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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Identification of severe potential drug-drug interactions using an Italian general-practitioner database

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Abstract
Objective To analyze prescriptions in a general-practitioner database over 1 year to determine the frequency, the characteristics, and the monitoring of the severe potential drug-drug interactions (DDIs).
Methods We retrospectively analyzed the clinical records from 16 general practitioners in the Veneto region, an area in northern Italy. The study covered the period from January 1 to December 31, 2004. We selected all severe and well-documented interactions according to the book *Drug Interaction Facts* by David S. Tatro (Facts and Comparisons, St. Louis, MO, 2006). We grouped severe potential DDIs according to their specific potential risk, and for the most frequently interacting drug pairs, we investigated whether some specific tests had been prescribed by physicians for safety monitoring.
Results During the study period, 16,037 patients (55% female) with at least one drug prescription were recorded, and a total of 185,704 prescriptions relating to 1,020 different drugs were analyzed. Ramipril was the most frequently prescribed drug followed by acetylsalicylic acid and atorvastatin. The final number of different types of severe potential DDIs was 119, which occurred 1,037 times in 758 patients (4.7% of the total number of patients). More than 80% of drugs involved in severe potential DDIs were cardiovascular drugs. Digoxin was the most frequently involved drug. Electrolyte disturbances, increase in serum digoxin levels, risk of hemorrhage, severe myopathy or rhabdomyolysis, and cardiac arrhythmias were the most commonly implicated potential risks. When considering patients using digoxin with loop or thiazide diuretics for more than 5 months, 72% had at least one test to monitor potential digoxin toxicity, whereas 28% had no tests. Sixty-four percent of patients using digoxin with amiodarone, verapamil, or propafenone had an ECG and/or digoxin monitoring, and 36% of them did not have any tests.
Conclusions The present study revealed that, in a group of Italian general practitioners, the risks of severe potential drug interactions are relatively low and the drugs concerned are few. Analyses of specific tests showed that physicians are generally aware of the potential risks caused by digoxin drug associations. However not all patients were closely monitored and this should be improved.

Keywords General practice · Severe potential drug-drug interactions · Monitoring

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Introduction

In the broadest sense, a drug-drug interaction (DDI) may be defined as the pharmacological or clinical response to the administration of a drug combination that is different from that anticipated from the known effects of the two agents when given alone and that can result in reduced effectiveness or increased toxicity [1]. A DDI can be the consequence of various situations that reflect the growing number of drugs available on the market. The increasing

complexity of polytherapy is a major source of DDIs. The very widespread practice of self-medication makes the situation more severe and difficult.

In the literature, most studies on drug interactions have analyzed patients in hospitals, and it has been estimated that drug interactions may affect up to 63% of all hospitalized patients [2–4]. Data about outpatients exposed to drug interactions are limited, and a few studies set in the context of general practice have generated a wide range of estimates. In primary health care, from 9 to 70% of patients are reported to use concomitant drugs with the risk of a potential DDI [5–10], even if these are serious only in a fraction of these patients (from 0.5 to 2%) [11, 12].

According to the literature, many factors contribute to these wide ranges, either in a hospital or an outpatient setting, including the target population, the number of prescribed drugs, or the differences in methods used.

Some studies have quantified the outcome of specific interactions [13, 14], however little or nothing is known about the actual number of patients with serious consequences resulting from potential DDIs in primary health care [15]. The few published studies are related to hospital settings. Some authors suggest that even if many patients use potentially interacting drugs, the real risk related to these associations seems to be low or modest [16, 17]. On the other hand, other authors suggest that DDIs are a major cause of adverse drug reactions [18, 19].

The purpose of this study was to analyze prescriptions in a general-practitioner database over 1 year to determine the frequency, the characteristics, and the monitoring of the severe potential DDIs.

Methods

We retrospectively analyzed the clinical records from 16 general practitioners (GPs) in the Veneto region, an area in northern Italy. The study covered the period from January 1 to December 31, 2004. During this year every physician used the same software to record all drug prescriptions, medical tests and the most important clinical events for each patient in a personal clinical record. Data from all computerized clinical records were pooled in a single database. Patients with at least one drug prescription during the study period were selected.

All drugs prescribed to each patient in the study period were registered, since in Italy a prescription by the GP is necessary to have the drug or the medical test reimbursed by the National Health System, which covers the majority of prescribed drug and test costs.

To define severe DDIs, we used the book *Drug Interaction Facts* by David S. Tatro, one of the primary sources for drug information [1, 20]. The author defines three levels of severity—major, moderate, and minor—and five categories of degree of documentation—established, probable, suspected, possible, and unlikely. Based on a combination of these two elements, he assigns a significance rating (from 1 to 5) to each DDI.

By excluding drugs not used in primary care and not available in the Italian market, a list of 895 DDIs with significance rating of 1 (major severity and established or probable or suspected documentation) were selected. In the database, we looked for patients who were concomitantly using these interacting drugs.

We assumed that consumption of a drug started the same day the drug was prescribed, and for each patient we calculated the period of exposure to each interacting drug by multiplying the number of defined daily doses (DDD) by the number of prescribed packs. Severe potential DDIs were identified when the exposure periods to two interacting drugs overlapped. Severe potential DDIs were grouped according to their specific potential risk, as described in [1].

We considered the most frequently interacting drug pairs and investigated whether some specific tests had been prescribed by physicians for safety monitoring of potentially interacting drugs.

Results

During the study period, 16,037 patients with at least one drug prescription were recorded by 16 GPs. Every physician had approximately the same number of patients. Table 1 shows the general characteristics of the patients in the database. The mean age was 53.1 years; the majority of individuals (66%) fell in the age range between 15 and 64 years, and there was an evident prevalence of women in older age groups (61% were female in the patients >75 years). A total of 185,704 prescriptions relating to 1,020 different drugs (available as single or combined formulations) were analyzed.

As shown in Fig. 1, most patients (48%) received two to five different drugs, whereas 35% of them had prescriptions for more than five drugs. Seventeen percent of patients

Table 1 Characteristics of general-practice patient database (16 GPs)

Characteristic	*n* (%)
Total number of patients	16,037
Female (%)	8,853 (55)
Number of patients per age group (%)	
0–14 years	243 (2)
15–64 years	10,726 (66)
65–74 years	2,694 (17)
>75 years	2,374 (15)
Total number of prescriptions	185,704
Number of different drugs prescribed	1,020

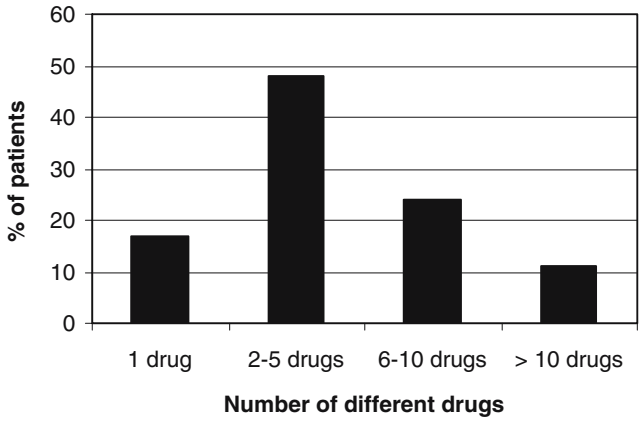

Fig. 1 Number of different drugs per patient

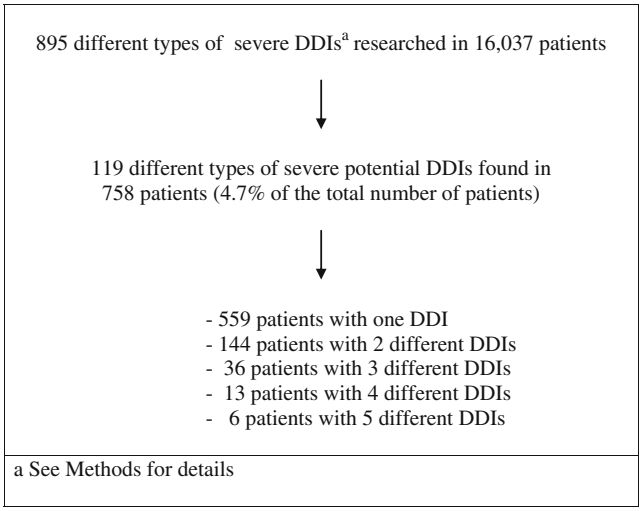

Fig. 2 Flow chart showing identification of severe potential DDIs

could not have DDIs because they received prescriptions for only one drug. The median number of different drugs per patient was three (range 1–35).

Table 2 shows the 10 most frequently prescribed drugs, expressed as total DDDs during the study year, and their ranking in the national consumption database in the same period. Ramipril was the most frequently prescribed drug followed by acetylsalicylic acid and atorvastatin. All drugs were present in the national top 10 list except for atenolol and the association ramipril-hydrochlorothiazide [21].

As shown in Fig. 2, we found 119 different severe potential DDIs (out of 895), which occurred 1,037 times in 758 patients (4.7% of the total number of patients). The majority of patients (74%) had only one potential DDI, but in six patients (0.04%), five different potential DDIs were detected.

Table 3 shows the severe potential DDIs occurring in more than 10 patients. The drug pairs listed in the table represent 69% of total potential interactions and the digoxin/furosemide pair was the most frequent one (23%). Forty-three severe potential DDIs occurred only once. More than 80% of involved drugs were cardiovascular drugs, and digoxin was the most frequently implicated drug (47% of total potential interactions). Diuretics, amiodarone, warfarin, verapamil, and ACE inhibitors were also frequently involved.

Among the antibacterial drugs, the macrolide azithromycin was associated with atorvastatin (18 patients) and simvastatin (13), and the fluoroquinolone levofloxacin was associated with amiodarone (17 patients). In 15 patients treated with acetylsalicylic acid, the nonsteroidal anti-inflammatory ketorolac was also used.

Table 4 lists the 1,037 severe potential DDIs grouped according to the potential risk as described in [1]. Electrolyte disturbances, increase in serum digoxin levels, risk of hemorrhage, severe myopathy or rhabdomyolysis, and cardiac arrhythmias were the most commonly implicated potential risks.

We focused on digoxin toxicity since it was the most frequently involved drug and looked for medical tests

Table 2 The top 10 prescribed drugs among study patients expressed in total DDD during the study period

Drugs	Total DDD	Rank in national prescription database in 2004
Ramipril	305,340	3
Acetylsalicylic acid	212,363	1
Atorvastatin	205,450	6
Furosemide	189,425	8
Amlodipine	181,356	2
Simvastatin	165,331	7
Atenolol	152,380	11
Levothyroxine sodium	136,883	9
Nitroglycerin	131,354	4
Ramipril–hydrochlorothiazide	122,598	>30

Table 3 Drug pairs causing severe potential DDIs concomitantly used in more than 10 patients and cumulative percentages

Drugs	No. of patients	Cumulative percentage
Digoxin-furosemide	243	23
Digoxin–hydroclorothiazide	127	36
Amiodarone-warfarin	59	42
Amiodarone–digoxin	57	47
Amiloride-ramipril	32	50
Digoxin-verapamil	28	53
Enalapril-spironolactone	27	55
Amiloride-enalapril	20	57
Atorvastatin–azithromycin	18	59
Amiodarone-levofloxacin	17	61
Acetylsalicylic acid-ketorolac	15	62
Lisinopril–spironolattone	15	63
Amiloride-perindopril	14	65
Ramipril-spironolactone	14	66
Azithromycin-simvastatin	13	67
Amiloride-losartan	12	69

Table 4 Severe potential DDIs (1,037) grouped according to their potential risk

Potential risk	Drug or drug class 1	Drug or drug class 2 (number of DDIs)	Total number of DDIs
Diuretic-induced electrolyte disturbances may predispose to digitalis-induced arrhythmias	Digoxin	Furosemide (243) or thiazide diuretics (142)	385
Elevated serum potassium concentrations (hyperkalemia) in certain high-risk patients	Potassium-sparing diuretics	ACE-inhibitors (178), angiotensin II-receptor antagonists (53), or potassium preparations (19)	250
Serum digoxin levels may be increased, resulting in an increase in the pharmacologic and toxic effects of digoxin	Digoxin	Amiodarone (57), verapamil (28), propafenone (7), clarithromycin (5), doxycycline (1), or quinidine (1)	99
Anticoagulant effect of oral anticoagulants may be enhanced, resulting in hemorrhage	Warfarin	Amiodarone (59), cotrimoxazole (5), sulfinpyrazone (1), macrolide antibiotics (8), fibric acids (5), azole antifungal agents (3), or metronidazole (1)	82
Severe myopathy or rhabdomyolysis may occur because of increased HMG-CoA reductase inhibitor levels	HMG-CoA reductase inhibitors	Macrolide antibiotics (48), cyclosporine (7), or gemfibrozil (3)	58
Risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased	Quinolones	Antiarrhythmic agents (21), tricyclic antidepressants (5), or phenotiazines (2)	28
Increased methotrexate toxicity	Methotrexate	NSAIDS (14), sulfasalazine (4), or amoxicillin (3)	21
Potentially life-threatening increases in blood pressure	Clonidine	Beta-blockers (18) or amitriptyline (3)	21
Serotonin syndrome may occur	SSRI	Risperidone (7) or selective 5-HT1-receptor agonists (11)	18
Effects of both drugs may be increased	Beta blockers	Verapamil	17
Increased risk of serious ketorolac-related side effects	Ketorolac	Acetylsalicylic acid	15
Ototoxicity may be increased	Aminoglycosides	Furosemide	11
	Other drugs		32

indicating physician awareness of potential risks. We investigated whether electrocardiograms were carried out or serum potassium or digoxin concentration levels were measured by physicians in patients treated for at least 5 months with digoxin in association with diuretics (165 patients) and anti-arrhythmics (53 patients). Tables 5 and 6 show the patients who underwent specific tests after the beginning of these drug associations. Thirty-five percent of patients had one test, 26% had two tests and 11% had three tests. However 28% of them were treated with the combination for more than 5 months without any testing. Sixty-four percent of patients using digoxin with amiodarone, verapamil, or propafenone had an ECG, digoxin monitoring or both, but 36% of them did not have any tests.

Discussion

The correct use of a drug is determined by several important factors, including the awareness of product characteristics, such as contraindications and warnings, followed by a careful evaluation of the patient in order to consider possible risk factors, concomitant pathologies, and harmful drug-drug interactions.

In the present study, the analysis of prescriptions by 16 GPs over 1 year showed that, in general practice, 4.7% of the patients concomitantly used drugs that could cause a severe potential DDI. Previous studies showed that 0.5–2% of patients are exposed to serious potential drug interactions

Table 5 Number of tests [ECG, digoxin level, potassium (K) serum level] in 165 patients with at least 5 months of co-administration of digoxin and diuretics

Number of tests	Patients tested (*n*, %)
No tests	47 (28)
One test (ECG, digoxin level, or K serum level)	57 (35)
Two tests (ECG + digoxin level, or ECG + K serum level, or digoxin + K serum level)	43 (26)
All (ECG + digoxin level + K serum level)	18 (11)

Table 6 Number of tests (ECG, digoxin level) in 53 patients with at least 5 months of co-administration of digoxin and amiodarone, verapamil, or propafenone

Number of tests	Patients tested (*n*, %)
No tests	19 (36)
One test (ECG or digoxin level)	29 (55)
All (ECG + digoxin level)	5 (9)

in primary health care [11, 12]. However differences in the selection of interactions or in the target population could explain these discrepancies. In our study, the most commonly interacting drugs were cardiovascular drugs (more than 80%). Bjerrum and colleagues showed that in primary health care most of the potential interactions emerged in patients treated with cardiovascular drugs (diuretics, ACE inhibitors, digoxin, beta-blockers and calcium channel blockers), NSAIDs, oral antidiabetics, and anticoagulants. Considering only major potential interactions, the most frequently involved drugs were potassium-sparing diuretics and anticoagulants [5]. A study relating to multiple-drug prescribing by GPs in Germany concluded that the most frequently found drug pairs implicated in potential DDIs were digitalis/diuretics, digitalis/calcium channel blockers, and theophylline/quinolones [22]. Other authors, looking at elderly outpatients, found that the most common potential interactions were between beta-adrenergic blockers and anti-diabetics, followed by potassium-sparing diuretics and potassium preparations [8].

In our results the most frequently interacting drug was digoxin, involved in almost half of total severe potential DDIs. Although this drug has been used for more than two centuries, its role in the management of chronic heart failure has been more precisely defined by recent clinical trials showing that digoxin therapy was associated with no beneficial effects on mortality, but only with a reduction in clinical symptoms and in the frequency of heart failure-related hospitalization [23, 24]. Therefore digoxin, even at low doses, is currently considered most beneficial in symptomatic patients who are already undergoing adequate diuretic therapy and taking ACE inhibitors with or without beta blockers [25, 26].

The relationship between diuretic-induced electrolyte depletion and digitalis-induced arrhythmia, as well as the connection between the toxic effects of digoxin and the use of anti-arrhythmic drugs, is known and widely accepted [13, 27, 28]. In an intensive-care study, patients treated with digitalis and diuretics had an approximately 1.5-fold higher risk of digoxin toxicity compared to those treated with digitalis alone [29]. In a review on digoxin, the association between digoxin and loop and thiazide diuretics proved among the most important drug interactions, causing a dose-dependent reduction in serum potassium and magnesium [30]. This reduction increases the arrhythmogenic effects of digoxin, particularly in patients with cardiac ischemia and heart failure [31].

The administration of amiodarone, verapamil, or propafenone to patients on stable doses of digoxin results in increased digoxin serum levels. The increase in serum digoxin level after the addition of amiodarone has been reported in the literature as between 69 and 800% [32, 33]. Verapamil and digoxin have additional effects to slow atrio-ventricular conduction; investigations in healthy volunteers and cardiac patients indicated that verapamil raises plasma digoxin concentrations 60–75% [28, 34]. In addition, verapamil decreased digoxin elimination [28], and total body digoxin clearance was reduced by approximately 35% [34]. There was an increase in premature ventricular contraction frequency in 1 out of 10 patients on the combination [35] and another study reported digoxin toxicity in 7 out of 49 patients treated with verapamil [36], but it is still unclear if an increased risk of digoxin-induced arrhythmias exists.

Due to the considerable risk of the above-mentioned interactions, many authors agree that some relevant parameters should be closely monitored and that the dosage of digoxin should be individualized and reduced when patients receive these medications concurrently [1, 30, 37]. In our study, 72% of patients using digoxin with loop or thiazide diuretics for at least 5 months had some tests relating to the monitoring of digoxin. On the other hand, in 28% no tests of any kind related to the risk of interaction were done, showing inadequate monitoring. General practitioners are probably aware of the risk of digoxin combinations and made the prescriptions because they thought the benefits of the drugs outweighed the risks. However our findings strengthen the need to improve their knowledge of the proviso that all patients should be monitored. It should be underlined that 322 out of 385 patients treated with digoxin and diuretics received concomitant administration of ACE inhibitors, sartans, potassium, or potassium-sparing diuretics, known to induce hyperkalemia. In this group, 162 patients (~50%) had at least one potassium serum level test, showing hyperkalemia (K>5.3 mEq/l) in 17 patients, and in only one case hypokalemia (K<3.5 mEq/l).

Physicians seem to be less aware of the risk from the combination of digoxin with amiodarone, verapamil, or propafenone; 36% of patients using these drug associations for at least 5 months had no related tests in the period following the prescription.

Potassium-sparing diuretics were commonly prescribed along with either ACE inhibitors, sartans, or potassium preparations by the physicians participating in this study. The risk of hyperkalemia due to this association is well documented in the literature. Many authors reported life-threatening hyperkalemia in patients treated with spironolactone associated with ACE inhibitors or sartans [14, 38–40], even if in other published studies this risk has been reported as infrequent [41].

In our study, 250 potential DDIs occurred between potassium-sparing diuretics and ACE inhibitors, sartans, or potassium supplements, although in all but four patients, loop or thiazide diuretics were concomitantly prescribed. This co-prescription could have reduced the risk of hyperkalemia in these patients.

Many patients with cardiac arrhythmias in our database received concomitant therapy with warfarin and amiodarone. This association requires a significant warfarin dose reduction, due to the risk of hemorrhage. Moreover thyroid disorders may affect warfarin sensitivity, with hypothyroidism and thyrotoxicosis resulting in increased or decreased warfarin requirements, respectively [42].

In the present study, about 50 patients were treated concomitantly with statins and macrolides, mainly represented by atorvastatin and azithromycin. The risk of myopathy and rhabdomyolysis, well documented in statin users, increases in cases of concomitant prescription with cytochrome P450 (CYP) inhibitors such as macrolides [43]. Simvastatin and atorvastatin are mostly metabolized by the isoenzyme CYP3A4.

Azithromycin shows a lower affinity to this isoenzyme compared to other macrolides [44–46]. Consequently, the associations with azithomycin are less risky, even if clinical case reports suggest there is some potential for drug interactions [44].

A recent study analyzed whether statin-macrolide concomitant prescriptions were commonly written by a group of Italian GPs. They concluded that 63.5% of GPs co-administered statins and macrolides at high risk of interaction at least once [47]. Other authors agree that co-prescription of medications not compatible with statins occurs frequently [48]. It is possible that physicians underestimate the risks of this interaction, given that other antimicrobial drugs could be used to avoid serious side effects.

The present study has some limitations. The reference book used to select severe DDIs is one of the primary sources for drug information, but many other sources could have been used [20].

Another limit is that over-the-counter drugs as well as drugs or tests done during hospitalization have not been registered in the database.

Moreover the period of exposure was calculated on the basis of the DDD prescribed, which does not necessary reflect the exact consumption by each patient (dosage, compliance).

Another aspect that should be emphasized is that the drug interactions found in this study were only potential: no actual outcomes or consequences were evaluated. Concerning the management of DDIs by general practitioners, the use of automated alerts could increase the recognition of drug interactions by GPs, but their perceived poor specifity may be an important obstacle to efficient utilization of information, and may prevent such alerts from improving patient safety [49, 50].

Conclusions

The present study revealed that, in a group of Italian general practitioners, the numbers of severe potential drug interactions are relatively low and the drugs concerned are few. The monitoring of patients treated with digoxin and other cardiovascular drugs should be improved. The use of concomitant drugs to compensate for hyperkalemia or hypokalemia induced by some cardiovascular drugs seems to indicate physicians′ awareness of potential electrolyte disturbances. Moreover precise and updated information on interacting drugs could prevent the occurrence of known interactions, particularly when therapeutic alternatives exist.

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