Editors' view

Classifying drug interactions

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Drug–drug interactions

There has been a small but important change in the presentation of drug interactions in Appendix 1 in the *British National Formulary* (BNF). Starting in issue 47, interacting drugs are now distinguished by the use of a blue typeface, enhancing the user-friendliness of this section enormously, at little cost.

The BNF was first published as a direct descendant of the *National War Formulary* in 1948, but gradually lost its usefulness and was discontinued in 1976. It was reborn in 1981, after a prolonged labour [1], in the format with which all UK prescribers are now familiar. Issue 1 weighed in at 387 pages, of which just over four were devoted to lists of drug interactions. Issue 47, like so many of us, is more obese; it runs to 868 pages, with

a rump of 81 pages on drug interactions, a disproportionate increase (Table 1). I have no time to analyse in detail the reasons for this, but a major contributor must be the extent to which our knowledge of CYP isoforms has burgeoned, since altered drug metabolism is a major mechanism underlying many important drug interactions, as illustrated by several papers in this issue of the *Journal*.

Classifying drug–drug interactions mechanistically gives major insights into how to predict, detect, and avoid them:

- Pharmaceutical interactions
- Pharmacokinetic interactions
 - Absorption
 - Distribution (protein binding, tissue binding)
 - Metabolism (hepatic, nonhepatic)
 - Excretion (renal, nonrenal)
- Pharmacodynamic interactions (direct, indirect)

But here I want to examine a different method of classifying drug interactions, based on individual susceptibility, which should inform the design of drug interaction studies. Broadly speaking there are two classes of susceptibility.

First, there are interactions to which all are equally susceptible. In such cases small studies should suffice. For example, induction of CYP3A4 will reduce the effects of drugs that are metabolized by that isozyme. Of course the degree of susceptibility will vary from individual to individual, but the overall susceptibility is such that one would expect to be able to detect such an interaction in a small study of unselected subjects. Kawaguchi *et al.* give a good example in this issue of the *Journal* (pp. 403–10), when they show that St John's

Table 1

The numbers of pages devoted to drug interactions in every fifth issue of the new *British National Formulary*

Issue number	Total number of pages	Pages of lists of drug interactions	Percentage
1	387	4	1.03
6	476	6	1.26
11	514	9	1.75
16	527	12	2.28
21	562	20	3.56
26	628	24	3.82
31	700	27	3.86
36	748	33	4.41
41	790	38	4.81
46	836	45	5.38

wort reduces quazepam concentrations, presumably by inducing the activity of CYP3A4, a predictable effect. Elsewhere, Park *et al.* (pp. 397–402) show that ketoconazole increases plasma rosiglitazone concentrations, perhaps by effects on CYP2C8 and CYP2C9.

Then there are interactions that affect only a subset of individuals. For example, quinidine inhibits the metabolism of dextromethorphan, but only in extensive metabolizers of CYP2D6, not poor metabolizers [2]. Of course, extensive metabolizers so outnumber poor metabolizers in the population that this type of interaction is detectable in small studies of unselected subjects. However, the fewer people an interaction affects the more difficult it will be to show it in a small study. Suppose only 10% of the population are susceptible, even a study in 30 patients would be unlikely to produce a significant result (since the upper 95% confidence limit of zero is three); most interaction studies recruit no more than a dozen participants. How then, short of doing much larger studies, should we design interaction studies when there may be variable susceptibility?

One way is to compare drugs. In this issue of the *Journal* (pp. 390–6) Kajosaari *et al.* show that although gemfibrozil increases repaglinide concentrations, bezafibrate and fenofibrate do not. This supports the view that the mechanism of the gemfibrozil interaction is inhibition of CYP2C8. It does not completely reassure us that the other fibrates do not also interact by a different mechanism in a small subset of the population, but that seems unlikely.

Another method is to do a formal study in the individuals in whom the interaction has been anecdotally observed or who have the suspected susceptibility; unfortunately, that is rarely if ever done. The usual method is to study a group of volunteers after observing a patient. For example, anecdotes attest to the fact that some antibiotics reduce the effect of oral contraceptives; however, this interaction has not been demonstrated in small formal studies [3]. Similarly, small studies of the interaction of paracetamol with coumarin anticoagulants have not shown an effect. In such instances a case-control study may be the only way to elucidate such an interaction [4], although perhaps pharmacogenomics will eventually contribute too. In this issue of the *Journal* Dieterle *et al.* (pp. 433–6) show that the renin inhibitor aliskiren did not alter the pharmacokinetics or pharmacodynamics of warfarin. This is reassuring, but they studied only 15 subjects and single-dose administration of warfarin, and we cannot be sure that aliskiren does not affect warfarin in a small subset of the population.

Finally, we lack systematic reviews of reports of interactions, which might give clues to the nature of individual susceptibility. We should be using different types of studies to elucidate different types of drug interactions.

Drug–disease interactions

We generally think of drug–disease interactions as occurring when a disease alters the pharmacokinetics or pharmacodynamics of a drug. Such interactions can be classified mechanistically in an analogous fashion to drug–drug interactions. However, consider an interaction in which the drug alters the nature of the disease: bacterial resistance induced by antimicrobial drugs, another unusual aspect of which is that the effect in one individual alters the response in another. It has been said that the more rigorously a country controls infections and the supply and use of antimicrobial drugs, the lower the rate of resistant strains [5]. However, good evidence is scarce. In this issue of the *Journal*, Vander Stichele *et al.* (pp. 419–28) show how to collect data on antimicrobial drug prescribing in different countries, information that will be needed if patterns of resistance among microorganisms are to be understood and combated.

This problem raises issues about balancing the benefit of treating individuals against the potential harm to the community. As an admirer of the late Jack Trevor Story [6], I am of the ‘live now, pay later’ school, although the dearth of new antimicrobial drugs with which to pay does give me pause.

References

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