Signalling possible drug–drug interactions in a spontaneous reporting system: delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazole

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Aims In spontaneous adverse drug reaction reporting systems, there is a growing need for methods facilitating the automated detection of signals concerning possible adverse drug reactions. In addition, special attention is needed for the detection of adverse drug reactions resulting from possible drug–drug interactions. We describe a method for detecting possible drug–drug interactions using logistic regression analysis to calculate ADR reporting odds ratios.

Methods To illustrate this method, we analysed the adverse drug reaction 'delayed withdrawal bleeding' resulting from a possible interaction between itraconazole and oral contraceptives in reports received by the Netherlands Pharmacovigilance Foundation LAREB between 1991 and 1998.

Results In total 5,503 reports were included in the study. The odds ratio, adjusted for year of reporting, age and source of the reports, for a delayed withdrawal bleeding in women who used both drugs concomitantly compared with women who used neither oral contraceptives, nor itraconazole, was 85 (95% CI: 32–230).

Conclusions Since spontaneous reporting systems can only generate signals concerning possible relationships, this association needs to be analysed by other methods in more detail in order to determine the real strength of the relationship. This approach might be a promising tool for the development of procedures for automated detection of possible drug–drug interactions in spontaneous reporting systems.

Keywords: drug interactions, itraconazole, oral contraceptives, pharmacovigilance, signal detection, withdrawal bleeding

Introduction

The Netherlands Pharmacovigilance Foundation Lareb maintains the spontaneous adverse drug reaction reporting system in the Netherlands [1]. Since 1996 Lareb is the national centre in support of the Medicines Evaluation Board. One of the major goals of this system is the timely detection of possible new adverse drug reactions (ADRs) and interactions. These signals are currently being detected by a systematic review of all individual reports that are received in a certain time span by a team of experts in this field. With the increasing number of reports, there is a growing need for a computerised system that aids in this process.

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Special cases are those ADRs resulting from drug–drug interactions. Reports to Lareb usually concern an event ascribed to only one suspected drug. Rarely the presence of a suspected interaction is mentioned, which makes the detection of possible drug–drug interactions difficult. The detection of possible interactions is based on the following concept: when a suspected ADR is reported more frequently on the combination of two drugs as compared with the situation where these drugs are used in absence of one each other, this association might indicate the existence of a drug–drug interaction.

In 1974 Finney described the concept of 'reaction proportion signalling'. Based upon all records in the database, contingency tables can be constructed and subsequently disproportional drug–ADR combinations are identified, and used for the detection of signals [2]. By means of these contingency tables, 'ADR reporting odds ratios' can be calculated. This concept, which was

previously described for analyzing reported ADRs in a case non-case design [3, 4], is applied for the analysis of possible interactions in this study.

The objective of the present article was to illustrate this method by analyzing a possible interaction between oral contraceptives (OCs) and the antifungal agent itraconazole.

Since the approval for marketing of itraconazole in the Netherlands, 19 reports of delayed withdrawal bleeding in women using OCs have been received. In 10 of these reports OCs and itraconazole were used concomitantly. Nine of these reports concerned OCs containing desogestrel. One other woman used a cyproterone-acetate containing OC and experienced a delayed withdrawal bleeding. Because of the unexpected high number of reports concerning a delay in the withdrawal bleeding where OCs and itraconazole were used concomitantly, our analysis was focussed on this association. Clinical details of this possible interaction were recently described as a case series on the basis of reports submitted to LAREB [5, 6].

Methods

Source

Health professionals send reports to LAREB on a voluntary basis, by means of a limited number of questions on a special report form. Information is collected about the patient and the suspected ADR. Also detailed information is requested about all drugs that were used at the time the reaction occurred. After being received by LAREB, information such as ADR(s) and indication for use is coded, and subsequently reports are filed in the LAREB database. This database can be used for further evaluation and analysis of the data. On 1 January 1998, it consisted of a total of approximately 19 500 reports.

		Reported suspected ADR	
		'Delayed bleeding' reported	No 'delayed bleeding' reported
Medication	Index group	a	b
	Reference group	c	d

Figure 1 Two by two table used for the calculation of ADR reporting odds ratios.

Selection of cases and non-cases

The domain was restricted to reports of women between the age of 15 and 50 years. In order to make an appropriate comparison between women who used itraconazole, which was licensed in the Netherlands in 1991, and women who did not use this antifungal drug, only reports with a reporting date later than January 1991 were included. In February 1998 we published an article concerning the possible association between the use of itraconazole and oral contraceptives in one of the major Dutch Journals [5]. To avoid the risk of reporting bias due to this publication, only reports received before January 1998 were used.

The following data were used in the study:

Source. A report might originate from either a physician or a pharmacist.

Age of the patients.

Reported reactions. All menstruation disorders and disorders of the withdrawal bleeding in the database were checked and, if necessary, recoded. If the WHO preferred term 'menses onset delayed' or 'missed withdrawal bleeding' was recorded on a report form, the ADR was labelled as 'delayed bleeding'. After checking the original description of the ADR, also some cases of 'amenorrhoea' or 'oligomenorrhoea' were recoded as 'delayed bleeding'. In all other cases, the ADR was coded as 'other ADRs'. One report of a woman reporting a 'delayed withdrawal bleeding' in association with an initial transient positive pregnancy test was coded as 'other ADR', because a miscarriage could not be ruled out.

Year of reporting.

Presence of itraconazole among the drugs used.

Presence of OCs among the drugs used.

Although on the forms received by LAREB, the health professional makes a distinction between suspected and non-suspected medication, all drugs were taken into account in the present study.

Cases were defined as patients who reported a 'delayed bleeding', while 'non-cases' consisted of all other reports. The reports were divided into three index groups:

Reports of women who used OCs, but no itraconazole at that time.

Reports of women who used itraconazole, but no OC at that time.

Reports of women who used itraconazole and OC concomitantly.

The reference group consisted of patients who used neither OCs, nor itraconazole.

Analysis

For the comparison of index and reference groups, ADR reporting odds ratios were calculated. These ratios are

defined as the ratio of the exposure odds of reported cases of 'delayed bleeding' to the exposure odds of other ADRs. The ADR reporting odds ratios were calculated as (a:c)/(b:d) (Figure 1) [4].

ADR reporting odds ratios were adjusted for source, year of reporting and age, and calculated by logistic regression analysis. Odds ratios were expressed as point estimates with 95% confidence intervals. For the comparison of the age of the patients between the three groups, analysis of variance was conducted. In order to analyze the source of the reports a Chi-square test was used. All statistical analyses were performed using SPSS 8.0.

Results

A total number of 5503 reports were included in the study. Altogether 1466 women used OCs but no itraconazole; 16 women used itraconazole but no OCs, and 23 women used both drugs. Mean age, source and number of reports for index and reference groups that were studied are presented in Table 1. There was a difference between these groups concerning the age of the patients ($P < 0.001$ analysis of variance), as well as the source of the reports ($P < 0.001$ Chi-square).

Differences in reported ADRs between the three groups are shown in Table 2. Delayed bleeding was reported by 10 patients who used itraconazole and OCs concomitantly. The other 13 patients in this group did not mention this side effect. If only OCs were used, 9 out of 466 patients mentioned 'delayed bleeding'. If only itraconazole was used none out of 16 patients reported the occurrence of this effect.

The ADR-reported odds ratios and 95% confidence intervals for all comparisons are shown in Table 2. Adjusted for year of reporting, age and source, the ADR reporting odds ratio for the risk of a 'delayed bleeding' in reports of women who used itraconazole and OCs concomitantly compared with the reports of women who used neither of these drugs was 85 (95% CI 32–230).

The ADR reporting odds ratio adjusted for year of reporting, age and source in the group where only OCs were used was 0.8 (95% CI 0.4–1.8). When only itraconazole was used, there were no cases.

Discussion

A major function of spontaneous reporting systems is generating new 'signals' [7]. For this purpose, all reports are individually reviewed and detection depends upon the skills and memory of the professionals involved. Since this procedure is time consuming and the number of reports is increasing, there is a growing need for an automated method that facilitates detection of ADRs. A special case is the detection of interactions, since they are often not reported. The analysis of possible drug-drug interactions is based on the concept that a suspected ADR is more often reported on the combination of two drugs compared with the situation where either of these drugs has been used in absence of the other one. The level of the odds ratio however, is of less importance, but provides an indication of the degree of disproportionality. Odds ratios tend to overestimate the relative risk [8], so interpretation is more difficult. However, the use of an odds ratio offers advantages since concomitant variables may be analysed by logistic regression analysis.

Possible drug-drug interactions might be analysed in different ways. In the first place, as was shown in this study, three index groups can be distinguished; two groups where both drugs are used in absence of one each other and one group where both drugs are used concomitantly. These index groups can be compared with a reference group in which none of the suspected drugs is used. The likelihood of a reaction being due to a suspected interaction is increased if the 95% confidence intervals of the group in which both drugs are used and the other two index groups are mutually exclusive.

Secondly, the analysis could also have been done by using a logistic model in which next to the use of both itraconazole and oral contraceptives as covariates subsequently an interaction term for the concomitant use of both drugs is added. In our example the logistic model for calculating the adjusted odds ratios would then look like:

$$\log(\text{odds}) = \beta_0 + \beta_2 A + \beta_3 S + \beta_4 Y + \beta_5 I + \beta_6 OC + \beta_7 OC * I$$

(A = age, S = source, Y = reporting year,
I = Itraconazole, OC = oral contraceptive)

Table 1 Age and source of reporting of index groups, reference group and total group.

	Index groups			Reference group	
	Only oral contraceptive	Only itraconazole	Itraconazole as well as oral contraceptive	Neither itraconazole nor oral contraceptives	Total
Mean age (years)	31.1	40.8	29.7	37.2	35.5
Source (percentage reporting by physicians)	71.6	43.7	56.5	77.3	75.6
Number of reports	1466	16	23	3998	5503

Table 2 Reporting odds ratios (OR) concerning the occurrence of a 'delayed bleeding' of reference and index groups.

	Cases n = 39	Controls n = 5464	Crude OR (95% CI)	Adjusted* OR (95% CI)
Neither itraconazole nor OC	20	3978	1	1
OC/no itraconazole	9	1457	1.2 (0.6–2.7)	0.8 (0.4–1.8)
Itraconazole no OC	0	16	0 (0–∞)	0 (0–∞)
Concomitant use of itraconazole and OC	10	13	153 (60–389)	85 (32–230)

*Adjusted for year of reporting, age and source.

The estimates resulting from this model do not differ from the previous method. This model can be compared with the model in which no interaction term ($\beta_7\text{OC}\cdot\text{I}$) is present. A likelihood ratiotest can be used to evaluate the effect of adding this term. Given the fact that the difference in $-2 \log$ likelihood follows a chi-square distribution with one degree of freedom, adding the interaction term in this case was statistically significant ($P < 0.01$).

The latter method can also be used for the automatic detection of drug interactions. The use of a computer in the detection of adverse drug interactions was already proposed by Amery [9]. In his approach the computer is instructed to look for pairs of a specific concomitant drug with a specific ADR. The fraction of patients showing the ADR under consideration is subsequently compared with the frequency of this ADR in all database patients. In our approach, the use of logistic regression analysis offers the possibility for correcting for covariates, and furthermore offers a possibility of analysing the use of interaction terms in more detail. As preliminary experiments indicate, analysing the effect of adding an interaction term by a likelihood ratiotest is a promising tool in the automated detection of drug interactions and will be further explored.

Internal validity

In general, as with the analysis of adverse drug reactions, selection bias might be present, since certain ADRs are more likely to be reported than others. In our example selection bias might be present in the index groups where OCs are used in contrast to the index group where no OCs are used. In the latter situation, a delay in the onset of the menstruation with a couple of days might be reported less likely because of acceptance of the normal physiological irregularity of the menstruation women might experience. A delay in the onset of the withdrawal bleeding during the use of OCs, however, might be experienced as a more unusual situation. Despite the fact that a delayed withdrawal bleeding rarely occurs with oral contraceptives this 'event' might be reported more frequently. This selection bias can cause an overestimation

of the odds ratio for the occurrence of a 'delayed bleeding' in reports where OCs are used. Selection bias, however, is not likely to have played a more prominent role in cases where both OCs and itraconazole were used than in cases where only OCs were used.

Increased reporting due to a recent introduction of a drug or attention for an adverse drug reaction in the media does not necessarily influence the reporting odds ratio, since non selective reporting bias has a similar effect of both numerator and denominator [3]. If there is a specific attention for an interaction however, reporting bias might occur.

Another point of attention is confounding. For instance, a third drug may act as a confounder when it is associated with one of the drugs or the concomitant use of both suspected drugs. For instance analgesics such as naproxen may cause a delay or interrupt menstruation in women who are not taking oral contraceptives [10]. NSAIDs were not prescribed to any of the case patients reported to LAREB, but in the Netherlands these drugs are also available for self-treatment. The indication for the use of itraconazole, mycotic infections, is seldom painful. This implies that there is little reason for the use of NSAIDs, which might influence the occurrence of a withdrawal bleeding. Although it is unlikely that self-medication could have acted as a confounder in these reports, the use of NSAIDs for self-treatment could be definitely ruled out in only one case. None of the patients in the group who used both drugs, also used NSAIDs.

External validity

Like the analysis of ADRs in a spontaneous reporting system, detection and confirmation of an association does not imply a causal relationship. Additional studies need to be done to confirm a true pharmacodynamic or pharmacokinetic interaction and to determine the strength of this association in daily practice. Because of the various degrees of underreporting, that are inextricably bound up with spontaneous reporting [11–13], it is difficult to estimate the true incidence of a possible interaction. In our example where the signal power strongly points at a true interaction, this estimation was not made, since data

concerning the degree of underreporting and prescription rates of drug are not available.

Itraconazole and oral contraceptives

The concomitant use of itraconazole and oral contraceptives might lead to an increase in reports of a 'delayed bleeding'. The chance of this ADR being reported was not increased in women who used itraconazole or an OC alone. The number of patients who used itraconazole in the absence of OCs is rather small. Since there were no cases, the odds ratio must be zero, but the corresponding confidence interval was large. Theoretically, the delay in withdrawal bleeding might have been caused by the use of itraconazole, but the reporting rate is much higher when oral contraceptives were used concomitantly. For this reason, the strong association between the concomitant use of itraconazole and OCs and the occurrence of a 'delayed withdrawal bleeding' therefore is suggestive of an interaction.

The mechanism underlying this suspected interaction remains to be explained. Itraconazole interacts with a variety of drugs [14]. Triazole compounds such as ketoconazole and itraconazole *in vitro* inhibit cytochrome P450-3A, an enzyme system involved in the biotransformation of steroid hormones [15, 16]. An increase in the levels of steroids might lead to a delay of the withdrawal bleeding. Of the ten women who reported this suspected side effect, nine women used a desogestrel containing OC, and one woman a cyproterone acetate containing OC. The reason for the high number of desogestrel containing OCs is not clear.

For our analysis we focussed on a comparison of the chances of 'events' being reported in the different groups. Nevertheless, different mechanisms may be responsible for the 'delayed bleeding' in these two groups. If a woman uses itraconazole without an oral contraceptive, the 'delayed bleeding' is in fact a delayed menstruation. In women using oral contraceptives, it refers to a delayed withdrawal bleeding. Since it is not clear if different mechanisms underlie these suspected ADRs, both ADRs were treated as one variable in our analysis.

Conclusions

In a spontaneous reporting system the automatic analysis of reports is usually limited to adverse drug reactions. In the method described, the index and reference groups originating from the database can be used to signal possible drug-drug interactions. In our example, the results strongly suggest that in women using OCs and

itraconazole concomitantly the withdrawal bleeding may be delayed due to a drug interaction, and illustrates that the method described might be a useful tool in analyzing possible interactions in spontaneous reporting systems.

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