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Editors' view

Drug interactions—information, education, and the *British National Formulary*

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The drug interactions appendix in the current issue of the *British National Formulary* lists about 3000 interactions or groups of interactions (the number of individual interactions is probably about 5000). Of those, about 900 (about 1500 individual interactions) are marked by a bullet, signifying 'interactions that are potentially hazardous and where combined administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring)'. The drugs or groups of drugs that earn the most bullet points are listed in Table 1.

Unfortunately, the lists of interactions in the BNF are difficult to read and understand. They do not clearly distinguish between interactions in which the named drug is affected by the interaction (the object drug) and those in which it causes the interaction (the precipitant drug). Mechanisms are not mentioned. The categorization of drugs is inconsistent; why, for example, are diuretics with disparate modes of action grouped together, while HIV protease inhibitors (amprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir) are all listed separately? And the print is small – over 100 individual interactions are crammed into each page.

Of course, the BNF is not a textbook, and it can be argued that bald lists are enough. Furthermore, the cost of producing it must be considered. But doctors need better guidance. For instance, the BNF says that 'prolonged regular use of paracetamol possibly enhances warfarin'. We are not told what 'prolonged' and 'regular' mean, nor what to do about the interaction. Is the combination to be avoided altogether? The answer is no, but the BNF doesn't tell us that.

Given the vast number of interactions that have been described, it is not surprising that the *British Journal of Clinical Pharmacology* publishes many papers on drug–drug and food–drug interactions and on drug elimination by cytochrome P450 isozymes and P glycoprotein. In 2002, for example, there were 32 such original papers in a total of 141 (23%). In this issue alone there are nine.

Table 1
Drugs or groups of drugs that are marked with at least ten bullet points in the drug interactions appendix in the *British National Formulary* (BNF 46)

Number of bullets	Drugs or groups of drugs
10–14	Amiodarone; antihistamines; barbiturates; beta-blockers; disopyramide; diuretics; oral contraceptives; indinavir; NSAIDs; quinidine; quinolone antibiotics; saquinavir; SSRIs; St John's wort; telithromycin
15–19	Antipsychotic drugs; calcium channel blockers; carbamazepine; erythromycin and other macrolides; monoamine oxidase inhibitors; nelfinavir; phenytoin; rifamycins; tricyclic antidepressants
20–24	Antifungal imidazoles and triazoles; ritonavir
25–29	Ciclosporin; warfarin

Ito, Brown, and Houston (pp. 473–86) tell us how to use *in vitro* studies to predict *in vivo* interactions whose mechanism is inhibition of drug metabolism. First you calculate the hepatic input concentration of the inhibitor (I_{in}) and the *in vitro* inhibition constant (K_i) for your enzyme. Then you use I_{in}/K_i to predict the change in clearance of the object drug, measured as the increase in the AUC when the inhibitor is present. In a database of 149 interactions mediated by CYP3A4, CYP2D6, or CYP2C9, 102 (68%) were correctly identified and only four were missed. This type of approach will probably

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not reduce the number of interaction studies needed for drugs that reach the market, but it should help manufacturers to screen potential inhibitors and regulatory authorities to avoid licensing such drugs as mibefradil and cerivastatin.

Now what about paracetamol and warfarin? Here is a brief summary, which does not do full justice to this interaction. Paracetamol potentiates the effect of warfarin in a dose- and time-related fashion: the more you take for longer, the bigger the effect is [1]. The mechanism may be pharmacodynamic [2], perhaps via an action on factor VII [3]. But this effect is not apparently shared by phenprocoumon and acenocoumarol [4–6], although if only a few individuals are susceptible, the studies may have been too small to detect them. Or perhaps they were poorly designed. Rather than looking for effects of paracetamol in a population of patients with INR values in the target range, it may be better to choose patients who have an INR of 6 or over and look for susceptibility factors. That is precisely what Visser *et al.* (pp. 522–4) did in their study of the interaction of laxatives with acenocoumarol or phenprocoumon; and they found that lactulose increased the risk of an INR over 6 by 3.4 times. These drugs are commonly used, and this may therefore be a clinically important interaction, even in the UK, if it turns out that lactulose affects warfarin as well.

Other papers in this issue of the *Journal* deal with inhibition of CYP-mediated drug metabolism by HIV protease inhibitors (pp. 436–40), trimethoprim (pp. 441–7), grapefruit juice (pp. 448–55), perhexilene (pp. 456–63), and fluvoxamine (pp. 487–94) and induction by St John's wort (pp. 495–9); and Davies *et al.* (pp. 464–72) remind us that elderly people are at increased risk of drug interactions because they often take drugs that affect CYP3A4 or CYP2D6—polypharmacy that is often inappropriate [7].

Lord Reith famously declared that the BBC had three purposes: to inform, educate, and entertain. Recently, one of his successors, Greg Dyke, sought to qualify those purposes with what he modernistically called six 'values': to maintain trust, purvey quality and value for money, respect the audience, foster creativity, pursue diversity, and encourage internal collaboration. The *British National Formulary* has, in my view, a duty to do most, if not all, of those things. Most doctors do not have specialized interactions textbooks to hand. The BNF should fill that gap. And it should educate as well as inform.

So what could be done to improve the presentation of information about drug interactions in the BNF? I would describe each individual drug interaction, with each drug in its own structured table, generally listing the interaction under the object drug, with a cross-reference from the precipitant drug, stating what the likely mechanism is, and giving advice about what to do. I appreciate that this would be a large task. But the BNF is a much-respected authority, and the section on interactions should be of the same exceptionally high standard as the rest of the text. Readability, comprehensibility, and clinical relevance should be favoured over compactness.

References

1 Hylek EM, Heiman H, Skates SJ, Sheehan MA. Singer DE. Acetaminophen and other risk factors for excessive warfarin anticoagulation. J Am Med Assoc 1998; 279: 657–62.

2 Gebauer MG, Nyfort-Hansen K, Henschke PJ, Gallus AS. Warfarin and acetaminophen interaction. Pharmacotherapy 2003; 23: 109–12.

3 Whyte IM, Buckley NA, Reith DM, Goodhew I, Seldon M, Dawson AH. Acetaminophen causes an increased International Normalized Ratio by reducing functional factor VII. Ther Drug Monit 2000; 22: 742–8.

4 Van den Bemt PM, Geven LM, Kuitert NA, Risselada A, Brouwers JR. The potential interaction between oral anticoagulants and acetaminophen in everyday practice. Pharm World Sci 2002; 24: 201–4.

5 Fattinger K, Frisullo R, Masche U, Braunschweig S, Meier PJ, Roos M. No clinically relevant drug interaction between paracetamol and phenprocoumon based on a pharmacoepidemiological cohort study in medical inpatients. Eur J Clin Pharmacol 2002; 57: 863–7.

6 Gadisseur AP, Van Der Meer FJ, Rosendaal FR. Sustained intake of paracetamol (acetaminophen) during oral anticoagulant therapy with coumarins does not cause clinically important INR changes: a randomized double-blind clinical trial. J Thromb Haemost 2003; 1: 714–17.

7 Aronson JK. Editors' view. In defence of polypharmacy. Br J Clin Pharmacol 2004; 57: 181–2.