

Pharmacodynamic and pharmacokinetic drug interactions reported to VigiBase, the WHO Global Individual Case Safety Report Database

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Key words: Pharmacovigilance, VigiBase, enzyme inhibition, additive effects

Word count: 2881

Tables included: Three

Figures included: -

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Abstract

Objective: Drug interactions resulting in adverse drug reactions (ADRs) represent a major health problem both for individuals and the community. Despite this, there is limited information in the literature regarding drug interaction categories responsible for causing ADRs. In this study we investigated the drug combinations most frequently co-reported as interacting in the WHO Global Individual Case Report (ICSR) Database, VigiBase, and categorised them in respect to the drug interaction mechanism. **Methods:** Reports with drug combinations co-reported as interacting on at least 20 reports in VigiBase during the past 20 years were included in the study. Each drug combination was reviewed in the literature to identify the mechanism of interaction and classified as pharmacodynamic and/or pharmacokinetic. Report characteristics were also analysed. **Results:** In total 3766 case reports of drug interactions from 47 countries were identified. Of 123 different drug combinations 113 were described in the literature to interact. The mechanism were categorised as: pharmacodynamic in 46(41%), pharmacokinetic in 28(25%), a combination of both types in 18(16%), and unidentified in 21(19%) drug interactions. Pharmacodynamic drug interactions primarily concerned pharmacological additive effects whereas enzyme inhibition was the most frequent pharmacokinetic interaction. The reviewed combinations primarily implicated drugs such as warfarin, heparin, carbamazepine and digoxin. **Conclusions:** Drug interactions reported on globally collected ADR reports covers both pharmacodynamic, specifically additive pharmacological effects, and pharmacokinetic mechanisms primarily accredited inhibition of hepatic CYP enzymes. These ADR reports often concerns serious threats to patients' safety, particularly related to usage of high risk drugs such as warfarin and heparin.

Introduction

Polypharmacy increases the complexity of therapeutic management and thereby the risk of clinically important drug interactions, which may result in adverse drug reactions (ADRs) or reduced therapeutic effect in individuals (1). However, the magnitude of ADRs related to drug interactions in the existing literature is inconsistent, probably reflecting the variety of settings and populations studied. A recently published study based on individual case safety reports (ICSRs) found that 22% of patients exposed to a potential drug interaction experienced an associated ADR (2), while in specific hospital settings drug interactions have been reported to cause up to 59% of all ADRs (3, 4).

A large proportion of potentially clinically significant drug interactions are reported to occur by alterations in the hepatic drug metabolism mostly in the activity of cytochrome P450 (CYP) enzymes such as CYP3A4, CYP2C9, CYP2C19, CYP1A2 and CYP2D6, glucuronidation and drug transporters such as P-glycoprotein. Hence pharmacokinetic properties and related drug interactions are often well supported in clinical studies referred to in SPC (Summary of the Product Characteristics) texts and specific drug interaction references. While pharmacodynamic interactions, which are apparent from the main pharmacological action of the drugs are often expected to be understood by prescribing physicians (5), are often undersupplied in drug reference texts unless the drug combination may result in serious toxicity such as prolonged QT interval.

Adverse effects due to drug interactions are a common and to a large extent a preventable health care issue. As ICSRs are reflections of drug related problems within health care, these reports can give insight into which drug interactions that are of particular concern and the characteristics of these. However, few studies have actually examined drug interaction categories responsible for causing ADRs. Subsequently, this study was conducted to explore the ICSRs with drug combinations most frequently co-reported as interacting in the WHO Global ICSR Database, VigiBase, and to categorise them with respect to the drug interaction mechanisms.

Methods and data

To study mechanisms of suspected drug interactions reported globally, drug combinations co-reported as interacting on at least 20 reports in VigiBase during the past 20 years were included in the study. Each drug combination was reviewed in the literature for the mechanism of interaction and classified according to pre-defined categories. To further characterise these suspected drug interactions reported to VigiBase, information on date of report, gender, reporter and country of origin were studied.

Data source

The WHO Programme for International Drug Monitoring was initiated in 1968 to detect previously unknown drug safety problems and still remains as one of the central elements for global safety surveillance (6). To maintain the programme's operation ICSRs (also referred to as spontaneous reports of suspected ADRs and synonymously referred to as *reports* in this paper) are collected in the WHO Global ICSR Database, VigiBase (7). The reports are collected on national basis by the individual member countries (n=104) of the WHO Programme for International Drug Monitoring, and then forwarded to, processed and stored in VigiBase.

Each report contains at least a drug, an ADR, the country submitting the report and an identification number. Drugs listed on the reports are assigned as 1) 'suspected' (drugs suspected for the reaction, but not explicitly as due to a drug interaction), 2) 'interacting' (if an adverse drug reaction is suspected of being related to a drug interaction between two or more

drugs), or 'concomitant' (drugs used concurrently but not suspected by the reporter to have caused the adverse event). Information on the reports are provided by a primary reporter or through a second evaluation performed by the National Centre. The individuals providing information listed on the reports are referred to as *reporter*. The reports also contain other information such as age, gender, type of report (spontaneous, study report) etc.

Classification

Drug interaction mechanisms were categorised into two main groups, pharmacokinetic and pharmacodynamic (8, 9). Pharmacokinetic interactions were further divided into mechanistic subgroups with additional sub-classifications given in brackets: absorption (changes in gastrointestinal pH, changes in gastrointestinal motility, chelation and adsorption, damage to gastrointestinal tract, induction or inhibition of drug transport proteins, reduction of gut flora); distribution (protein-binding 'displacement', induction or inhibition of drug transport proteins); metabolism (hepatic uptake - induction or inhibition of drug transport proteins, enzyme induction, enzyme inhibition); and excretion (hepatic secretion into the bile - induction or inhibition of drug transport proteins, changes in urinary pH, active tubular secretion - induction or inhibition of drug transport proteins). Pharmacodynamic interactions were initially divided into two categories: 'direct effect at receptor function', 'interference with a biological or physiological process. In a pilot phase we discovered that many of the pharmacodynamic drug combinations concerned additive pharmacological effects rather than synergistic effects. Additive pharmacological effects were therefore included as a subgroup of pharmacodynamic mechanisms, even though these are not covered by the general definition of a drug interaction

(“pharmacological or clinical response of one drug is changed in the presence of another drug” (8)) as its effects are not changed. Pharmacodynamic interactions were divided into the following subgroups: ‘direct effect at receptor function’, ‘interference with a biological or physiological control processes’ and ‘additive/opposed pharmacological effect’.

Those drug combinations established to interact but with an unidentified mechanism were listed as ‘unidentified mechanism’. Drug combinations concluded with negative results for a potential drug interaction were noted as ‘no interaction’. Drug combinations without published information of a possible interaction were classified as ‘unknown in the literature’.

Analyses

Reports with drug combinations co-reported as interacting on at least 20 reports in VigiBase during the past 20 years were scrutinized. To characterise this subset of suspected drug interactions, information on date of report, gender, reporter and country of origin were retrieved and analysed. Selected drug combinations were reviewed in the literature for the mechanism of interaction and classified according to the pre-defined categories. The following literature sources were reviewed for interaction mechanism in given order: 1) Stockley’s Drug Interaction (10), 2) FASS (Swedish Drug Compendium) (11), 3) DrugDex (12) and 4) PubMed (13). When the information in Stockley’s Drug Interaction, FASS for health care professionals and DrugDex was consistent no further literature search in PubMed was made. For combinations where more than one mechanism was suggested for the interaction all

mechanisms of interaction were listed. To clarify the involvement in each mechanism drugs were classified as object (the affected drug) and precipitant (induced the interaction) (14). Both drugs were noted as object in cases where the interaction was documented to result in an additive or synergistic effect. From the literature further information for each mechanism were extracted: expected outcome specified as toxic effect or reduced efficacy and type of pharmacological effect noted as additive, synergistic or antagonistic for pharmacodynamic interactions.

Supplementary analyses

As a drug may be involved in several clinically important mechanisms, all mechanisms found for the drug in the literature review were summarised. To investigate if reported response (based on reports in Vigibase) corresponded to the expected outcome of verified drug interactions, top reported ADR terms (15) for a drug combination were reviewed.

Results

From January 1990 to February 2010, 4149345 reports were entered in VigiBase, of these included 18409 reports two drugs as interacting. During the study period 123 drug combinations were co-reported as interacting on at least 20 reports (in total 3766 reports) and thus included in the analysis. The analysis included reports from 47 countries with the majority (67%) from Europe; this contrasts general distribution of reports in VigiBase whereof USA represents 50%. When excluding reports lacking gender specification, females (52%) were slightly more common than males (48%) which also disparities from the general distribution where 60% of VigiBase reports concerns females. In total 83% of the reports were submitted from health care professionals (physicians (78%), pharmacists (4%), nurses and dentists (1%)). This also contrasts to VigiBase in general, where 63% are received from health care professionals.

Mechanisms

Of the 123 reviewed drug combinations, 113 were verified in the literature to interact. In total were 65 pharmacodynamic and 68 pharmacokinetic mechanisms acknowledged in the literature (table I). Interactions via additive pharmacological effects and inhibition of metabolic pathway were most common among the studied drug combinations. Of the interactions acknowledged to a specific enzyme, CYP3A4 and CYP2C9 were particularly frequent, these accounted for 42% and 24%, respectively. Other enzymes involved were CYP1A2, CYP2B6, CYP2C19, CYP2C8 and epoxide hydrolase. For 40 drug combinations more than one mechanism

was accredited for the interaction. Whereas some were purely pharmacokinetic as for digoxin and clarithromycin involving drug distribution (induction or inhibition of drug transport proteins (10, 12) and reduction of gut flora (10-12)), and excretion (changes in renal blood flow (10-12)); or as a mix of pharmacodynamic and pharmacokinetic mechanisms as for warfarin and celecoxib that functions via additive pharmacological effect (10, 11) and enzyme inhibition (10, 12)(table II). For the reviewed drug combinations, protein-binding displacement, inhibition of drug transport proteins and inhibition of the gut flora were often described as minor mechanisms and rarely reported as exclusively responsible for the drug interaction.

When reviewing the unique nature of the 113 verified interactions, 46 (41%) were identified as purely pharmacodynamic; 28 (25%) as pharmacokinetic; and 18 (16 %) were a mix of both types. For 11 otherwise purely pharmacodynamic and pharmacokinetic interactions additional mechanisms, yet unidentified, were proposed, as the main mechanism of action was assumed to not explain the interaction's total effect. In addition, 21 (19%) drug combinations (e.g. selective serotonin re-uptake inhibitors (SSRIs) with lithium, or warfarin with tramadol or warfarin with norfloxacin) were reported to interact though without detailed description of a mechanism in the literature, though the interactions had been acknowledged on case reports or case series.

Reported characteristics

The reviewed combinations primarily concerned well established drugs, i.e. drugs that have been marketed for more than 10 years. Among pharmacodynamic interactions antithrombotic agents were most frequent (table III), while pharmacokinetic interactions involved a range of drugs that inhibit or compete for hepatic CYP enzymes. The substantial influence of antithrombotic agents amongst frequently reported pharmacodynamic interactions were reflected by the overall ADR pattern reported for pharmacodynamic interactions in Vigibase (ordered by total number of reports): gastrointestinal haemorrhage, haematoma, melaena and prothrombin level decreased. While for pharmacokinetic interactions the variety of drugs involved reflected the range of ADRs reported but also alterations in therapeutic effect (ordered by total number of reports): drug level increased, prothrombin level decreased, rhabdomyolysis and therapeutic response increased. ADRs reported for verified interactions were well associated with the expected effect of the object drug (table II). This is shown with the increased frequency of reports for warfarin related effects (increased international normalised ratio (INR) and or decreased prothrombin level) during concurrent use of roxithromycin and miconazole, or risk of statin induced rhabdomyolysis during concurrent use of gemfibrozil.

None interacting drug combinations

For ten drug combinations, the literature did not include information of a possible interaction. Among these none interacting drug combinations were warfarin and digoxin; three drug combinations involving drugs used in standard tuberculosis regime (ethambutol with

pyrazinamide, ethambutol with rifampicin, and isoniazid with pyrazinamide); a vitamin K antagonist, fluindione, with various agents (amiodarone, ceftriaxone, ciprofloxacin, fluconazole and ofloxacin) with all reports submitted from France; and acetylsalicylic acid (ASA) with abciximab, whereas the drugs' antithrombotic effects are used in combination for patients undergoing percutaneous coronary intervention (11).

Discussion

This study demonstrated that the scope of drug interactions reported on globally collected ADR reports is broad and concerns interactions with both pharmacokinetic, foremost inhibition for hepatic CYP enzymes, and pharmacodynamic mechanisms primarily as additive pharmacological effects. This is particularly noteworthy since pharmacodynamic interactions have been reported to have less clinical impact than pharmacokinetic interactions (5). Moreover, ICSRs of suspected drug interactions often concerns serious threats to patients' safety, particularly related to usage of high risk drugs such as warfarin and heparin (16, 17).

Even though the spontaneous reporting system is a cornerstone of the early detection of previously unknown single drug- single ADR combinations (18), there is a clear over-representation of established associations. We deliberately used this phenomenon when selecting drug combinations (inclusion criteria ≥ 20 reports) to identify drug interaction categories reported on ICSRs. There were a range of mechanisms reported, and the scrutinised combinations were often the expression of more than one mechanism. CYP3A4 was the most common metabolic pathway in this subset, and this is expected from its general involvement in drug metabolism. Even if the proportion of CYP2C9 (24%) interactions was higher than expected these were explained by the numerous adverse drug interactions involving warfarin. Furthermore, were enzyme inhibition more common than enzyme induction in this subset, which may be because of various reasons: its general occurrence; or that induction more rarely

leads to an effect that has clinical impact; or that enzyme inhibition is more easily associated to drug use as its ADR response occurs more rapidly (8, 9).

Drug combinations not reported in the literature which in general are interesting in from signalling value (19), were explain by common drug therapies whereas the individual drugs for the combination were likely to interact with a range of other drugs (e.g. digoxin – warfarin, ASA - abciximab and drug combinations involving drugs used in standard tuberculosis regime driven by the fact that rifampicin induces the metabolism of isoniazid); or a reflection of lack of information in the international literature as for the vitamin K antagonist, fluindione, for which several of the suspected interacting agents are established to interact with the more widely used vitamin K antagonist, warfarin (12).

This subset primarily concerned well established drugs which are expected since information for well established drugs increases over time. Even though we focused on well known drug interactions in this analysis, previous reports have shown that there is a continuous need for monitoring of well established drugs as new problems, such as drug interactions related to the concurrent use of new drugs, are still being discovered (20-22). This is also emphasised from other reviews of drug safety issues which to a large extent concerns drugs well known to interact (23, 24).

The reporting patterns for this subset of reports contrast the general reporting in VigiBase in two perspectives: drug interactions are to a greater extent reported by health care professionals; and reports for females were less frequent in this subset (25). A higher rate of reports from health care professionals are expected as greater pharmacological knowledge is required to understand the more complex character having more than one drug associated to the adverse outcome. For gender distribution Leone *et al.* found a similar result, where the proportions of potential interactions were greater for females, though men were more likely to experience an ADR related to a drug interaction (2). However, considering the nature of data and the small set of drug interactions used in this analysis, disparities for gender in terms of experiencing drug interactions needs to be further investigated.

This descriptive analysis did not intend to present the frequency of mechanisms for drug interactions outside this subset, or the frequency of these drug combinations in VigiBase related to their background reporting or outside the database. Though, it is possible that certain mechanisms are more frequently acknowledged and therefore are drug combinations more frequently reported, or reversely, the literature is more limited for some mechanisms such as transport proteins and therefore are these less well represented in the subset.

Furthermore, VigiBase is heterogeneous with respect to origin of data and level of suspicion such as assignment of drugs related to ADRs varies between member countries. For example drugs involved in a drug interaction may be assigned as interacting or as suspected, for the latter

the suspected drug interaction may then be noted in the case narratives or as an ADR term. However these notations lack of assignment to the specific drugs involved in the interaction as many more drugs may be listed as suspected on the individual case report. Subsequently, there is a clear under-reporting of drug interactions listed in the drug assignment in VigiBase, which results in a selection bias of drug combinations undertaken for this review. However, this is not necessarily a problem as the reports in this analysis were received from a variety of countries. Increased reporting related to increased publicity is one of the general limitations of the ADR surveillance system, that may have amplified further differences in drug assignment as interacting on the individual case report (26), or could have lead to increased reporting and hence inclusion in this review.

Despite that adverse effects due to drug interactions are common, ICSRs have previously been limitedly used in the early discovery of drug interactions signals. This analysis has contributed to identify which drug interactions that are of particular concern and the mechanistic scope of these. Overall are much more efforts are needed to appropriately manage and acknowledge the risk of potential drug interactions to prevent these in the early stage of prescribing or monitor them thoroughly.

Conclusion

Drug interactions reported on globally collected ADR reports covers both pharmacodynamic, specifically additive pharmacological effects, and pharmacokinetic mechanisms primarily via CYP inhibition in the liver. These ADR reports often concerns serious threats to patients' safety, and particularly related to usage of high risk drugs such as warfarin and heparin, and other well established agents. Finally, post-marketed reported drug interactions do not only concern problems related to the drugs' pharmacological action but also to how the drugs are used.

Acknowledgements

The authors are indebted to the National Centres that contribute data. The opinions and conclusions in this study are not necessarily those of the various centres, nor of the World Health Organisation (WHO).

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Table I. Overview of mechanisms acknowledged in the literature for drug combinations co-reported as interacting on at least 20 reports in Vigibase between January 1990 and February 2010. In total were 123 drug combinations reported in the subset whereof 113 were verified to interact. Several mechanisms may be relevant for the same drug interaction.

Overall mechanism	Mechanism	No. of DI	No. of DI reported to result in toxicity	No. of DI reported to result in reduced efficacy
Pharmacodynamic	Direct effect at the receptor level	0	0	0
	Interference with control process	5	4	1
	Additive/ pharmacological effect	57	57	-
	Opposed pharmacological effect	1	-	1
	Pharmacodynamic (total)	65¹	63	2
Pharmacokinetic	Drug absorption ²	3	3	0
	Drug distribution ³	7	7	0
	Drug metabolism ⁴	53	41	12
	Drug excretion ⁵	7	7	0
	Pharmacokinetic (total)	70	58	12
Unidentified mechanism		34	25	8
Unknown in the literature		9	-	-
No interaction		1	-	-

Abbreviations: DI=drug interactions

¹ Two pharmacodynamic mechanisms with toxic outcome could not be categorised further into subgroups.

² Drug absorption: Induction or inhibition of drug transport proteins, Reduction of gut flora

³ Drug distribution: Protein-binding 'displacement', Induction or inhibition of drug transport proteins

⁴ Drug metabolism: Hepatic uptake - induction or inhibition of drug transport proteins, Enzyme induction, Enzyme inhibition

⁵ Drug excretion: Changes in urinary pH, Active tubular secretion - induction or inhibition of drug transport proteins

Table II. Most frequently drug combinations co-reported as interacting in VigiBase during the past 20 years with interaction mechanism/s and top three reported ADRs.

Drug A	Drug B	No. of ICSRs	Mechanism	Top reported (brackets)
ASA	Clopidogrel	155	Additive/opposed pharmacological effect ⁽¹⁰⁻¹²⁾	Haematom Anaemia (2 GI haemorr
Digoxin	Amiodarone	150	Induction or inhibition of drug transport proteins ^(10, 26) Protein-binding 'displacement' ⁽¹⁰⁾ Drug excretion ^(10-12, 26) Changes in renal blood flow ^(10-12, 26) Interference with a biological or physiological control process ⁽¹⁰⁻¹²⁾	Bradycardia Vomiting (3 Drug level i
Digoxin	Clarithromycin	150	Induction or inhibition of drug transport proteins ^(10, 12) Reduction of gut flora ⁽¹⁰⁻¹²⁾ Changes in renal blood flow ⁽¹⁰⁻¹²⁾	Drug level i Therapeuti Nausea, Bra
Gemfibrozil	Cerivastatin	113	Hepatic uptake - induction or inhibition of drug transport proteins ⁽²⁷⁻²⁹⁾ Enzyme inhibition ⁽²⁷⁻³⁰⁾ Additive/opposed pharmacological effect ⁽²⁷⁾	Rhabdomyo Myalgia (26 Renal failur
Valproic acid	Lamotrigine	111	Drug metabolism ^(10, 31) Enzyme inhibition ⁽¹⁰⁻¹²⁾	Drug intera Stevens-Joh
ASA	Heparin	102	Additive/opposed pharmacological effect ⁽¹⁰⁻¹²⁾	Haematom Anaemia (1 Cerebral ha
ASA	Enoxaparin	97	Additive/opposed pharmacological effect ⁽¹⁰⁻¹²⁾	Haematom Anaemia (2 Melaena (1
ASA	Diclofenac	93	Additive/opposed pharmacological effect ⁽¹⁰⁻¹²⁾ Unidentified mechanism ^(10, 12)	GI haemorr Melaena (2 Abdominal
Warfarin	Roxithromycin	89	Enzyme inhibition ^(10, 12, 32) Unidentified mechanism ^(10, 32)	Prothrombi INR inc. (25 Haematuria
Isoniazid	Rifampicin	75	Enzyme induction ^(10, 12)	Nausea (9) Jaundice, H
Digoxin	Furosemide	71	Interference with a biological or physiological control process ⁽¹⁰⁻¹²⁾	Vomiting (2 Bradycardia Drug toxicit
Spironolactone	Furosemide	71	Additive/opposed pharmacological effect ⁽¹¹⁾	Renal failur Hyperkalae Hyponatrae
Warfarin	Miconazole	69	Enzyme inhibition ⁽¹⁰⁻¹²⁾	Prothrombi INR inc. (16 Haematuria
Warfarin	Celecoxib	60	Enzyme inhibition ^(10, 12) Additive/opposed pharmacological effect ^(10, 11)	Prothrombi INR inc. (9) Purpura(5)
ASA	Fluindione	59	Additive/opposed pharmacological effect ⁽¹⁰⁾	Anaemia (2 Melaena (1 Prothrombi

Table III. Mechanisms acknowledged for drugs most frequently implicated in drug interactions reported to VigiBase.

	Drug	PD	PK	Pharmacodynamic		Pharmacokinetic				
				Interference with control process	Additive/opposed effect	Absorption		Distribution	Metabolism	
						Induction or inhibition of DTPs	Reduction of gut flora	Protein-binding displacement	Hepatic induction or inhibition of DTPs	Enzyme induction
Pharmacodynamic	Acetylsalicylic acid	14	3	1	13			3		
	Warfarin	12	16		12			1		
	Furosemide*	7	1	2	5					
	Heparin	6			6					
	Fluindione	5			5					
	Amiodarone*	4	7	2	2	1		1		
	Spironolactone	4	2		4			1		
	Enoxaparin	4			4					
	Clopidogrel	4			4					
Pharmacokinetic	Warfarin	12	16		12			1		
	Carbamazepine**	1	13		1					
	Digoxin*	3	11	2	1	2	1	2		
	Valproic acid**	1	8		1			1		
	Amiodarone*	4	7	2	2	1		1		
	Clarithromycin	-	7			1	1			
	Simvastatin***	2	6		1					
	Phenytoin	-	5					1		
	Gemfibrozil***	2	3		1				1	

Abbreviations: PD=pharmacodynamic, PK=Pharmacokinetic, DTPs=drug transport proteins

Asterisks: For some interactions the mechanism was given on a general level without further specification (*excretion, **metabolism, *** pharmacodynamic interaction). Valproic acid interactions were reported twice to be involved in metabolism; otherwise there were single occurrences for mechanisms listed as asterisks.