiëntenpopulaties te bepalen. Hierbij is geneesmiddel-geïnduceerde trombocytopenie, een tekort aan trombocyten (bloedplaatjes) veroorzaakt door geneesmiddelgebruik, als voorbeeld gebruikt. Van een groot aantal geneesmiddelen is in medische literatuur beschreven en bij bijwerkingregistratiesystemen gemeld dat ze trombocytopenie, maar ook andere bloedbeeldafwijkingen zoals bijvoorbeeld aplastische anemie (tekort aan een of meerdere type bloedcellen) en agranulocytose (tekort aan granulocyten, een vorm van witte bloedcellen) kunnen veroorzaken. In de meeste gevallen lijkt de oorzaak

van de bloedbeeldafwijking te liggen in overgevoeligheid van het lichaam voor het geneesmiddel, waarbij het lichaam antistoffen aanmaakt tegen eigen bloedcellen. De oorzaak kan echter ook liggen in verminderde aanmaak van bloedcellen ten gevolge van schadelijke effecten van het geneesmiddel op het beenmerg waar de vorming van nieuwe bloedcellen plaatsvindt. In de afgelopen decennia zijn meerdere geneesmiddelen van de markt gehaald, of in gebruik beperkt, omdat ze ernstige bloedbeeldafwijkingen bleken te kunnen veroorzaken. Ondanks het grote aantal meldingen van geneesmiddel-geïnduceerde bloedbeeldafwijkingen, is er nog maar weinig kennis over de frequentie waarin deze bijwerkingen voorkomen en over de risicofactoren die hieraan ten grondslag liggen. Daarnaast is voor de meeste geneesmiddel-geïnduceerde bloedbeeldafwijkingen niet bevestigd wat het oorzakelijke mechanisme is. Ook zijn er geen stoffen bekend die door een toename of afname in het bloed een indicator kunnen zijn voor het optreden van bijwerkingen, zogenaamde biomarkers. Daarnaast is nog niet veel bekend over de manier waarop in de praktijk met het risico op geneesmiddel-geïnduceerde bloedbeeldafwijkingen wordt omgegaan. In de onderzoeken die gepresenteerd worden in dit proefschrift is geprobeerd om gebruikmakend van in de zorg vastgelegde patiëntgegevens meer te leren over deze aspecten van geneesmiddel-geïnduceerde trombocytopenie.

HOOFDSTUK 2

Voor vier van de vijf in dit proefschrift gepresenteerde onderzoeken zijn gegevens gebruikt uit de Utrecht Patient Oriented Database (UPOD). UPOD is een nieuwe databank voor epidemiologisch onderzoek die in het kader van dit promotieonderzoek is gerealiseerd. In **Hoofdstuk 2** wordt UPOD in detail beschreven. UPOD bevat elektronisch vastgelegde laboratoriumuitslagen en gegevens over medicatieblootstelling van alle patiënten die een behandeling hebben ondergaan in het Universitair Medische Centrum Utrecht (UMC Utrecht). In aanvulling op deze laboratoriumuitslagen afkomstig uit het laboratorium informatie systeem bevat UPOD unieke gegevens over het bloedbeeld van patiënten welke tijdens de routine zorg zijn bepaald met behulp van moderne bloedceltellers die in het diagnostisch laboratorium van het UMC Utrecht worden gebruikt. Daarnaast bevat UPOD gegevens van deze patiënten over ziektediagnoses die worden vastgelegd bij ontslag uit het ziekenhuis, medische verrichtingen en demografische kenmerken. Naast de oorsprong van de data worden in Hoofdstuk 2 de mogelijkheden voor farmaco-epidemiologisch onderzoek (het bestuderen van effecten en het gebruik van geneesmiddelen in patiëntenpopulaties) besproken die geboden worden door

de binnen UPOD gerealiseerde koppeling van laboratoriumuitslagen met gegevens over geneesmiddelblootstelling. Hierbij wordt in het bijzonder aandacht besteed aan de mogelijkheden voor het bestuderen van biochemisch detecteerbare bijwerkingen zoals geneesmiddel-geïnduceerde bloedbeeldafwijkingen. Mogelijkheden omvatten onder andere het kwantificeren van het risico op bijwerkingen, het identificeren van risicofactoren voor bijwerkingen, het bestuderen van mogelijke biomarkers voor bijwerkingen en het onderzoeken hoe laboratoriuminformatie bij het starten en het vervolgen van de behandeling met geneesmiddelen in de praktijk gebruikt wordt.

HOOFDSTUK 3

Het onderwerp van **Hoofdstuk 3** van dit proefschrift is het schatten van het risico dat patiënten hebben op het ontwikkelen van trombocytopenie tijdens blootstelling aan geneesmiddelen door gebruik te maken van databanken met zorggegevens.
Het in *Hoofdstuk 3.1* gepresenteerde onderzoek had tot doel om op populatieniveau het verband tussen blootstelling aan geneesmiddelen en het optreden van trombocytopenie te onderzoeken. De geneesmiddelen die in dit onderzoek werden bestudeerd zijn geneesmiddelen waarvan in de medische literatuur het meest frequent melding is gemaakt dat ze trombocytopenie kunnen veroorzaken. Het onderzoek was een retrospectief patiënt-controle onderzoek. Er werd gebruik gemaakt van gegevens uit het PHARMO Record Linkage System. Dit is een Nederlandse onderzoeksdatabank waarin momenteel van meer dan 2 miljoen personen zorggegevens kunnen worden gekoppeld ten behoeve van farmaco-epidemiologisch onderzoek. Om patiënten met trombocytopenie te identificeren werd gebruik gemaakt van gegevens over medische diagnoses die door ziekenhuizen worden geregistreerd als een patiënt uit het ziekenhuis wordt ontslagen, zogeheten ontslagdiagnoses. In de databank werden 705 patiënten met een ontslagdiagnose voor trombocytopenie geïdentificeerd. Er werden 2.658 geschikte controle-patiënten, patiënten zonder een ontslagdiagnose voor trombocytopenie, geselecteerd uit de databank. Er werd een sterke relatie gevonden tussen het gebruik van β-lactam antibiotica en het optreden van trombocytopenie (gecorrigeerde odds ratio 7,4; 95% betrouwbaarheidsinterval 1,8-29,6). Daarnaast werd een mogelijk verband gevonden met het gebruik van 'disease-modifying antirheumatic drugs' (ziekteverloop beïnvloedende geneesmiddelen tegen reuma) en het gebruik van het antibioticum co-trimoxazol. Deze verbanden konden echter niet statistisch worden bevestigd. Er werd geen verband gevonden tussen trombocytopenie en

het gebruik van anticonvulsiva, cinchona alkaloiden (kinine, kinidine), diuretica, 'non-steroidal anti-inflammatory drugs' (ontstekkingsremmende geneesmiddelen) en tuberculostatica. De resultaten van dit onderzoek dragen bij aan onze kennis over het verhoogde risico op het optreden van trombocytopenie tijdens het gebruik van β-lactam antibiotica. Dat voor de overige geneesmiddelen geen significante associatie tussen blootstelling aan het geneesmiddel en het optreden van trombocytopenie werd gevonden kan mogelijk veroorzaakt zijn door onvoldoende grote patiëntenaantallen in de bestudeerde subgroepen en daarmee het beperkte onderscheidingsvermogen ('power') van het onderzoek.

In epidemiologische onderzoeken naar een verband tussen blootstelling aan geneesmiddelen en het optreden van mogelijke bijwerkingen wordt veelvuldig gebruik gemaakt van gegevens over ontslagdiagnoses om te bepalen of bij de patiënt wel of niet een mogelijke bijwerking is opgetreden. De registratie van ontslagdiagnoses is echter gevoelig voor foutieve codering en met name incompleetheid, omdat de registratie is gebaseerd op interpretatie van de ontslagbrief van de arts door codeurs. Dit kan consequenties hebben voor de betrouwbaarheid van het onderzoek dat met deze gegevens wordt uitgevoerd. Voor bijwerkingen die detecteerbaar zijn met een laboratoriumtest geldt dat het gebruik van laboratoriumuitslagen een alternatieve methode is voor het identificeren van patiënten met mogelijke bijwerkingen voor onderzoek naar een verband tussen blootstelling aan geneesmiddelen en het optreden van mogelijke bijwerkingen. In het in *Hoofdstuk 3.2* gepresenteerde cross-sectioneel onderzoek is het gebruik van ontslagdiagnoses en laboratoriumuitslagen voor het identificeren van patiënten met mogelijk geneesmiddel-geïnduceerde trombocytopenie vergeleken. Voor dit onderzoek is gebruik gemaakt van gegevens uit UPOD over de periode 2004-2005. In de studiepopulatie van 41.112 patiënten werden zeven keer zoveel patiënten met een mogelijke geneesmiddel-geïnduceerde trombocytopenie gevonden op basis van een laag trombocytenaantal (minder dan 100×10^9 trombocyten per liter bloed) in vergelijking met ontslagdiagnoses voor trombocytopenie (103 versus 14 patiënten). Uit deze resultaten concluderen wij dat het aannemelijk is dat het gebruik van laboratoriumgegevens leidt tot een completere identificatie van patiënten met mogelijke geneesmiddel-geïnduceerde trombocytopenie dan wanneer ontslagdiagnoses voor trombocytopenie worden gebruikt. Echter, het gebruik van alleen het trombocytenaantal om patiënten met mogelijke geneesmiddel-geïnduceerde trombocytopenie te identificeren zal leiden tot de identificatie van veel patiënten waarbij hier in werkelijkheid geen sprake van is (vals positieven). Een laag trombocytenaantal is namelijk geen specifiek kenmerk voor geneesmiddel-geïnduceerde trombocytopenie, omdat het ook een kenmerk

is van veel verschillende ziekten en het gevolg van medische ingrepen kan zijn. Om een goede selectie van patiënten met mogelijk geneesmiddel-geïnduceerde trombocytopenie te maken moet naast het trombocytenaantal nadere informatie in beschouwing worden genomen, op basis waarvan kan worden bekeken of het aannemelijk is dat er mogelijk sprake is van een geneesmiddel-geïnduceerde trombocytopenie. Voorbeelden van dit soort informatie zijn gegevens over de ernst van de trombocytopenie, het tijdstip waarop de trombocytopenie zich ontwikkelde en de aanwezigheid van ziekten of medische ingrepen die de trombocytopenie kunnen verklaren. Vervolgonderzoek kan zich richten op het bestuderen van de beste methode om patiënten met geneesmiddel-geïnduceerde trombocytopenie te identificeren in zorgdata.

HOOFDSTUK 4

In **Hoofdstuk 4** worden drie onderzoeken gepresenteerd. Elk onderzoek heeft betrekking op een ander aspect van het bestuderen van biochemisch detecteerbare bijwerkingen van geneesmiddelen waarvoor een databank met gekoppelde gegevens over laboratoriumuitslagen en medicatieblootstelling een waardevol instrument kan zijn:

- het schatten van de incidentie van een bijwerking (*Hoofdstuk 4.1.1*);
- het identificeren van biomarkers voor een bijwerking (*Hoofdstuk 4.1.2*);
- en het bestuderen of aanbevelingen om tijdens de behandeling met geneesmiddelen laboratoriumtesten uit te voeren met tot doel bijwerkingen te detecteren in de praktijk worden gevolgd (*Hoofdstuk 4.2.1*).

De eerste twee onderzoeken (*Hoofdstukken 4.1.1* en *4.1.2*) hebben betrekking op chemotherapie-geïnduceerde trombocytopenie. Het derde onderzoek (*Hoofdstuk 4.2.1*) heeft betrekking op heparine-geïnduceerde trombocytopenie.

Van een groot aantal verschillende cytostatica, geneesmiddelen die worden toegepast bij de behandeling van kanker en ook wel chemotherapeutica worden genoemd, is bekend dat ze trombocytopenie kunnen veroorzaken. In de meeste gevallen veroorzaken cytostatica trombocytopenie omdat ze de aanmaak van trombocyten in het beenmerg remmen. Trombocytopenie kan echter ook veroorzaakt worden door een overgevoeligheidsreactie van het lichaam tegen cytostatica. Hierbij worden antistoffen tegen trombocyten gevormd, wat kan leiden tot een verhoogde afbraak van trombocyten.

Ondanks dat trombocytopenie een bekende bijwerking is van cytostatica, is er weinig bekend over de frequentie waarin trombocytopenie voorkomt bij patiënten die in de klinische praktijk behandeld worden met cytostatica. In het bijzonder is er weinig bekend over de frequentie waarin trombocytopenie ten gevolge van een overgevoeligheidsreactie tegen het cytostaticum voorkomt. Met tot doel het bepalen van de frequentie waarmee trombocytopenie voorkomt in patiënten die in de dagelijkse praktijk met cytostatica behandeld worden, is een retrospectief cohort onderzoek uitgevoerd (*Hoofdstuk 4.1.1*). Voor dit onderzoek werden gegevens uit UPOD en uit de regionale kankerregistratie Midden-Nederland over de periode 2004-2006 gebruikt. In het onderzoek werden 614 patiënten met een solide tumor (een vaste tumor waarbij sprake is van abnormale celdeling in een bepaald orgaan zoals de long of darm) die in het UMC Utrecht behandeling met cytostatica ondergingen bestudeerd. Per patiënt werd de eerste aaneengesloten periode van behandeling met cytostatica sinds de diagnose van de tumor geselecteerd. Trombocytopenie was aanwezig als de patiënt minstens één keer een trombocytenaantal lager dan 100×10^9 trombocyten per liter bloed had op enig moment tijdens de behandeling. Trombocytopenie werd waargenomen in 21,4% van de patiënten. Het meest frequent werd trombocytopenie waargenomen bij patiënten die behandeld werden met alleen het cytostaticum carboplatin (81,8%), combinaties van carboplatin met andere cytostatica (58,2%), combinaties van gemcitabine met andere cytostatica (64,4%) en combinaties van paclitaxel met andere cytostatica (59,3%).

In het onderzoek is ook onderzocht of trombocytopenie 'geïsoleerd' voorkwam, waarmee wordt bedoeld dat er ten tijde van de trombocytopenie geen sprake was van anemie (een te laag gehalte aan hemoglobine in het bloed) of van leukopenie (tekort aan witte bloedcellen). Het optreden van geïsoleerde trombocytopenie werd in dit onderzoek beschouwd als een surrogaat uitkomst voor trombocytopenie veroorzaakt door een overgevoeligheidsreactie. In 6,2% van de patiënten werd geïsoleerde trombocytopenie waargenomen. De hoogste frequentie van geïsoleerde trombocytopenie werd waargenomen bij patiënten die behandeld werden met combinaties van cytostatica waar oxaliplatin deel van uit maakte (28,6%) en combinaties met gemcitabine (28,8%).

De resultaten van dit onderzoek dragen bij aan onze kennis over de frequentie waarin chemotherapie-geïnduceerde trombocytopenie bij patiënten met solide tumoren voorkomt. Vervolgonderzoek moet zich richten op het onderzoeken van de mechanismen waardoor verschillende cytostatica trombocytopenie veroorzaken alsook het identificeren van risicofactoren en biomarkers voor chemotherapie-geïnduceerde trombocytopenie.

Wanneer trombocytopenie optreedt bij een patiënt die behandeld wordt met cytostatica, is het, met het oog op het vervolg van de behandeling, van belang om de oorzaak van de trombocytopenie te kennen. Als de trombocytopenie het gevolg is van een overgevoeligheidsreactie tegen het cytostaticum moet worden voorkomen dat de patiënt opnieuw blootgesteld wordt aan het cytostaticum dat de trombocytopenie veroorzaakt, omdat dit tot een nog ernstigere trombocytopenie kan leiden. Als de trombocytopenie het gevolg is een verminderde aanmaak van trombocyten in het beenmerg kan de behandeling vaak wel voortgezet worden. In dit geval kan de kans op (ernstige) trombocytopenie in het vervolg van de behandeling worden verkleind door de doseringen van de cytostatica te verlagen. Een laboratoriumtest waarmee de onderliggende oorzaak van de chemotherapie-geïnduceerde trombocytopenie eenvoudig en eenduidig kan worden vastgesteld is mogelijk van waarde voor het maken van beslissingen over het voortzetten van de behandeling in patiënten waarin trombocytopenie optreedt. Een dergelijke laboratoriumtest kan worden beschouwd als een biomarker voor het mechanisme van chemotherapie-geïnduceerde trombocytopenie. Uit eerder onderzoek is gebleken dat laboratoriumparameters die informatie geven over de grootte van trombocyten bruikbaar zijn om onderscheid te maken tussen trombocytopenie ten gevolge van een antistofreactie en trombocytopenie ten gevolge van onderdrukking van de aanmaak van trombocyten in het beenmerg. Twee van deze parameters zijn het gemiddelde volume van trombocyten en de spreiding in het volume van trombocyten. Wij stelden de hypothese dat het gemiddelde volume van trombocyten en de spreiding in het volume van trombocyten kunnen worden gebruikt om onderscheid te maken tussen trombocytopenie ten gevolge een overgevoeligheidsreactie tegen een cytostaticum en trombocytopenie ten gevolge van beenmergdepressie veroorzaakt door een cytostaticum. Deze hypothese is getoetst in het onderzoek dat wordt beschreven in *Hoofdstuk 4.1.2*. Voor dit retrospectief cohort onderzoek werd een subgroep van de patiënten uit het onderzoek beschreven in Hoofdstuk 4.1.1 geselecteerd. De subgroep betrof patiënten waarvoor gegevens over het gemiddelde volume van de trombocyten en de spreiding in het volume van de trombocyten beschikbaar waren in UPOD. Deze parameters werden vergeleken tussen 34 patiënten met geïsoleerde trombocytopenie (beschouwd als surrogaat uitkomst voor trombocytopenie veroorzaakt door een overgevoeligheidsreactie) en 63 patiënten zonder geïsoleerde trombocytopenie (beschouwd als surrogaat uitkomst voor trombocytopenie ten gevolge van beenmergdepressie). Er werden geen statistisch significante verschillen gevonden. Hieruit kan worden geconcludeerd dat het aannemelijk is dat onze hypothese onjuist is. Vervolgonderzoek naar een biomarker voor het mechanisme

van chemotherapie-geïnduceerde trombocytopenie kan zich richten op het aantal 'reticulated' trombocyten (de jongste vorm van trombocyten in het bloed) en de fractie 'jonge' trombocyten in de perifere circulatie. Deze twee parameters geven informatie over de activiteit van de aanmaak van trombocyten in het beenmerg.

Voor een groot aantal geneesmiddelen wordt in bijsluiters van geneesmiddelen en klinische richtlijnen aanbevolen om tijdens de behandeling bij patiënten laboratoriumtesten uit te voeren om eventueel optredende bekende bijwerkingen te detecteren. Een voorbeeld van een dergelijke aanbeveling is het advies om regelmatig het trombocytenaantal te controleren bij patiënten die behandeld worden met heparine-achtige bloedstollings-remmende geneesmiddelen om eventueel optredende heparine-geïnduceerde trombocytopenie (HIT) te detecteren. HIT is een bijwerking die ernstige consequenties kan hebben omdat er trombose kan optreden. Het was onbekend of de aanbeveling om het trombocytenaantal regelmatig te controleren in patiënten die worden behandeld met heparine-achtige geneesmiddelen wordt gevolgd in het UMC Utrecht. Dit werd onderzocht in het onderzoek dat wordt gepresenteerd in *Hoofdstuk 4.2.1*. Voor dit retrospectief cohort onderzoek werd gebruik gemaakt van gegevens uit UPOD over de periode 2004-2005. Patiënten die tijdens ziekenhuisopname ten minste vijf achtereenvolgende dagen werden behandeld met een van de laagmoleculaire heparines dalteparine en nadroparine werden geselecteerd voor het onderzoek. Het werd onderzocht in welk percentage van de geselecteerde patiënten de aanbevelingen om het trombocytenaantal regelmatig te controleren werden gevolgd. Daarnaast is ook bestudeerd in welk percentage van de patiënten waarbij een grote daling in het trombocytenaantal optrad er aan de mogelijke diagnose HIT werd gedacht. Dit was gebaseerd op de aanbevelingen aan de behandelaar uit bijsluiters en klinische richtlijnen, om bij verdenking op een mogelijke HIT een test op de aanwezigheid van heparine-plaatjes factor-4 antistoffen aan te vragen en een behandeling met een alternatief bloedstollings-remmend geneesmiddel, danaparoid, te starten. In het onderzoek is de behandeling van 6.804 patiënten bestudeerd. In 26,3% van de patiënten die werden behandeld met dalteparine werden de aanbevelingen om het trombocytenaantal regelmatig te controleren gevolgd. Dit gold voor 35,6% van de patiënten die werden behandeld met nadroparine. In 5,4% van de patiënten waarbij tijdens de behandeling een grote daling in het trombocytenaantal optrad werd een test voor de aanwezigheid van heparine-plaatjes factor-4 antistoffen uitgevoerd. In geen van deze patiënten werd behandeling met danaparoid gestart. De resultaten van dit onderzoek laten zien dat de aanbevelingen om een eventueel optredende HIT te detecteren slechts bij een klein aantal patiënten werden gevolgd.

Vervolgonderzoek moet uitwijzen wat de redenen zijn waarom deze aanbevelingen niet worden gevolgd. Met het oog op de veiligheid van patiënten die behandeld worden met heparines is het belangrijk dat de aanbevelingen voor het regelmatig controleren van het trombocytenaantal worden gevolgd. Wij zijn van mening dat het van belang is om beleid en instrumenten te ontwikkelen om het volgen van dergelijke aanbevelingen te verbeteren. Elektronische waarschuwingen voor het aanvragen en beoordelen van laboratoriumuitslagen voor patiënten die behandeld worden met heparine-achtige geneesmiddelen zijn hierbij mogelijk bruikbaar.

HOOFDSTUK 5

Uit de resultaten van de in dit proefschrift gepresenteerde onderzoeken kan worden geconcludeerd dat een databank met op patiëntniveau gekoppelde gegevens over laboratoriumuitslagen en medicatieblootstelling grote meerwaarde heeft voor het bestuderen van bijwerkingen van geneesmiddelen nadat deze geneesmiddelen op de markt zijn toegelaten, waaronder onderzoek naar geneesmiddel-geïnduceerde bloedbeeldafwijkingen zoals trombocytopenie. In **Hoofdstuk 5**, de algemene discussie, wordt het gebruik van dit instrument bediscussieerd in het licht van de gewenste verbetering van de methoden en instrumenten voor farmacovigilantie, alsook in het kader van de bevordering van veilig medicatiegebruik in de klinische praktijk. Daarnaast worden in dit hoofdstuk aanbevelingen gedaan voor verder onderzoek met zorgdata naar geneesmiddel-geïnduceerde bloedbeeldafwijkingen in het algemeen en geneesmiddel-geïnduceerde trombocytopenie in het bijzonder.

DANKWOORD

DANKWOORD

Als groot wielerfan fantaseer ik dat deze laatste momenten van het werken aan mijn proefschrift een parallel vertonen met de rondjes over de Champs-Élysées die de deelnemers aan de Tour de France traditiegetrouw maken aan het einde van de Ronde. Ik stel me voor dat de wielrenners onder de stralende zon en onder luide aanmoediging van het publiek voldaan nagenieten van de voorbije weken waarin ze de strijd met de klok aangingen, fysieke en mentale tegenslagen moesten overwinnen, ereplaatsen behaalden met geweldig ploegenspel en de champagne rijkelijk vloeide na die ene daverende eindsprint.

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UPOD is het resultaat van een samenwerking van de vakgroep Farmacoepidemiologie en Farmacotherapie van de Faculteit Farmaceutische Wetenschappen van de Universiteit Utrecht en verschillende afdelingen binnen het UMC Utrecht, waaronder naast het Laboratorium voor Klinische Chemie en Haematologie en de afdeling Klinische Farmacie, de Directie Informatie Technologie en de afdeling Zorginformatie en Systemen van de Directie Informatievoorziening en Financiën. Veel dank aan allen waarmee ik de afgelopen jaren intensief heb samengewerkt bij het realiseren van UPOD. Een aantal mensen wil ik graag in het bijzonder noemen. Kirana van Oosterhout, Evert Jan van den Brink, Ton Wesseling, Ful van der Wel (allen Directie Informatie Technologie), Marcel Schinkel (Apotheek), Jacq. Berk (IC-centrum), Leslie Beks (Directie Informatievoorziening en Financiën) en André Ringeling (LKCH) veel dank voor al jullie werk, het bespreken van alle ins and outs van de patiëntgegevens die in het UMC Utrecht worden vastgelegd en de verschillende systemen die daarvoor worden gebruiken. Maar ook zeker voor het enthousiasme en het plezier waarmee dit gepaard ging.

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LIST OF PUBLICATIONS

PUBLICATIONS RELATED TO THIS THESIS

Ten Berg MJ, Huisman A, van den Bemt PMLA, Schobben AFAM, Egberts ACG, van Solinge WW. [in Dutch] Database koppelt gegevens laboratorium en apotheek. UPOD-project verruimt mogelijkheden farmaco-epidemiologie. *Pharm Weekbl* 2005;140:1602-1603.

Ten Berg MJ, Huisman A, Souverein PC, Schobben AFAM, Egberts ACG, van Solinge WW, van den Bemt PMLA. Drug-induced thrombocytopenia: A population study. *Drug Saf* 2006;29:713-721.

Ten Berg MJ, Huisman A, van den Bemt PMLA, Schobben AFAM, Egberts ACG, van Solinge WW. Linking laboratory and medication data: New opportunities for pharmacoepidemiological research. *Clin Chem Lab Med* 2007;45:13-19.

Ten Berg MJ, van Solinge WW, van den Bemt PMLA, Huisman A, Schobben AFAM, Egberts ACG. Platelet measurements versus discharge diagnoses for identification of patients with potential drug-induced thrombocytopenia: A cross-sectional study in The Netherlands. *Drug Saf* 2009;32:69-76.

Ten Berg MJ, van den Bemt PMLA, Huisman A, Schobben AFAM, Egberts ACG, van Solinge WW. Compliance with recommendations for platelet count monitoring and management of possible heparin-induced thrombocytopenia in hospitalized patients receiving low molecular weight heparin. *Ann Pharmacother* (in press).

Viergever RF, ten Berg MJ, van Solinge WW, Hoepelman AIM, Gisolf EH. Changes in hematological parameters after switching treatment of HIV-infected patients from zidovudine to abacavir or tenofovir D.F. *HIV Clinical Trials* (in press).

Zwart-van Rijkom JEF, Uijtendaal EV, ten Berg MJ, van Solinge WW, Egberts ACG. Frequency and nature of drug-drug interactions in a Dutch University Hospital. *Br J Clin Pharmacol* (in press).

ABOUT
THE AUTHOR

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Maarten ten Berg was born on 29 March 1978 in Utrecht, The Netherlands, were he also completed secondary school (Atheneum) at the St-Gregorius College in 1996. Subsequently, he started his studies in Pharmacy at Utrecht University. As part of his studies he completed a research traineeship (supervisor Prof. Tom Einarson) at the Leslie Dan Faculty of Pharmacy at the University of Toronto, Canada. He obtained his Master's degree in Pharmacy in 2001, followed by his Pharmacist's degree in 2003.

Thereafter, he worked as a junior research associate at the PHARMO Institute for Drug Outcomes Research in Utrecht. In 2005 he started his PhD research at the Division of Pharmacoepidemiology & Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences, Faculty of Science, Utrecht University in affiliation with the Department of Clinical Chemistry and Haematology and with the Department of Clinical Pharmacy of the University Medical Center Utrecht. During this period he obtained a Master of Science degree in Epidemiology at the EMGO Institute of the VU University Amsterdam.

End of 2008, he started as a resident in clinical chemistry (supervisor Prof.dr. Wouter W. van Solinge) at the Department of Clinical Chemistry and Haematology of the University Medical Center Utrecht.

Maarten is married to Laureen Lammers.