- adverse effects can be associated with long-term treatment
- drug interactions can alter drug effects, both pharmacokinetic and pharmacodynamic.

Regular monitoring is necessary to ensure that the effects of treatment remain stable; drug dosages should be altered when they do not. Remember that the balance of benefit-to-harm can change with time.

Conflicts of interest

None.

Further reading

1 Aronson JK, Hardman M, Reynolds DJ. *ABC of monitoring drug therapy*. London: British Medical Journal Publishing Group, 1993.

2 *British National Formulary*. Sections on prescribing and appendices. [A BNF for children is in preparation.]

3 Grahame-Smith DG, Aronson JK. *The Oxford textbook of clinical pharmacology and drug therapy*, 3rd edn. Oxford: Oxford University Press, 2002.

4 Richards D, Aronson JK. *The Oxford handbook of practical drug therapy*. Oxford: Oxford University Press, 2005.

5 Shenfield GM (ed). Therapeutic drug monitoring beyond 2000. Review. *Br J Clin Pharmacol* 2001;**52**(Suppl 1):3S–4S.

Adverse drug interactions

John Feely MD FRCP, Professor of Pharmacology and Therapeutics

Michael Barry PhD FRCPI, Senior Lecturer, Trinity College

Department of Pharmacology and Therapeutics, University of Dublin, Trinity Centre for Health Sciences, St James's Hospital, Dublin

Clin Med 2005;**5**:19–22

Background

The average prescription for elderly patients who are taking five or more medicines is likely to have some potential for drug interactions. It is not always clear from the computerised programmes widely adopted by pharmacists, which do not grade interactions according to their clinical importance, whether this is of sufficient import to justify an alteration in drug choice, a modification of dosage or initiation of special surveillance. On the other hand, when harm arises, judicial review in this area continues to ascribe the major responsibility to the prescriber rather than to the dispenser. The British National Formulary Appendix 1[1] highlights reactions that may be of clinical relevance, but even this source lists interactions that may not be of sufficient importance to modify drug choice.

Clinical relevance

In a recently published prospective study of 18,820 patients admitted to hospital, the prevalence of adverse drug reactions was 6.5%, with the reaction leading directly to admission in some 80% of cases.[2] Low-dose aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and warfarin headed the list of culprits. Of these adverse reactions, one in six was due to a drug–drug interaction. Common examples are shown in Table 1.

Interference of one drug by another can lead to a spectrum of responses, from an enhanced effect which may be toxic but is sometimes beneficial, to a reduced effect that results in lack of efficacy. In some cases, the onset may be subtle, for example, reduced plasma levels of ciclosporin or protease inhibitors. The ultimate consequences, rejection of a transplanted organ or reactivation of HIV infection, are not immediate. There are no early warning signs and only in certain settings will the 'all or none' consequences occur. The persistent induction of liver drug metabolising enzymes by, say, anti-epileptics, may come to light only in a non-therapeutic setting such as paracetamol overdose with an increased likelihood of hepatotoxicity. The potential for interaction extends beyond prescription medicines

Key Points

- **Drug interactions should be anticipated**
- **The British National Formulary and pharmacy computer programmes should be used for reference**
- **Clinical problems arise with (i) risky drugs (warfarin, non-steroidal anti-inflammatory drugs, digoxin) and (ii) risky patients (elderly, those with renal insufficiency)**
- **The mechanisms most commonly involved are hepatic: cytochrome P450 induction/inhibition**
- **The P-glycoprotein transporter system is now implicated**
- **The final decision rests with the prescriber**

KEY WORDS: cytochrome P450, drug interaction, P-glycoprotein

Table 1. Examples of drug interactions commonly leading to hospital admission.

Drug combination	Adverse event
Warfarin and aspirin	GI haemorrhage
NSAIDs and aspirin	GI adverse effects
Warfarin and interacting drugs	Bleeding
Diuretic combinations	Renal failure
Diuretics and ACEIs	Renal failure
Digoxin and interacting drugs	Digoxin toxicity

ACEI = angiotensin-converting enzyme inhibitor; GI = gastrointestinal; NSAID = non-steroidal anti-inflammatory drug.

Table 2. Classification of interactions by severity.

Severity	Sequelae
Major	Life-threatening or involving permanent damage
Moderate	Requiring additional treatment
Minor	Unnoticeable or not sufficient to affect the therapeutic outcome

into what are, for many prescribers, unfamiliar fields – up to one-third of the population frequently take alternative therapies. Herbal medicines and food substances, including alcohol, can also result in interactions.

Classification of drug interactions

Interactions are best considered in terms of drug kinetics and dynamics. Most of the commonly encountered interactions are kinetic in nature, resulting in increased or decreased exposure to one or other drug. The outcome will depend on the steepness of the dose–response curve for the agent and the relation between drug concentration and effect. Interactions can also be classified on the basis of their significance (Table 2).

Kinetic interactions

Most interactions can be attributed to impaired drug elimination, particularly through interference with hepatic metabolism, transcellular transport or renal excretion.

Hepatic metabolism

Drug interactions that affect hepatic metabolism can be predicted from an understanding of the function of specific microsomal isoenzymes of cytochrome P450 (CYP). These enzymes, of which CYP3A4 is by far the most abundant, are subject to:

- relatively specific *induction* by other drugs, increasing the amount of the enzyme, therefore reducing the plasma concentration of the induced drug, or
- *inhibition*, where the plasma concentration of the inhibited drug rises.

Examples are shown in Table 3.

Most interactions resulting from inhibition of metabolism occur relatively early after taking the combination of drugs, reaching their maximum effect after an interval determined by the elimination half-life of the affected drug. It takes 4-5 half-lives to reach a new steady-state plasma concentration. Clearly, the threshold concentration for the individual drug's toxicity will be important in determining the clinical manifestations and the time of their onset. Drugs with a low therapeutic index, such as oral anticoagulants, anti-epileptics and aminoglycosides, are examples of at-risk drugs. Patients with already impaired excretory or homeostatic processes, for example due to a diminished reserve capacity, as seen in the elderly or in patients with liver failure, represent at-risk patients.

An important inhibition interaction is an example of a food-induced drug interaction. This involves grapefruit juice and drugs that are substrates for the CYP3A4 enzyme system. The extent to which this inhibition interaction occurs varies from batch to batch of grapefruit juice and is not usually seen with freshly squeezed fruits, emphasising the unpredictable nature of some interactions and the need for vigilance.

The effects of inhibition are usually short-lived once the inhibitor is withdrawn. However, where there is irreversible binding of an enzyme system, for example by monoamine oxidase inhibitors (MAOIs), it may take several weeks for the effect to dissipate and for the formation of new enzymes. Induction, by contrast, requires new enzyme formation, so the onset of effect is usually more gradual and may not be maximal for 1–2 weeks; similarly, when the inducer is withdrawn, the effect of enzyme induction can take a week or more to dissipate.

Mutual induction or inhibition can also occur. For example, the dosage of anti-epileptic drugs used in combination may require adjustment because of mutual induction. Another example is the combination of lamivudine and zalcitabine where competition for activation by the same enzyme leads to therapeutic failure in HIV infection because insufficient amounts of active metabolite are formed. In general, the consequence of a drug interaction that involves metabolism depends on the dosage of inducing or inhibiting agent. Examples of common substrates with their relatively specific inducers and inhibitors are shown in Table 3.

Transcellular transport

Drug interactions also affect the function of P-glycoprotein, the recently discovered xenobiotic transporter system involved in drug absorption from the gastrointestinal (GI) tract, transport within the liver and elimination by the kidney as well as within the brain or target tissues. The complexity of this system is

Table 3. Examples of substrates of different CYP isoenzymes, with inducers and inhibitors of their metabolism. Some have multiple pathways and 2C9 and 2D6 exhibit genetic polymorphism.

Substrates	Inducers	Inhibitors
CYP1A2		
theophylline	carbamazepine, phenytoin, rifampicin	cimetidine, ciprofloxacin, erythromycin
CYP2C9		
aspirin and most NSAIDs, diazepam, (S)-warfarin	carbamazepine, phenobarbital, phenytoin, rifampicin	amiodarone, fluvoxamine (other SSRIs weak) metronidazole, omeprazole, ritonavir, tolbutamide
CYP2D6		
β-blockers (several), codeine, encainide, flecainide, phenothiazine, propafenone, tricyclic antidepressants		amiodarone, chlorphenamine, encainide, fluoxetine, haloperidol, ketoconazole, nefazodone, paroxetine, phenothiazines, quinidine, ritonavir, sertraline, TCAs, venlafaxine
CYP3A4		
atorvastatin, cerivastatin, calcium channel blockers, felodipine, simvastatin, verapamil, (R)-warfarin, OCs, cisapride, ciclosporin, midazolam, triazolam, sildenafil	barbiturates, carbamazepine, dexamethasone, ethosuximide, phenytoin, rifampicin, rifabutin	amiodarone, calcium channel blockers (especially diltiazem), clarithromycin, ciclosporin, danazol, erythromycin, fluconazole, fluvoxamine, fluoxetine, grapefruit juice, ketoconazole, itraconazole, indinavir, lansoprazole, metronidazole, nefazodone, nelfinavir, norfloxacin, omeprazole, propoxyphene, quinine, ritonavir, saquinavir, sertraline, tacrolimus, tamoxifen, TCAs, venlafaxine, zafirlukast

NSAID = non-steroidal anti-inflammatory drug; OC = oral contraceptive; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

becoming apparent, with the recognition that it, too, exhibits genetic polymorphism and is subject to induction and inhibition interactions just like the CYP drug metabolising enzyme system and involving a similar range of inducers and inhibitors. Table 4 lists some drugs that are substrates for P-glycoprotein.

Protein binding displacement

Drug interactions seldom occur solely because of protein binding displacement. Those interactions once ascribed to this mechanism, such as that between certain NSAIDs and warfarin, are in fact usually the result of either impaired metabolism or enhanced effect.

Renal excretion

Relatively few drugs undergo predominantly renal elimination. For those with a low therapeutic index, such as digoxin, lithium and aminoglycosides, an increase in plasma concentration is often associated with drug toxicity:

- NSAIDs compete with methotrexate for renal excretion and resultant toxicity has been fatal.
- Quinidine reduces the renal clearance of digoxin, but other mechanisms involving P-glycoprotein probably contribute to digoxin toxicity.
- NSAIDs (including cyclooxygenase 2 inhibitors), thiazides and loop diuretics, and to a certain extent angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists, reduce the renal excretion of lithium.
- Plasma lithium concentration should be monitored more often in this context.

In elderly patients, who have a diminished glomerular filtration rate, a relatively small reduction in renal elimination may result in a disproportionate level of drug toxicity.

Dynamic interactions

Dynamic interactions result from a combination of drugs with similar pharmacological effects which are likely to be additive. The most important example concerns drugs that affect bleeding or coagulation, such as NSAIDs, aspirin and anticoagulants. Elderly women, it seems, are at disproportionately high-risk of GI haemorrhage because of drug interactions. Other examples include drugs that act to depress the central nervous system or on the renal tubule to affect electrolyte and water reabsorption.

Table 4. P-glycoprotein substrates.

Cardiac drugs	digoxin, quinidine, losartan
Immunosuppressants	ciclosporin, tacrolimus
Calcium channel blocker metabolites	diltiazem, verapamil
Antihistamines	terfenadine, cimetidine
CNS drugs	ondansetron, morphine, phenytoin
Anticancer drugs	dactinomycin, etoposide, doxorubicin, vinblastine
Antibiotics	erythomycin, rifampicin
HIV protease inhibitors	indinavir, nelfinavir, ritonavir

CNS = central nervous system.

Although genetic polymorphisms at a receptor level are much less important than those affecting pharmacokinetics, they may explain increased or decreased responsiveness to drugs that act at dopamine D_3 receptors such as phenothiazines.

Certain drug interactions involve both kinetic and dynamic mechanisms. For example, the combination of macrolide antibiotics, such as erythromycin or clarithromycin, with phenothiazines, some atypical antipsychotics, or the histamine H_1 antagonist terfenadine, can result in QT prolongation, torsade de pointes and cardiac arrest. This results from inhibition of CYP3A4 enzymes as well as from a direct effect on cardiac conduction – a mixed kinetic and dynamic interaction with a lethal outcome.

Preventing drug interactions

The fact that most serious interactions are predictable suggests that a higher level of clinical suspicion and vigilance could prevent them. Plasma drug monitoring of at-risk drugs in at-risk patients may help to detect an increased concentration prior to toxicity or a low concentration prior to therapeutic failure. The concentrations of digoxin, lithium, aminoglycosides, anti-epileptics, ciclosporin, methotrexate and protease inhibitors can all be measured. Renal function and the effect of warfarin can also be monitored. An understanding of how drug interactions occur, based on a knowledge of pathways of drug elimination (eg hepatic enzymatic, P-glycoprotein transport or renal) will also highlight a risk of serious drug interactions and allow the effects of new drugs to be anticipated.

The use of simple measures such as patient information cards and the labelling of medicines with standard warnings can also be effective in reducing risk. For example, MAOIs and their potential to cause interactions with analgesics, psychoactive agents, sympathomimetics and food substances are now sufficiently well flagged that such interactions have become quite rare. Surveillance of coprescribing using computer programmes is expected to be further refined by using individualised patient data, including laboratory results, to produce more specific and graded warnings in the future. However, the final decision will continue to rest with the prescriber.[3-5]

Conflicts of interest

None.

References

1 British National Formulary 2004. Appendix 1.

2 Pirmohamed M, James S, Meakin S, Green C *et al.* Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 2004;**329**:15–9.

3 Bertz RJ, Granneman GR. Use of *in vitro* and *in vivo* data to estimate the likelihood of metabolic pharmacokinetic interactions. Review. *Clin Pharmacokinet* 1997;**32**: 210–58.

4 Stockley I. *Drug interactions*, 6th edn. London: Pharmaceutical Press, 2002.

5 Hansten P, Horn J (eds). *Managing clinically important drug interactions*, 2nd edn. Philadelphia: Lippincott, Williams and Wilkins, 2004.

IMPORTANT ERRATA

Tunbridge A, Read RC. Management of meningitis. *Clin Med* 2004;**6**:499–504.

1. An **important amendment to Table 6** in the above paper follows:

   Row 1, column 6: The duration of empiric treatment of bacterial meningitis for neonates and infants less than 3 months old should be at least two weeks, and **at least three weeks for Gram-negative bacteria**.

2. In Table 3 in the above paper, columns 4 and 5 erroneously showed numbers instead of arrows. The correct version of the Table is shown below.

Table 3. Cerebrospinal fluid analysis.

Cause	Predominant leukocytes	WCC number /μmol	Glucose (cf serum glucose)	Protein
Normal	Lymphocytes	<5	~2/3	<400 g/dl
Bacterial	Polymorphonucleocytes*	50–5,000	↓↓	↑↑
Viral	Lymphocytes	10–200	→	↑
Tuberculous	Lymphocytes	50–500+	↓	↑↑
Fungal	Lymphocytes	10–200	↓/→	↑
Protozoa	Polymorphonucleocytes	400–26,000	↓/→	↑
Treponemal	Lymphocytes	10–200	↓	↑

* Lymphocytic picture predominates in meningitis due to *Listeria monocytogenes*.
WCC = white cell count.