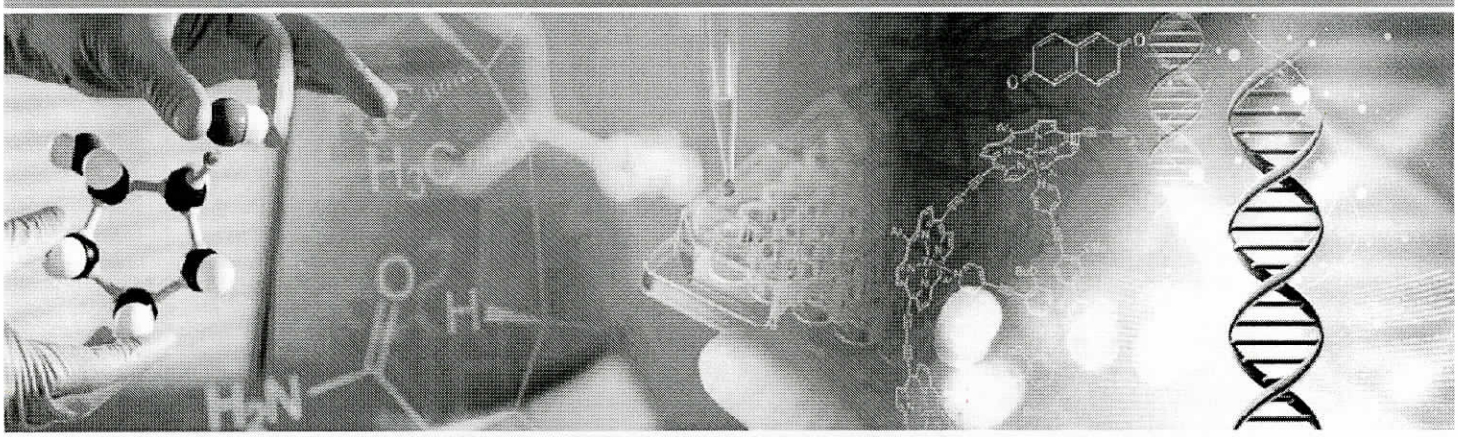
Proceeding of The Eighth Indochina Conference on Pharmaceutical Sciences

PHARMA INDOCHINA VIII

ASEAN Pharmacy - Integration for Development



4th – 5th December 2013,
Ho Chi Minh City, Vietnam

Organized by
The University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam

In association with
Hanoi University of Pharmacy, Vietnam
Mahidol University, Thailand
Universiti Kebangsaan Malaysia, Malaysia

Supported by
Ministry of Health, Vietnam

NHÀ XUẤT BẢN Y HỌC

Clinical Pharmacy

PO-CP-13

AN EVALUATION OF DRUG-DRUG INTERACTIONS IN A DATABASE OF SPONTANEOUSLY ADVERSE DRUG REACTIONS REPORTING IN VIETNAM

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Abstract
Drug-drug interactions (DDIs) are an important cause of adverse drug reactions (ADRs). The list of potential DDIs is very long. However, not all potential DDIs necessarily have clinically significant consequences and occur in all patients. A spontaneous reporting database could be a valuable source for detection of ADRs associated with DDIs in clinical practice. This study determined the prevalence of ADR reports related to DDIs from a database of spontaneous reporting of ADRs in Vietnam and evaluated the relationship between DDIs and ADRs described in such reports for identifying ADRs associated with DDIs. Data were retrieved from the national ADRs database handled by The National Center of Drug Information and Adverse Drug Reactions Monitoring (from January 2008 to December 2010). All reports containing at least two drugs were selected and a list of drug pairs was drawn up. The presence of potential DDIs in ADR reports was checked by MICROMEDEX software. For each report containing a potential DDI, we verified whether the reported ADRs were associated with the identified DDI. From 3334 ADR reports containing at least two drugs, potential DDIs were identified in 1237 reports (37.1%). The total number of DDI pairs was 180, of which 4 DDI pairs (2.22%) were contraindicated and found in 23 ADR reports, and 44 DDI pairs (24.44%) were considered having major and found in 1026 ADR reports. The prevalence of reports describing ADR possibly associated with DDIs is 11.5% (142 of 1237 reports containing at least one potential DDI). The total number of DDI pairs possibly associated with ADR is 8, of which the most frequently reported interactions were related to anti-tuberculosis drugs: isoniazid-rifampicin and pyrazinamide-rifampicin which were associated with hepatotoxicity such as hepatic enzymes increased, jaundice, hepatitis, bilirubinaemia. In general, the spontaneous reporting database in Viet Nam was showing that more than one in ten patients exposed to a potential DDI experienced a related ADR.
Keywords: adverse drug reactions, drug interactions, pharmacovigilance.

Introduction

Drug-drug interactions are an important issue in drug safety; reduce the effectiveness of treatment and may also cause serious effects in patient [1]. The list of potential DDIs is very long. However, not all potential drugs interactions necessarily have clinically significant consequences and occur in all patients [2]. Recently, computerized drug alert systems have been set up to help prevent DDIs; however, these systems have not promoted the role to supporting physicians in prescribing process. A spontaneous reporting database could be a valuable source for detection of ADRs associated with DDIs in clinical practice [1]. Therefore, this study was conducted to determine the prevalence of ADR reports related to DDIs from a database of spontaneous reporting of ADRs in Vietnam and evaluate the relationship between DDIs and ADRs described in such reports.

Materials and Methods

Data source

The data were obtained from a database containing all the report of suspected ADRs from the The National Center of Drug information and Adverse drug reactions monitoring (from January 2008 to December 2010).

Data analysis

This study was used observational research methods without intervention based on retrospective databases in the period 2008-2010.

All reports containing at least two drugs were selected and a list of drug pairs was drawn up. The information in the report and drug interactions was recorded to the data collection form. The potential DDIs in ADR reports were checked by MICROMEDEX software (Thomson Reuters). The ADR reports were classified into 3 groups: reports describing an ADR associated with a DDI (Group A), reports containing a potential DDI (Group B) and reports related to patients treated with at least two non-interaction drugs (Group C).

Assessment criteria

The DDIs in the ADR reports: the prevalence of reports containing a potential DDI, the prevalence of reports according to the severity of the DDIs and the mechanism of the DDIs, the most common DDIs, and the DDIs identified at contraindicated and major severity interactions.

The relationship between DDIs and ADRs: the prevalence of ADR reports related to DDIs, the factors related to the occurrence of drug-drug interactions (age, sex, number of drugs in the report), and the DDIs associated with ADR in the reports.

Data processing

All data were stored, managed and processed using SPSS 15 and Excel 2007. The study samples were represented by the ratio % or means value ± standard deviation. Using ANOVA test with Dunnette post-test analysis (post-hoc) compare mean values between groups. The difference is statistically significant at $p < 0.05$.

Results and Discussion

Potential DDIs in the spontaneous reporting database

A total of 3334 ADR reports containing at least two drugs were collected in the spontaneous reporting database, of which 1237 (37.10%) reports were contained at least one potential DDI associated with 180 different drugs interactions pairs. The frequency of occurrence of these drug interaction pair in the ADR reports is 2256. The majority of potential DDIs were classified, according to the MICROMEDEX criteria, as belong of minor (15%) or moderate (58.33%) or major (24.44%) severity; only 2.22% of potential DDIs were contraindicated.

The percentage of reports with potential DDIs increased in relation to the number of concomitantly administered drugs, ranging from 7.81% to 64.10% for two drugs and six drugs, respectively (Figure 1).

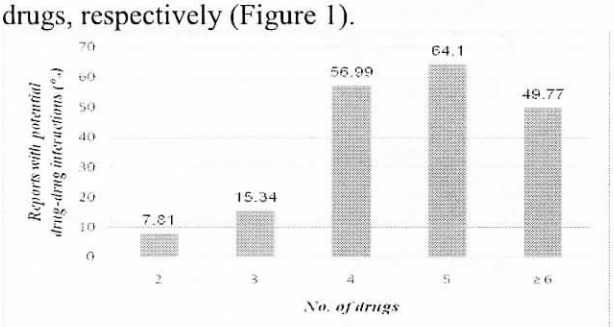

Figure 1: Percentage of reports with potential drug-drug interactions in relation to the number of drugs

The most frequently reported DDIs pairs and clinically significant DDIs pairs

Table 1 showed ten DDI pairs and table 2 showed ten clinically significant DDIs pairs that were reported the most frequently in the database, and describe the interaction effect according to MICROMEDEX software.

Table 1: *The 10 DDI pairs that were reported the most frequently*

DDI pairs	Interaction effect (according to Micromedex)	Severity	No. of reports (%, n=3334)
Pyrazinamide – Rifampicine	Severe hepatic injury	Major	918 (27.53)
Isoniazide – Rifampicine	Hepatotoxicity	Major	916 (27.47)
Ceftriaxone – Ringer lactate	The precipitation of calcium-ceftriaxone complexes in the lungs and is contraindicated in infants	Contraindicated	20 (0.60)
Lamivudine – Sulfamethoxazole/ Trimethoprime	Increased risk of lamivudine adverse effects (gastrointestinal disturbances, headache, fatigue, myalgia, and rarely neutropenia)	Minor	16 (0.48)
Ampicilline – Gentamicine	Loss of aminoglycoside efficacy	Minor	16 (0,48)
Aspirin – Enoxaparin	Increased risk of bleeding	Moderate	13 (0.39)
Clopidogrel – Enoxaparin	Increased risk of bleeding	Major	13 (0.39)
Clopidogrel – Aspirin	Increased risk of bleeding	Minor	12 (0.36)
Amoxicilline – Gentamicine	Loss of aminoglycoside efficacy	Minor	10 (0,30)
Fentanyl – Midazolame	Additive respiratory depression	Major	8 (0.24)

Table 2: *The 10 clinically significant drug pairs that were reported the most frequently*

Drug combination	Interaction effect (according to Micromedex)	Severity	Mechanism	No. of reports (%, n=3334)
Ceftriaxone – Ringer lactate	The precipitation of calcium-ceftriaxone complexes in the lungs and is contraindicated in infants	Contraindicated	Pharmacokinetic	20 (0.60)
Dihydroergotamine - Clarithromycin	Increased risk of acute ergotism (nausea, vomiting, vasospastic ischemia)	Contraindicated	Pharmacokinetic	1 (0.03)
Promethazine - Thioridazine	Increased risk of QT interval prolongation	Contraindicated	Pharmacodynamic	1 (0.03)
Nifedipine – Rifampicin	Decreased nifedipine effectiveness	Contraindicated	Pharmacokinetic	1 (0.03)
Pyrazinamide – Rifampicin	Severe hepatic injury	Major	Unknown	918 (27.53)
Isoniazid – Rifampicin	Hepatotoxicity	Major	Pharmacokinetic	916 (27.47)
Clopidogrel – Enoxaparin	Increased risk of bleeding	Major	Pharmacodynalic	13 (0.39)
Midazolam – Fentanyl	Additive respiratory depression	Major	Pharmacodynalic	8 (0.24)
Vancomycin – Amikacin	Additive ototoxicity and/or nephrotoxicity	Major	Pharmacodynalic	7 (0.21)
Vancomycin - Gentamicin	Nephrotoxicity	Major	Pharmacodynalic	6 (0.18)

The interaction between pyrazinamide and rifampicin, and isoniazid and rifampicin, which were associated with hepatotoxicity, was most frequently reported. The number of reports containing these 2 drugs pairs were 918 reports (27.53%) and 916 reports (27.47%) respectively. Then, the interaction between ceftriaxone and calcium in ringer lactate (0.60%), which is also contraindicated interaction pairs were most commonly reported (20 reports). The total number of DDI pairs was 180, of which 4 DDI pairs (2.22%) were contraindicated and found in 23 ADR reports, and 44 DDI pairs (24.44%) were considered having major and found in 1026 ADR reports.

The prevalence of ADR reports related to DDIs

Table 3: *The prevalence of ADR reports having DDIs and DDIs related to ADRs*

	No. of reports	% (n=3334)	% respectively
No. of reports containing a potential DDI (n=3334)	1237	37,1	
Reports containing a potential DDI associated with an ADR (n=1237) (Group A)	142	4,3	11,5
Reports containing a potential DDI is not associated with an ADR (n=1237) (Group B)	1095	32,8	88,5

142 of 1237 reports (11.5%) containing at least one potential DDI was described an ADR associated with a DDI. This number of the total number of ADR reports in the database from 2008 to 2010 was 2.24%.

Main risk factors for drug interactions

Table 4: *Risk factors for drug interactions*

Risk factors	Group A	Group B	Group C
Patient age (mean ± SD)	47,17 ± 22,76	46,96 ± 19,19	38,40 ± 21,90
Sex (rate of male:female)	1,11	0,96	1,08
No. of drugs (mean ± SD)	4,47 ± 1,46	4,50 ± 1,18	3,34 ± 1,36

ANOVA test was used to evaluate main risk factors for DDIs including the mean age and the number of drugs between 3 groups. The result showed that the differences between these groups were statistically significant ($p < 0.001$). The mean age and the mean number of drugs were higher in Groups A and B compared with Group C. The mean number of drugs were smaller in Group A compared with Group B.

Adverse Drug Reactions associated with drug interactions

Table 5: *The list of drug interaction pairs associated with ADRs*

Drug 1	Drug 2	Severity	Interaction effect (according to Micromedex)	ADR	No. of reports
Isoniazid	Rifampicin	Major	Hepatotoxicity	Hepatic enzymes increased	56
				Jaundice	47
				Hepatitis	41
				Bilirubinaemia	11
Pyrazinamide	Rifampicin	Major	Severe hepatic injury	Hepatic enzymes increased	51
				Hepatitis	44
				Jaundice	43
				Bilirubinaemia	11
Clopidogrel	Enoxaparin	Major	Increased risk of bleeding	Purpura	7
Dapson	Zidovudine	Major	Hemotoxic	Anaemia	1

Aspirin	Enoxaparin	Moderate	Increased risk of bleeding and an increased risk of hematoma when neuraxial anesthesia is employed	Purpura	7
Ethambutol	Ethionamide	Moderate	Excessive adverse effect (GI distress, headache, confusion, neuritis, and hepatotoxicity).	Hepatic enzymes increased	1
Isoniazid	Ethionamide	Moderate	Peripheral neuritis, hepatotoxicity, and encephalopathy	Hepatic enzymes increased	1
Aspirin	Clopidogrel	Minor	Increased risk of bleeding	Purpura	7

The DDI pairs of anti-tuberculosis drugs, which were most frequently reported, were isoniazid-rifampicin and pyrazinamide-rifampicin. The two DDI pairs were associated with hepatotoxicity such as hepatic enzymes increased, jaundice, hepatitis, bilirubinaemia. In there, hepatic enzymes increased were most commonly reported (56 reports with isoniazid-rifampicin and 51 reports pyrazinamide-rifampicin). Clopidogrel-enoxaparin, aspirin-enoxaparin and aspirin-enoxaparin associated with purpura were reported in 7 patients.

The study showed the relatively high percentage of spontaneous reports with potential DDIs (37.1%) in which the percentage of reports containing at least a DDI associated with an ADR was 11.5%. These results in our study were very similar to some studies on a spontaneous reporting database in some other countries. Leone and colleagues identified the percentage of reports with potential DDIs on the Italy spotaneous reporting database was 30.2%. This rate in the study of Tavassoli et al. on the French Pharmacovigilance database was 35.5%. However, the percentage of reports containing at least an ADR associated with a DDI in our study (11.48%) was very smaller than the result of these studies in French and Italy (Italy: 21.7 %; France: 31.4 %) [1,3].

The total number of DDI pairs was 180. These drug interaction pairs were most frequently reported including: the combination of anti-tuberculosis drugs [isoniazid-rifampicin (918 reports), pyrazinamide-rifampicin (916 reports)], the combination of antibiotic drugs [ceftriaxone-ringer lactate (20 reports), ampicllin-gentamicin (16 reports)]... This result is different from the results of the studies in Italy and French. Of there, the most frequently interactions were related to cardiovascular drugs such as digoxin, and anticoagulants and antiplatelet drugs or neurological drugs [1,3]. However, these results were conformed to the situacion of the spotaneous reporting activities in Vietnam. The numbers of reports relate to antibiotics and antituberculosis drugs were rather larger (beta-lactam antibiotics: 26.33%, anti-tuberculosis: 10-15%). Therefore, the frequency of the interaction pairs such as isoniazid-rifampicin, pyrazinamide-rifampicin, and antibiotic drugs were higher than other interactions.

The most frequently reported interaction pairs were the interaction of anti-tuberculosis drugs including isoniazid-rifampicin and pyrazinamide-rifampicin which were associated with hepatotoxicity such as hepatic enzymes increased, jaundice, hepatitis, bilirubinaemia; and the drug interactions related to purpura such as aspirin-enoxaparie, aspirin-clopidogrel, and clopidogrel-enoxaparin. To explain this result, the first cause, the number of ADR reports related to anti-tuberculosis was large. The second cause, the described ADRs were easy to detect. Besides, the causality assessment between ADRs and drugs were also difficult due to the reports have not a specific test related to ADRs. The reported ADRs were easily observed. For example, the interaction which do increase or decrease the concentration of drug in the blood leads to increase or decrease therapeutic efficacy and toxicity of drugs do not seem to be monitored and evaluated. This is partly due to the information relate to drug interaction omitted during physician's prescription.

Some limitations of the study should be considered when the outcome measures include: the quality of ADR reports is not high; many reports have not enough the necessary information to research lead to difficulties during the process of collecting all ADRs and drug information to evaluate drug interactions; the number of reports in our sample was too large, the evaluation of the relationship between drug-drug interactions and ADRs by presentiment and comparison that there is not method to accurately assess this relationship.

Conclusion

The percentage of reports containing at least a DDI include clinical significance interactions on a spotaneous reporting database in Vietnam from 2008 to 2010 was quite high, but he percentage of describing ADR possibly associated with DDIs was lower. Age and the number of drugs in ADR reports were risk factors lead to increase the drug interactions. The interactions may be related to ADR were mainly drug interactions of anti-tuberculosis drugs. This result is the basis for the need to strengthen monitoring of drug interactions in the treatment process, assessment and prevention of serious adverse events associated with DDIs.

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