Other factors

Interactions tend to be much more prevalent in older people (who may receive multiple medications for multiple diseases) and in those with liver and/or kidney disease. Genetic factors and/or frailty may explain why some individuals are more susceptible to the adverse consequences of a particular combination of medicines. At this time it is not possible to predict which patients are more susceptible to pharmacokinetic interactions. However, if there is evidence that the dosage in a particular person may already be too high (e.g. from therapeutic monitoring data or signs of adverse events) or too low (e.g. from breakthrough bleeding in a woman taking the contraceptive pill) special care would obviously need to be taken.

Examples of clinically important drug interactions

The following examples illustrate the diverse mechanisms by which medicines can interact. Also included is a discussion of the possible strategies that might be employed by a pharmacist when faced with such an interaction.

Example 1: medicines that inhibit warfarin metabolism

This is an example of a clinically significant interaction arising from inhibition of metabolism. Warfarin has a narrow therapeutic index and relies almost exclusively on metabolism for its elimination from the body. Moreover, the metabolism of warfarin is susceptible to inhibition. A number of agents (including ketoconazole, metronidazole, amiodarone, oral miconazole[1–3] and cimetidine), have been found to inhibit the metabolism of warfarin and lead to the risk of excessive bleeding.

When faced with a prescription for one of these medicines in a patient stabilised on warfarin, the first course of action would be to consider the use of a similar medicine that does not interact (e.g. use ranitidine instead of cimetidine). Another option would be to decrease the dose of warfarin and closely monitor the patient's clotting status (INR). Either way, the prescriber should be consulted so that appropriate action can be discussed in an informed manner. Whether or not a dose reduction is implemented, the patient should be counselled to be especially aware of the signs of abnormal bleeding and what action to take if this occurs. Warfarin has a half-life of about one day so a new steady-state plasma level should be achieved within a few days. The effect on INR is dependent on the half-lives of the clotting factors and lags behind the effect on warfarin plasma levels.

Example 2: medicines that reduce the effectiveness of oral contraceptives

Oral contraceptives are relatively safe, but the consequences of even a transient reduction in efficacy (i.e. a pregnancy) are significant. This is in contrast with many other medicines, where a reduction in efficacy is usually short-lived and easily remedied. Pharmacists need to be particularly diligent in providing appropriate counselling when dispensing a medicine that can alter the pharmacokinetics of oral contraceptives.

Anti-epileptic agents, St John's wort and rifampicin induce metabolism of oestrogens, reducing their effectiveness as oral contraceptives. In patients taking 'enzyme inducers', a high-dose contraceptive pill or an alternative form of contraception could be considered. Broad-spectrum antibiotics are believed to interfere with the enterohepatic recycling of oestrogens and may decrease their effectiveness in a small percentage of women. The timing and duration of the course of antibiotics is important. Often it is not possible to identify women at risk of oral contraceptive ineffectiveness. However, women who have in the past experienced signs of contraceptive ineffectiveness may be especially vulnerable to the effects of oral antibiotics.

Example 3: theophylline, caffeine and smoking

This is an example of how ceasing a substance that is a drug-metabolising enzyme inducer can lead to potential toxicity. Smoking tobacco is known to accelerate the metabolism of caffeine and related medicines such as theophylline. Studies have found that cessation of smoking can be associated with a threefold increase in the plasma concentration of caffeine despite no change in caffeine consumption. It has been suggested that these increased caffeine levels may contribute to the perceived symptoms of tobacco withdrawal syndrome, including headache and agitation. When counselling a patient who plans to stop smoking, it is good advice to suggest that they also reduce their caffeine intake.

Example 4: NSAIDs, COX-2 inhibitors, ACE-inhibitors, angiotensin II receptor antagonists

These classes of medicines can influence renal haemodynamics via different mechanisms. Post-marketing surveillance has linked the combinations to serious deterioration in renal function. The interaction is more likely in patients with under-perfused kidneys (e.g. congestive cardiac failure) or with pre-existing renal disease (including age-related renal decline). Therefore, renal function should be checked before a NSAID or a COX-2 inhibitor is started in patients taking