Non-sedating antihistamine drugs and cardiac arrhythmias – biased risk estimates from spontaneous reporting systems?

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

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

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

Conclusions Our data suggest that nonsedating antihistamines might have an increased risk for inducing arrhythmias. Our findings, however, strongly suggest that the increased risk identified can at least partly be explained by reporting bias as a result of publications about and mass media attention for antihistamine induced arrhythmias.

Keywords: adverse drug reactions, bias, cardiac arrhythmias, nonsedating antihistamines, pharmacovigilance, spontaneous reports

Introduction

Background

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

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

One of the available strategies to identify rare adverse events is to evaluate spontaneous reports of adverse drug reactions (ADRs) using the concept of 'reaction proportion signalling' described firstly by Finney [9] and consequently applied by several others [10–12]. This

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method includes the calculation of an adverse drug reaction reporting odds ratio, which is used as an estimate of the risk of developing a certain event for patients using the index drug(s) relative to patients using reference drug(s). A large odds ratio indicates that the studied drug represents a disproportionate share of the reports of the adverse reaction of interest compared with the share of reports of other adverse reactions [9]. In other words, the drug is associated to the specific adverse reaction. The validity of the method has, however, been criticised because the fact that reports on adverse reactions on a voluntary basis can be biased. So far most concern has been expressed in relation to the persistent feature of underreporting. However, also attention in the media may result in selective reporting of certain adverse events [13]. In the Netherlands lots of attention to antihistamine-induced arrhythmias was raised at the beginning of 1998 when the Dutch government in accordance with many other countries decided that, for safety reasons, the former over-the-counter drugs terfenadine and astemizole could no longer be obtained without a prescription.

Objectives

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

Methods

Source

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

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

Selection of cases and noncases

The method of 'reaction proportion signalling' compares the use of certain drugs among cases (those with a defined adverse reaction) and noncases (all other reported adverse reactions).

In our study all ADRs coded by means of the WHO-ART as 'Heart rate and rhythm disorders' (System Organ Class 1030) were defined as cases. All other reports were defined as noncases.

Exposure definition

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

Potential confounders

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

Data analysis

For the comparison of exposed and nonexposed patients with respect to the risk of developing cardiac arrhythmias, ADR reporting odds ratios were calculated. These ratios are defined as the ratio of exposure odds among reported arrhythmia cases to the exposure odds of all other ADRs. Multivariable logistic regression analysis was used to adjust for the following potential confounders: type of health care professional that reported the ADR (pharmacist or physician), year of reporting, age and gender of the patient involved, drugs known to be able to cause QTc prolongation (including antiarrhythmics (see Appendix)), other cardiac therapies (ATC code C01A, C01C, C01D, C01E), antihypertensive drugs (ATC code C02), potassium-sparing diuretics (ATC code C03AB, C03BB, C03CB, C03D, C03E), non potassium-sparing diuretics (ATC code C03AA, C03AH, C03BA, C03BK, C03CA, C03CC), peripheral vasodilatating drugs (ATC code C04), beta-blocking agents (ATC code C07), calcium channel blocking agents (ATC code C08), drugs acting on the RAAS system (ATC code C09), lipid lowering drugs (ATC code C10), laxatives (ATC code A06), systemic corticosteroids (ATC code H02),

systemic β-agonists (ATC code R03C) and inhibitors of cytochrome P450–3A4 (see Appendix).

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

Results

Until July 1999, Lareb received 737 cases of cardiac arrhythmias, categorized according to WHO-ART as system organ class 1030: 'heart rate and rhythm disorders' (3.0% of all included reports $n=24\,414$). The most commonly reported arrhythmia was 'palpitation' (71.2%), followed by 'tachycardia' (8.4%) and 'arrhythmia not otherwise specified' (6.4%) (see Table 1). On average cases were a little older than the noncases (51.2 s.d. 17.4 *vs* 50.3 s.d. 19.7) and cases were more often female (67.3% *vs* 64.3%). Forty-three of the cases (5.8%) used a non-sedating antihistamine drug on the index-date compared with only 2.9% of the noncases. In most instances this non-sedating antihistamine was terfenadine (44.2%), followed by cetirizine (23.3%) and loratadine (16.3%).

Characteristics of the cases and noncases are presented in Tables 2 and 3. The number of the various nonsedating antihistamine drugs used by the cases on the index-date is listed in Table 4.

Non-sedating antihistamines were associated with reports of arrhythmia to a greater extent in comparison

Table 1 Number of adverse drug reactions reported to LAREB until July 1999 categorized according to WHO-ART as system and organ class 1030 'heart rate and rhythm disorders' sorted by type of arrhythmia.

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

Table 2 General characteristics of cases and noncases.

	Cases n = *737*	*Non-cases* n = *23,677*
Age		
<20 years	3%	7%
20–39 years	24%	23%
40–59 years	38%	34%
60–79 years	33%	32%
≥80 years	3%	5%
Female gender	67%	64%
Reported by pharmacist	27%	29%
Year		
1986–87	5%	8%
1988–89	7%	9%
1990–91	7%	8%
1992–93	10%	11%
1994–95	16%	18%
1996–97	31%	27%
1998–99	24%	20%

Table 3 Drugs mentioned in the adverse drug reaction reports.

	Cases n = *737*	*Non-cases* n = *23,677*
Non-sedating antihistamines	6%	3%
CYP3A4 inhibitors	12%	13%
CYP3A4 inhibitors and nonsedating antihistamines	1%	<1%
QT-prolonging drugs	14%	13%
Other cardiaca	7%	6%
Antihypertensive drugs	2%	2%
Potassium-sparing diuretics	4%	5%
Non potassium-sparing diuretics	9%	7%
Peripheral vasodilatating drugs	1%	1%
β-adrenoceptor blocking agents	15%	12%
Calcium channel blocking agents	13%	8%
Drugs acting on the RAAS system	13%	11%
Lipid lowering drugs	6%	7%
Laxatives	2%	3%
Systemic corticosteroids	4%	3%
Systemic β-adrenoceptor agonists	2%	1%

Table 4 Number of reports of arrhythmias associated with various nonsedating antihistamines.

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

Table 5 Results of logistic regression analysis, overall and before and after the regulatory action in 1998. ADR reporting odds ratios and 95% confidence intervals.

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

with other drugs (crude ADR reporting odds ratio 2.10 (95% CI: 1.53, 2.89)), which did not essentially change after adjustment for potential confounding factors (2.05 (95% CI: 1.45, 2.89)). Concomitant use of CYP3A4 inhibitors did not modify the effect of the nonsedating antihistamines significantly (adjusted OR nonsedating antihistamines plus CYP3A4 inhibitors: 1.53 (95% CI: 0.60, 3.91)). After stratification for time before or after regulatory action the adjusted ADR reporting odds ratios changed notably. There was no association between the use of nonsedating antihistamines before 1998 (adjusted OR 1.37 (95% CI: 0.85, 2.23)). However, after the regulatory action, there was a clear association between the use of nonsedating antihistamines and reports of cardiac arrhythmias (adjusted OR 4.19 (95% CI: 2.49, 7.05)). The results of the logistic regression analysis are presented in Table 5.

Discussion

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

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

Another factor strengthening this finding is supported by taking a closer look at ADRs of terfenadine only. The majority of publications in the medical literature of antihistamine induced arrhythmias are published during our study period, the number of which increased over time. These publications again may have caused an increase vigilance for such events with health care professionals. We investigated if there is a time trend in the arrhythmia ADR reports associated with the use of terfenadine and indeed found an increase of these reports over time in our database (Pearson chi-square test for trend, $P=0.001$).

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

One can argue whether the broad definition of arrhythmias we used, including rather non specific rhythm disorders like palpitation, tachycardia or non specified arrhythmia, has influenced our results. This broad definition might have diluted the found association, since not only specific validated QTc related arrhythmias were included. On the other hand, we think this outcome definition enabled us to study the effect of media attention on specific reporting in more detail, than when we would have only included the specific cases. We have now included reports from health care professionals, who are not able to diagnose a specific type of arrhythmia (like GPs or pharmacists), but might as well be influenced by the media attention.

Conclusions

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

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

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Appendix

CYP3A4 inhibitors:

amiodarone	fluvoxamine	nelfinavir
cimetidine	indinavir	norfloxacine
ciprofloxacine	isoniazide	quinine
clarithromycine	itraconazole	ritonavir
delaviridine	ketoconazole	saquinavir
diltiazem	metronidazole	sertraline
erythromycin	mibefradil	troleandomycin
fluconazole	miconazole	verapamil
fluoxetine	nefazodone	

Non-antihistamine QTc prolonging drugs:

antipsychotics	fluoroquinolone antibiotics
tricyclic antidepressants	pentamidine
cisapride	trimethoprim
halofantrine	probucol
chloroquine	bepridil
quinine	antiarrhythmics
macrolide antibiotics	

