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Letter to the Editors

Drug–drug interactions – a preventable patient safety issue?

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Spontaneous reporting systems remain the cornerstone of the early detection of previously unknown adverse drug reactions (ADRs) [1]. However, a large proportion of ADRs are known and preventable and they are often due to the coadministration of drugs known to interact [2]. Spontaneous reports of known ADRs can provide insight into the inappropriate co-prescribing of medications.

The World Health Organization (WHO) ADR Database (Vigibase) contains more than 3.8 million suspected ADR reports from 82 countries [3]. We examined the coreporting in Vigibase of all drugs classified as 'established' and 'clinically important' in the Swedish, Finnish, INteraction X-referencing drug–drug interaction database (SFINX database) [4] used in a Swedish patient record system. Thirty-five 'established and clinically important' drug–drug interactions (DDIs) were identified. Co-prescribing of these drugs was then searched for in VigiBase. Subsequently, data were retrieved on the severity and evidence for interactions involving these pairs, and actions recommended in Stockley's Interaction Alert [5].

Of those 35 'established and clinically important' drug pairs, 31 were reported in Vigibase, involving 9547 reports from 50 countries. The reported DDIs are listed in Table 1. The serious nature of many of the ADRs listed in Table 1 makes this a major patient safety issue. Also, seven pairs had had only theoretical evidence previously available, and another four pairs had had no previous evidence.

Amongst a wide range of drugs, the majority of reports concerned anticonvulsants and anticoagulants. Many of the most reported drug pairs included drugs with narrow therapeutic indexes, such as warfarin, carbamezepine, phenytoin and theophylline. This was further emphasized by the nature of the adverse events reported for the drug pairs: 'therapeutic level increased', 'drug level increased', 'drug level decreased' and 'therapeutic level decreased'.

Spontaneous reports sometimes lack detail, which makes the analysis difficult. For example, risperidone/carbamezepine and convulsions could be due to underlying disease or an overdose effect of risperidone on discontinuation of carbamazepine.

In many reports one drug only was reported as 'suspected'. For example, only 149/661 cases of decreased prothrombin and 197/408 cases of gastrointestinal haemorrhage with warfarin and acetylsalicylic acid were reported as co-suspected or interacting. Judging by attribution of suspicion, it seems that potential interactions were not recognized, although we should not assume that all reports are necessarily results of inappropriate use.

The continuing reporting of seemingly well-established interactions strongly suggests insufficient impact of drug information on routine prescribing practices. For example, the US Food and Drug Administration (FDA) has warned of concurrent therapy of rosiglitazone and insulin [6], as it was associated with increased risk of cardiac failure [7]. Since that FDA warning in May 2004, 402 reports of the pair, 52 reports of cardiac failure and 46 reports of the most common symptom, peripheral oedema, have been entered into VigiBase. Studies have shown that education can improve both doctors' and medical students' prescribing patterns [8], and electronic advice can significantly improve recognition of dangerous drug combinations [9]. This review has focused on an analysis of spontaneous reports, with no estimate of drug use. The raw number of reports of combinations should not be interpreted as an estimate of incidence. For some combinations, increased recent reporting might be explicable by increased drug use. Many of the drug pairs have been marketed for several years, and for two-thirds of the pairs reporting started >10 years ago. Our results illustrate a longstanding international problem of comedication of contraindicated drugs. This is in

Table 1

Clinically important drug–drug interactions

Drug A	Drug B	Total DDI	Rep. after 2000	Rep. before 2000	DDI information from Stockley's Interaction Alert			
					Actions	Severity	Evidence	Most reported ADRs
Anticoagulants								
Warfarin	ASA	3956	2913	1043	Adjust	Severe	Extensive	Prothrombin decreased (661)
Warfarin	Metronidazole	300	183	117	Monitor	Severe	Study	Prothrombin decreased (92)
Warfarin	Diclofenac	281	115	166	Monitor	Severe	Case	Prothrombin decreased (25)
Anticonvulsants								
Carbamazepine	Risperidone	719	460	259	Monitor	Severe	Study	Somnolence (49)
Carbamazepine	Clozapine	422	158	264	Monitor	Severe	Case	Leucopenia (59)
Carbamazepine	Erythromycin	254	50	204	Avoid	Severe	Extensive	Drug level increased (39)
Carbamazepine	Quetiapine	253	243	11	Monitor	Moderate	Theoretical	Convulsions (22)
Carbamazepine	Ethinylestradiol	10	1	9	Adjust‡	Severe‡	Theoretical‡	†
Carbamazepine	Levonorgestrel	65	29	36	Informative	Nothing expected	Theoretical	Pregnancy unintended (22)
Phenytoin	Cimetidine	485	65	420	Monitor	Severe	Study	Rash (63)
Phenytoin	Irinotecan	40	40	0	Monitor	Moderate	Case	Convulsions (11)
Statins								
Simvastatin	Ritonavir	10	9	1	Avoid	Severe	Study	Myocardial infarction (3)
Simvastatin	Indinavir	10	7	3	Avoid	Severe	Theoretical	Myocardial infarction (3)
Simvastatin	Nelfinavir	8	7	1	Avoid	Severe	Study	Rhabdomyolysis (4)
Simvastatin	Saquinavir	3	3	0	Avoid	Severe	Theoretical	†
Simvastatin	Tipranavir	1	1	0	NA*	NA*	NA*	†
Antineoplastic agents								
Methotrexate	Probenecid	7	6	1	Adjust	Severe	Study	Sepsis (3)
Ciclosporin	Idarubicin	6	4	2	Adjust	Severe	Study	Thrombocytopenia (2)
Irinotecan	Phenobarbital	8	8	0	Informative	Unknown	Theoretical	Sepsis (4)
Irinotecan	Primidone	1	1	0	NA*	NA*	NA*	†
Irinotecan	Carbamazepine	14	11	3	NA*	NA*	NA*	Vomiting (5)
Busulfan	Metronidazole	13	12	1	NA*	NA*	NA*	Bilirubinaemia (5)
Antihypertensive agents								
Propranolol	Chlorpromazine	166	42	124	Informative	Moderate	Theoretical	Hypotension (11)
Diltiazem	Midazolam	99	44	55	Monitor	Severe	Study	Hypotension (20)
Others								
Insulin	Rosiglitazone	857	857	0	Avoid	Severe	Study	Weight increase (165)
Paroxetine	Venlafaxine	567	431	136	Monitor	Severe	Case	Suicide attempt (83)
Cimetidine	Theophylline	466	46	420	Adjust	Severe	Extensive	Drug level increased (81)
Aminophylline	Cimetidine	162	13	149	Monitor	Severe	Study	Death (13)
Erythromycin	Verapamil	152	33	119	Monitor	Severe	Case	Nausea (13)
Clomipramine	Fluvoxamine	138	77	61	Adjust	Moderate	Study	Drug level increased (16)
Diazepam	Rifampicin	74	24	50	Monitor	Moderate	Study	Hepatitis (9)

Summary of reporting of clinically important drug–drug interactions (DDIs) in the WHO-ADR database grouped by major therapeutic areas. *NA, No information available. †Several different ADR *terms* were recorded in this/these reports, but only one occurrence of each term. ‡Referring to combined hormonal contraceptives. Study = Information based on formal study [5]. Case = Information based either on a single case report or a limited number of case reports [5]. Theoretical = Information based on a theoretical interaction or lack of interaction [5].

agreement with national studies that have shown that physicians fail to recognize [9] and continue to prescribe contraindicated drugs [10].

We contend that VigiBase and other available data sources could, and should, be utilized to identify preventable ADRs through active screening for potential DDIs. Also, much more effort is needed to communicate patient safety findings appropriately to healthcare providers and patients.

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