Editors' view

Communicating information about drug interactions

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Drug interactions are bread and butter to journals of clinical pharmacology, and their ramifications are varied. In this issue, for example, we publish evidence that clarithromycin increases plasma glibenclamide concentrations, probably by inhibition of P glycoprotein [1]; this presumably explains previous reports of hypoglycaemia in patients taking this combination. In another report, a suspected interaction of fluvoxamine and tizanidine, via inhibition of CYP1A2, caused fatigue, loss of energy, drowsiness, and dizziness; when milnacipran was used instead of fluvoxamine, piloerection occurred and was attributed to α_1 -adrenoceptor stimulation by endogenous noradrenaline, after re-uptake inhibition by milnacipran [2]. Elsewhere, we learn that artemisinin can induce its own metabolism [3], in what might be regarded as a narcissistic drug interaction; the semi-physiological model that was used to analyse this phenomenon was also of interest.

Sources and quality of information

Drug interactions, for example hypoglycaemia precipitated by clarithromycin in a patient taking glibenclamide, can be dangerous. However, we do not know from most reports of drug interactions how often an interaction is likely to be important and which patients are most likely to be affected. This creates difficulties for those who are in the business of informing prescribers. It therefore comes as no surprise to read in this issue of the *Journal* that there was a lack of consistency in the inclusion and grading of nearly 1100 drug interactions, involving 50 drugs, listed in four different sources of information, the *British National Formulary* in the UK, Vidal's *Interactions médicamenteuses* in France, and *Drug Interaction Facts* and the *Micromedex Drug-Reax System*, both in the USA [4]. This study complements an

earlier study of 109 reported drug interactions involving amiodarone, as listed in eight different sources of information published in France, the Netherlands, New Zealand, Switzerland, the UK, and the USA, which showed similarly variability [5].

There are different systems for describing important interactions in different sources of information [4]. The *British National Formulary* uses a bullet to mark drug combinations that are potentially hazardous and that should be avoided or only prescribed with caution and appropriate monitoring. Vidal's *Interactions médicamenteuses* includes four levels of seriousness based on the recommended clinical management – contraindicated, avoid, precaution, and “take into account” (i.e. no specific recommendation). *Drug Interaction Facts* classifies the severity of an interaction into three categories – major, moderate, and minor – and the degree of documentation into five categories – established, probable, suspected, possible, and unlikely; it also assigns a significance of 1–5 to each interaction, based on a combination of these two categorizations. The *Micromedex Drug-Reax System* classifies the severity of an interaction into three categories – major, moderate, and minor – and the degree of documentation into five categories – excellent, good, fair, poor, and unlikely.

No single source was significantly better than another: up to 44% of the drug interactions that were classified as major in any one source were not listed in the other sources. For example, 80 interactions that were classified as “hazardous” in the *British National Formulary* and 18 interactions that were highlighted there with the advice “avoid” or “contraindicated” were not listed in the other sources of information. Several reasons for the discrepancies were identified:

Table 1

Three categories of potential harm from drug interactions (adapted from reference 5)

Category	Meaning	Implication	Example
●(●) Red	Danger	Do not prescribe	Warfarin and azapropazone
○○(○○) Double amber	Danger ahead	Act to avoid the danger	Warfarin and erythromycin
○(○) Amber	Possible harm	Be aware and warn the patient	Warfarin and allopurinol

- different inclusion criteria;
- the inclusion or exclusion of different sources of evidence (for example, articles in different languages, manufacturers' unpublished data);
- different assumptions about so-called class effects;
- lack of consensus about the classification of the severity of an interaction and the best way of assessing its clinical relevance (i.e. seriousness).

The importance of this report is not in highlighting the possible deficiencies of any one source, but in showing how difficult it is to purvey reliable and useful information to prescribers.

Ideally, prescribing information about a drug should list its potential interactions, together with the following information about each interaction: its mechanism, its relation to the doses of both drugs, its time course, the factors that alter an individual's susceptibility to it, its seriousness and severity, and the probability of its occurrence [5,6]. In practice, however, this information is rarely available. Most drug interactions are documented as anecdotal reports or as effects in small studies, in which interactions may be missed if they are limited to a susceptible subset of the population [7]. Anecdotal reports of harms in general are often not confirmed by subsequent systematic studies [8], and even when an interaction is firmly established, it can be difficult to predict the risk in an individual patient.

A proposed system

What we need is a standardized form of information that would communicate to the prescriber in simple terms the nature of the risk about a drug interaction and the quality of the evidence on which the association is based. Elsewhere, Ferner and I [5] have suggested such a system, using two types of information:

- a warning about the degree of potential harm and the action to take; this involves three categories of potential harm, based on UK railway traffic signals, as illustrated in Table 1;

- a representation of the quality of the evidence, indicating whether the evidence is based on:
 - A – Anecdotes (case reports or case series);
 - D – Data from laboratory (animal or cellular) experiments or extrapolated from theory; or
 - R – Randomized trials or observational studies.

To illustrate this system, important drug interactions with amiodarone are categorized in this way in Table 2.

Education

It is important to provide prescribers with clear and simple information about drug interactions, but the information will be worthless if the prescriber does not understand the need to look for such information, how to obtain it, how to interpret it, and how to act on it. There is abundant evidence that education improves prescribing [9]. It is therefore important that medical students should be taught about drug interactions, their mechanisms and effects, how to obtain information about them, and how to avoid them. However, there is also evidence that they are not being exposed to such teaching. The results of a study briefly published in this issue of the *Journal*, after its presentation in December 2006 at the 75th anniversary meeting of the British Pharmacological Society in Oxford, showed that doctors in their first foundation year in a UK hospital wanted to have had more undergraduate teaching about prescribing for special groups, adverse drug reactions, and drug interactions; 55% of them had witnessed a drug interaction, some of which had resulted in patient morbidity or mortality [10]. Elsewhere, as reported in this issue, when final year students received extra teaching in various aspects of drug therapy, including drug interactions, 96% strongly agreed that it had helped them to avoid medication errors [11].

Perhaps practical demonstrations of drug interactions would also help to fix them in students' minds. Japanese undergraduate medical students who in their final year took part in a laboratory investigation of the interaction of furosemide with probenecid, subsequently, when they

Table 2

Important interactions of amiodarone with other drugs, classified by the degree of harm (see Table 1) and the quality of the evidence (see text)

Interacting drug	Category of harm	Evidence
Anaesthetics	○○	R
Astemizole	●	D
Beta-adrenoceptor antagonists	○	D
Calcium channel blockers	○	R
Ciclosporin	○○	A
Cimetidine	○	A
Colestyramine	○	R
Dextromethorphan	○	R
Digoxin	○○	R
Disopyramide	○○	R
Drugs that prolong the QT interval	●	A
Erythromycin i.v.	○○	R
Fentanyl	○	R
Flecainide	○○	R
Fluoroquinolones	○○	R
Grapefruit juice	○	A
Ibutilide	○	R
Lidocaine	○	A
Lithium	○○	A
Macrolide antibiotics	○○	A
Oxygen, high dose	○○	A
Phenytoin	○○	A
Procainamide	○○	R
Protease inhibitors	○	D
Quinidine	○○	D
Rifampicin	○	R
Simvastatin	○	A
Sparfloxacin	○○	R
Thioridazine	●	R
Warfarin	○○	R

were qualified, recognized all drug interactions better than those who had not taken part in such a study [12]. However, it is not always possible to conduct practical experiments of this sort in medical schools, desirable though that may be.

In a study of the reasons for admissions to hospital in 18 820 patients, interactions were responsible for adverse drug reactions in about 17% of admissions to hospital and for about 17% of all adverse drug reactions [13]. Examples of those interactions included aspirin with warfarin (causing gastrointestinal bleeding), aspirin with other NSAIDs (leading to gastrointestinal adverse

effects), renal insufficiency associated with the use of combinations of diuretics or the concomitant use of diuretics and ACE inhibitors, and increased anticoagulation and digoxin toxicity through co-prescription of interacting drugs. All of these interactions should be well enough known to be avoidable. Better information and better teaching should help.

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