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Identifying Adverse Drug Reactions Associated with Drug-Drug Interactions

Data Mining of a Spontaneous Reporting Database in Italy

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Abstract

Background: Drug-drug interactions (DDIs) are an important cause of adverse drug reactions (ADRs). Many studies have recently considered this issue, but most of them focus only on potential interactions and are often related to the hospital setting. A spontaneous reporting database could be a valuable resource for detection of ADRs associated with DDIs; however, data in the literature are limited.

Objective: To detect those patients treated with potentially interacting drugs and the cases where reported adverse reactions are a possible consequence of DDIs, using an Italian spontaneous reporting database.

Methods: The data were obtained from a database containing all reports of suspected ADRs from five Italian regions (January 1990 to December 2007) that are the main contributors to the Italian spontaneous reporting system. All reports containing at least two drugs, reported as being suspected of causing the ADR or as concomitant medication, were selected and a list of drug pairs was drawn up. We performed a search to verify which drug pairs are considered a potential DDI, using the Internet version of the DRUGDEX® system. For each report containing a potential DDI, we verified whether the description of the adverse reaction corresponded to the interaction effect.

Results: The database contained 45 315 reports, of which 17 700 (39.1%) had at least two reported drugs. We identified 5345 (30.2%) reports with potential DDIs, and in 1159 (21.7%) of these reports a related ADR was reported. The percentage of reports with potential DDIs increased in relation to the number

of concomitantly administered drugs, ranging from 9.8% for two drugs to 88.3% for eight or more drugs. The percentages of serious or fatal reports of ADRs associated with a DDI were significantly higher than other reports analysed. The mean age, percentage of male patients and the mean number of drugs were also significantly higher in reports with DDIs than in other reports. In 235 of 1159 reports (20.3%), both interacting drugs were recognized as suspect by the reporter. This percentage varies in relation to the drugs involved, ranging from 2% to about 65%. The most frequently reported interaction was digoxin and diuretics, but no fatal ADRs were reported with this combination. The combination of anticoagulant and antiplatelet agents was responsible for the greatest number of serious reactions and deaths.

Conclusions: This study validates that spontaneous reporting, despite its limitations, can be an important resource for detecting ADRs associated with the concomitant use of interacting drugs. Moreover, our data confirm that DDIs could be a real problem in clinical practice, showing that more than one in five patients exposed to a potential DDI experienced a related ADR.

Background

Drug-drug interactions (DDIs) have been considered an important issue in drug safety and a potential cause of adverse drug reactions (ADRs) for many years.[1] Moreover, fatal drug interactions have been reported[2-6] and some drugs have been withdrawn from the market because of serious adverse reactions associated with DDIs.[7,8] In the literature, little is known about the actual number of patients with adverse reactions resulting from DDIs, and most of the studies available are related to the hospital setting. The estimates of hospital admissions associated with DDIs vary from 0% to 2.8%.[9] Up to 15% of hospitalized geriatric patients may experience mild to moderate ADRs related to DDIs.[10] Recently, computerized drug alert systems have been set up to help prevent DDIs; however, these systems are not always available and some data suggest that the warnings regarding potentially serious drug interactions are often ignored by physicians.[11,12]

A spontaneous reporting database could be a valuable resource for detection of ADRs associated with DDIs; however, data in the literature are limited. Some authors have developed a method for detecting DDIs using a database for spontaneous ADRs, and have concluded that spontaneous reporting systems have the potential for signal detection and the analysis of possible DDIs.[13,14] Ellis and colleagues[15] consulted the US FDA Spontaneous Reporting System (SRS) database to search for specific ADRs related to DDIs. In another recent study, other authors, also consulting the FDA's SRS database, found a possible but not well known association between the concomitant use of topiramate and valproic acid and the induction of hypothermia.[16] A study using the French pharmacovigilance database identified potential DDIs with the three cholinesterase inhibitors marketed in France, and evaluated those resulting in ADRs.[17] Strandell and colleagues[18] examined, in the WHO ADR database, VigiBase, the reporting of all DDIs classified as 'established' and 'clinically important' in a DDI database, and described the most frequently reported ADRs for each DDI.

Our aim was to consult the Italian Interregional Group of Pharmacovigilance (GIF) database, which is a spontaneous reporting database, in order to detect those patients treated with potentially interacting drugs and the cases where reported adverse reactions are associated with DDIs.

Methods

Data Source

The data were obtained from a database containing all the reports of suspected ADRs from the Italian regions of Emilia Romagna, Lombardy, Tuscan, Sicily and the Veneto region. All these regions have a Regional Pharmacovigilance Centre, operating within the framework of the national pharmacovigilance network of the Italian Medicines Agency. These regions had an estimated population of about 28 000 000 inhabitants in 2007 (about 47% of the Italian population) and are the main contributors to the Italian spontaneous reporting system (accounting for about 74% of all Italian reports). The main sources of the reports are physicians (92.9%), followed by pharmacists (4.0%), nurses (1.2%), dentists (1.0%), patients (0.2%) and other healthcare personnel (0.7%). Drugs are classified according to the Italian Codifa system, which is linked to the Anatomical Therapeutic Chemical (ATC) classification. Reactions are classified according to the WHO Adverse Reaction Terminology.[19] Each report in the database is assessed for causality according to the WHO criteria.[20]

Data Analysis

In this study we analysed only the spontaneous reports, collected between January 1990 and December 2007, with a 'certain', 'probable' or 'possible' causality assessment. All reports containing at least two drugs, reported as being suspected of causing the ADR or as concomitant medication, were selected and a list of drug pairs was drawn up. At least one of the two drugs should have been indicated as suspected by the reporter. We then performed a search to verify which drug pairs were considered a potential DDI, using the Internet version of the DRUGDEX® system for the assessment and classification of drug interactions.[21]

For each report containing a potential DDI, we verified whether the description of the adverse reaction corresponded to the interaction effect as described in DRUGDEX®. Moreover, the dosage of drugs, any patient-predisposing or confounding factors and the time to ADR onset were taken into account to establish whether a combination of drugs was associated with a DDI. This assessment was made by a panel of five experts, including physicians, pharmacists and pharmacologists, considering all available information in the reports and consulting, when deemed necessary, the reporter.

The reports with adverse reactions associated with a DDI were analysed in detail to describe the demographic characteristics of the patients, the source of reports, the fatal cases and the severity of reactions, classified as serious or non-serious on the basis of the WHO definition.[20] Means, percentages and their 95% confidence intervals were used to compare the characteristics of these reports with the reports of patients treated with at least two potentially interacting drugs or non-interacting drugs. We classified the DDIs identified at four levels of severity: (i) contraindicated (the drugs are contraindicated for concurrent use); (ii) major (the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects); (iii) moderate (the interaction may result in an exacerbation of the patient's condition and/or require an alteration in therapy); and (iv) minor (the interaction would have limited clinical effects according to DRUGDEX®. Manifestations may include an increase in the frequency or severity of side effects but generally would not require a major alteration in therapy), using the same terminology and assessment reported in DRUGDEX®.[21] Finally, the reports were grouped by drugs according to their pharmacological classes, at different levels of ATC classification.

Results

Potential Drug-Drug Interactions in the Interregional Group of Pharmacovigilance Database

A total of 45 315 ADR reports were collected in the GIF database from January 1990 to December 2007, 27 615 (60.9%) of which reported only one suspected drug without concomitant drugs. Therefore, the search for DDIs was performed on the remaining 17 700 reports with at least two reported drugs (7428 men and 10 272

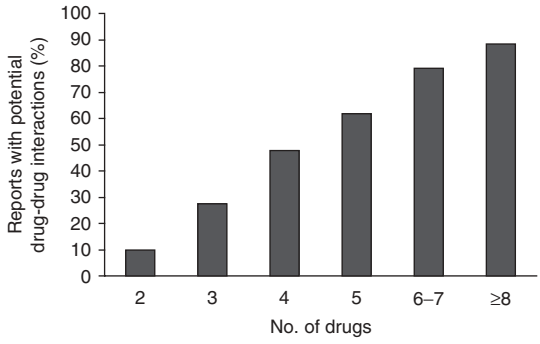

Fig. 1. Percentage of reports with potential drug-drug interactions in relation to the number of drugs.

women). On analysing reports with two drugs listed, we identified 34 822 different pairs of drugs administered concomitantly to patients. We found that 2506 (7.2%) of these different drug pairs were likely to cause any ADR of varying severity according to the DRUGDEX® terminology described in the methods section. Overall, the number of reports containing at least one potential DDI was 5345 (30.2%). As expected, the percentage of reports with potential DDIs increased in relation to the number of concomitantly administered drugs, ranging from 9.8% to 88.3% for two drugs and eight or more drugs, respectively (figure 1). The majority of potential DDIs were classified, according to the DRUGDEX® criteria, as being of moderate (58.3%) or major (32.1%) severity; only 7.8% of potential DDIs were minor and 1.9% contraindicated.

Adverse Drug Reactions Associated with Interactions

We identified 1159 reports describing an ADR associated with a DDI. These reports represent 2.6% of all reports in our database, 6.5% of reports regarding patients treated with at least two drugs and 21.7% of reports regarding patients exposed to a potential DDI.

Table I shows the main features of these reports (Group A) in comparison with those containing a potential DDI (Group B) and with the other reports related to patients treated with at least two non-interacting drugs (Group C). The percentages of serious and fatal reports of ADRs, the mean age, and the mean number of drugs were higher in Groups A and B compared with Group C, but also in Group A compared with Group B. Furthermore, it is worth noting that the percentage of contraindicated and major severity interactions were higher in Group A.

Finally, we observed an unexpected failure of therapy in 100 patients, i.e. a type F adverse reaction according to the ADR classification by Edwards and Aronson.[22]

Drugs Most Frequently Involved in ADRs Caused by Interactions

We found 583 different drug pairs involved in DDIs. Table II shows the drug pairs with more than 15 reports, and describes the most important adverse reactions and the interaction effects

Table I. Main features of reports describing an adverse drug reaction (ADR) associated with a drug-drug interaction (DDI) [Group A], reports containing a potential DDI (Group B) and reports related to patients treated with at least two non-interacting drugs (Group C)

Features of reports	Group A (n = 1159)	Group B (n = 4186)	Group C (n = 12 355)
Patient age [y, mean (95% CI)]	68.4 (67.5, 69.3)	65.0 (64.5, 65.5)	50.5 (50.1, 50.9)
Males [% (95% CI)]	48.4 (45.5, 51.3)	42.2 (40.7, 43.7)	41.3 (40.4, 42.2)
Source of reports [% (95% CI)]			
general practitioners	39.6 (36.8, 42.5)	46.9 (45.4, 48.4)	54.9 (54.0, 55.8)
hospital doctors	57.3 (54.4, 60.2)	50.0 (48.5, 51.5)	41.5 (40.6, 42.4)
other health staff	2.3 (1.5, 3.4)	2.1 (1.7, 2.6)	2.7 (2.4, 3.0)
not available	0.8 (0.4, 1.4)	1.0 (0.7, 1.4)	0.9 (0.7, 1.1)
Serious ADRs [% (95% CI)]	67.3 (64.5, 70)	51.1 (49.6, 52.6)	42.5 (41.6, 43.4)
Fatal ADRs [% (95% CI)]	4.2 (3.1, 5.5)	2.6 (2.1, 3.1)	1.4 (1.2, 1.6)
No. of drugs [mean (95% CI)]	4.9 (4.8, 5.0)	4.5 (4.4, 4.6)	2.7 (2.68, 2.72)
Contraindicated and major interactions [% (95% CI)]	41.2 (38.4, 44.1)	31.9 (30.5, 33.3)	0

Table II. Drug pairs with more than 15 reports of adverse drug reactions (ADRs) corresponding to the interaction effect

Drug combination (no. of reports)	Most relevant reported ADRs corresponding to the interaction effect	Interaction effect (according to DRUGDEX®[21])
Digoxin/furosemide (70)	Rhythm disorders, such as bradycardia, tachycardia and atrial fibrillation, were reported in 18 cases	Digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
Aspirin [acetylsalicylic acid/nitroglycerin] (52)	Thrombocytopenia was reported in 15 cases	Increase in nitroglycerin concentrations (with headache and syncope) and additive platelet function depression
Aspirin/clopidogrel (32)	Haemorrhage was reported in 20 patients, thrombocytopenia in 12	Increased risk of bleeding
Allopurinol/enalapril (32)	Two cases of Lyell syndrome and one case of acute generalized exanthematous pustulosis were notified	Hypersensitivity reactions (Stevens-Johnson syndrome, skin eruptions, anaphylactic coronary spasm)
Aspirin/furosemide (27)	Six cases of acute renal failure were reported	Salicylate toxicity
Aspirin/ticlopidine (23)	Thrombocytopenia was reported in eight cases	Increased risk of bleeding
Amiodarone/digoxin (21)	Rhythm disorders, such as bradycardia, tachycardia and atrial fibrillation, were reported in seven cases	Digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
Aspirin/heparin (20)	Thrombocytopenia was reported in nine cases	Increased risk of bleeding
Digoxin/hydrochlorothiazide (18)	Rhythm disorders, such as bradycardia, tachycardia and atrial fibrillation, were reported in four cases	Digoxin toxicity (nausea, vomiting, cardiac arrhythmias)
Diltiazem/simvastatin (17)	12 muscular disorders (myopathies, creatine phosphokinase increases) and 3 liver disorders were reported	An increased serum concentration of simvastatin with consequent toxicity
Levofloxacin/prednisone (16)	13 tendonitis and 3 tendon rupture cases were reported	An increased risk for tendon rupture

according to DRUGDEX®. Table III shows the interactions reported, grouped by the pharmacological classes of the drugs, with the percentage of serious and fatal ADRs. The interactions considered are the ones with at least 30 reports (which accounted for about 60% of the total).

Table III. Interactions between drugs grouped by pharmacological classes. Those with at least 30 reports of adverse drug reactions associated with the interaction are listed

Drug 1	Drug 2	No. of total reports	Serious reports [n (%)]	Fatal reports [n (%)]
Digoxin	Diuretics	95	49 (51.6)	0
Anticoagulant or antiplatelet drugs	Aspirin	88	83 (94.3)	6 (6.8)
Aspirin (acetylsalicylic acid)	NSAIDs	56	51 (91.1)	0
Diuretics	NSAIDs	53	35 (66.0)	0
Nitroglycerin	Aspirin	52	29 (55.8)	2 (3.8)
Anticoagulant or antiplatelet drugs	Anticoagulant or antiplatelet drugs	50	50 (100)	7 (14.0)
ACE inhibitors	Diuretics	46	25 (54.3)	1 (2.2)
Corticosteroids	Fluoroquinolones	43	20 (46.5)	0
ACE inhibitors	Allopurinol	36	18 (50.0)	1 (2.8)
ACE inhibitors	NSAIDs	35	27 (77.1)	0
Antiarrhythmic drugs	Digoxin	32	24 (75.0)	1 (3.1)
Anticoagulant or antiplatelet drugs	NSAIDs	30	30 (100)	1 (3.3)

The interaction between digoxin and diuretics was most frequently reported, although there were no fatal cases, and anticoagulant and antiplatelet drugs were responsible for the greatest number of serious reactions and deaths.

In 235 of 1159 reports (20.3%), both interacting drugs were recognized as suspect by the reporter. This percentage varies in relation to the drugs involved, ranging from 2% in the case of interaction between fluoroquinolones and corticosteroids or diuretics and NSAIDs, to about 65% in the case of anticoagulant/antiplatelet drugs and NSAIDs or NSAIDs and aspirin (acetylsalicylic acid).

Discussion

In the literature, multiple drug administration has been shown to be one of the risk factors for potential DDIs.[1,23] Glintborg and colleagues[24] also carried out a logistic regression analysis showing an association between the number of drugs taken and potential DDIs. In accordance with these results, our study shows that the percentage of reports with potential DDIs increases in relation to the number of concomitantly administered drugs.

Data regarding the actual contribution that DDIs make to ADRs are scarce and most studies have focused on the population in a hospital setting. From two important prospective analyses on very large hospital populations, it has been estimated that between 16.6% and 59.1%[25,26] of ADRs needing hospital care are related to drug interactions. This result is very different from our finding of 2.6%, but differences in the target population and in the selection of interactions could explain the discrepancy. The studies cited were conducted in the hospital setting whereas our data come from spontaneous reporting where reports from hospital physicians make up only a certain proportion of all reports (about 40%). Furthermore, our percentage is probably underestimated since the concomitant drugs are often not mentioned in spontaneous reports. In our study, the percentage of patients exposed to a potential DDI and experiencing an ADR associated with the same DDI (21.7%) is consistent with values previously reported in the hospital setting (14%) and geriatric outpatients (25.5%).[27,28] Since, like other authors,[29] we assume that the occurrence of ADRs in a population is random, our percentage could be considered representative of the general population. In a study very similar to ours, Tavassoli and colleagues[17] identified 1058 spontaneous reports in the French Pharmacovigilance database that involved cholinesterase inhibitors. Of these, 376 (35.5%) contained at least one potential DDI, and in 118 (31.4%), DDIs were related to ADRs, which is in line with our results of 30.2% and 21.7%, respectively.

Our finding highlighted the characteristics of patients treated with at least two drugs and presenting ADRs associated with DDIs. The percentage of serious and fatal ADR reports with DDIs is higher than reports of patients treated with at least two interacting or not interacting drugs. These findings are related to known risk factors such as age and number of drugs used, both higher in patients with DDIs than other patients. The prevalence of polypharmacy increases with age,[30,31] and it has been shown that two-thirds of medication users aged over 70 years take from two to four medications, and one-fifth take five or more drugs.[32] Therefore, as is well established in the literature, the risk of DDIs increases with age.[28] At the same time, it is well known that patients needing hospital care tend to be older. Moreover, in the literature, the number of hospital admissions in the elderly population associated with DDIs is higher than that in the general population. The estimates range from 2.9% to 6.2%.[33,34] Other known risk factors could be considered, such as the presence and type of previous and/or concomitant pathologies, individual genetic differences and environmental factors. However, this information is generally lacking in spontaneous reporting and therefore it is very difficult in this context to evaluate the contribution of each factor. These risk factors could also explain the difference, even if less relevant, that we found between patients with DDIs associated with an ADR compared with patients with potential DDIs. However, it is worth noting that patients experiencing ADRs associated with

DDIs are older, are treated with a higher number of drugs, and are more exposed to contraindicated combination of drugs or those leading to DDIs classified as major (i.e. the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects) according to DRUGDEX®.

Our findings showed that men were more likely to experience a DDI associated with an ADR than women (7.53% vs 5.8% of total reports). This result could be explained by the fact that in our study the majority of drugs involved in the DDIs are drugs used in cardiovascular diseases, and studies have demonstrated a link between this type of disease and male sex as a risk factor.[35-37]

The combination most frequently causing adverse reactions attributable to DDIs was digoxin and diuretics. This finding is in line with a previous analysis by our group, aimed at determining severe potential DDIs in a general practitioner (GP) database, where the combination of digoxin and diuretics represented 69% of total potential interactions in a group of patients from 16 GPs in the Veneto region.[38] The prescribers were probably aware of the risk of digoxin combinations. In fact, in our above-cited article, 72% of patients using digoxin with loop or thiazide diuretics for at least 5 months had tests relating to the monitoring of digoxin. In the present study, most adverse reactions attributable to a digoxin/diuretics combination consisted of gastrointestinal disorders; only one in four patients experienced rhythm disorders and no fatal cases were reported, supporting the evidence of physicians' ability to manage these situations.

In our present study, we found that the increased risk of bleeding deriving from combinations of anticoagulant, antiplatelet agents and NSAIDs were related to more severe consequences than other drug combinations; almost all these adverse reaction reports were serious and the percentage of fatalities ranged from 3.3 to 14.0 (see table III). Oral anticoagulants are recognized as being highly efficacious, but their use is limited by the well founded fear of bleeding, frequently associated with interaction with other drugs and with food.[39] Many studies have found that bleeding was one of the most common ADR admission diagnoses, and higher rates of hospital admissions were found in elderly patients who are likely to be receiving multiple medications for long-term illnesses.[25,40,41] Furthermore, case reports of life-threatening bleeding attributable to interactions involving antiplatelet, anticoagulant drugs and NSAIDs have been published in the literature.[42,43] These interactions are therefore well known and documented. In our analysis, however, only one drug was indicated by the reporter as suspected in more than one-third of patients, showing a poor awareness among healthcare providers of the danger of this combination.

The analysis of our database also highlighted the consequences of less known interactions and ones that are poorly documented in the literature. This is the case in the combination of allopurinol with captopril or enalapril, two commonly used ACE inhibitor drugs. DRUGDEX® recommends careful monitoring for hypersensitivity reactions when allopurinol and enalapril or captopril are used together, and there is only one published case report concerning a fatal incident of Stevens-Johnson syndrome in a patient receiving captopril and allopurinol.[44] In our database, there were two cases of Lyell syndrome and one of acute generalized exanthematous pustulosis in patients treated with allopurinol and enalapril.

It is well known that fluoroquinolones can cause tendon disorders.[45,46] However, doctors are probably less aware of the increasing risk of the concurrent use of corticosteroids.[47] In the present investigation, this interaction was explicitly recognized in only 2% of patients with tendon disorders treated with concomitant fluoroquinolones and corticosteroids.

Our results show that an ADR database can be an important resource for analysing known ADRs related to the concomitant use of interacting drugs. Other methodologies have been proposed to detect unknown DDIs through spontaneous reporting systems.[48] Limitations of these systems are, of course, well known and include under-reporting of ADRs, the presence of reports with missing information such as concomitant drugs, and the lack of denominator data such as the user population and drug exposure patterns. At the same time, spontaneous reports

have specific characteristics, which are certainly not comparable with personal clinical records, but are recognized as being one of the systems providing essential information of clinical importance.[49] An additional limitation of our study could be the use of only one source of DDIs among those available. It should be emphasized, however, that the DRUGDEX® system is one of the most frequently cited sources and an important aid in making clinical decisions.[50]

Conclusions

Our findings confirm that ADRs associated with DDIs could be a problem in clinical practice, showing that more than 20% of patients exposed to a potential DDI experienced a related ADR. The passage from potential to real DDIs increases the clinical relevance of our results and represents the true strong point of our work. Moreover, the data highlighted different types of harmful situations: the most common derives from an inadequate clinical or laboratory monitoring in patients treated with drugs known to be potentially interacting. In other cases doctors prescribe contraindicated combination of drugs underestimating the risk of ADRs. Preventive measures such as thorough patient monitoring, more educational training for prescribers and the use and quality of automated safety alerts for interactions should be improved in order to minimize the risk of interactions.

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