tubules. There are separate systems for weak acids and weak bases. Competition between two weak acids (e.g. probenecid and penicillin, NSAIDs and high-dose methotrexate) can lead to an increase in the plasma concentration of the affected medicine (penicillin and methotrexate, respectively).

Medicines that are relatively non-polar may undergo passive tubular reabsorption, whereby the medicine passes from tubular urine back into blood. Thus, for a given rate of administration, the plasma concentration will increase if reabsorption is enhanced, and vice versa. The reabsorption of relatively non-polar weak acids and bases (e.g. salicylates and amphetamines) can be altered by changes in urinary pH. For example, an increase in urinary pH tends to favour tubular reabsorption of amphetamine, nicotine and morphine derivatives (because a greater proportion of the drug will be in the un-ionised, and therefore diffusible, form), which can lead to an increase in the plasma concentrations. The clinical significance of this mechanism is small because although many drugs are weak acids or bases almost all are largely metabolised in the liver to inactive compounds and few are excreted unchanged in the urine. In cases of overdose, urinary alkalinisation has been used to increase the excretion of drugs such as phenobarbitone and salicylates.[1]

Drugs that influence renal haemodynamics can also affect the excretion of renally cleared medicines by decreasing filtration rate. See 'Acute renal failure associated with commonly used medicines' in 'Dosing in renal impairment', Section D.

Factors determining the clinical importance of a pharmacokinetic interaction

In making a judgment about whether a reported pharmacokinetic interaction is likely to be important in a particular setting, several factors need to be taken into consideration.

Therapeutic index and steepness of the dose–response curve

Subtle changes in the plasma concentration of a medicine will normally be of little consequence if the affected medicine has a wide therapeutic index (e.g. most oral antibiotics, diuretics, beta-blockers, NSAIDs). However, an interaction will be more important if a relatively small change in the plasma concentration is associated with a substantial change in therapeutic or toxic response—that is, if the medicine has a narrow therapeutic index or a steep dose–response curve (e.g. digoxin, lithium, warfarin, theophylline, phenytoin, aminoglycosides). As a general rule, a narrow therapeutic index medicine is one for which some form of patient monitoring is used to guide therapy. This may include therapeutic drug monitoring (see 'Optimal medicine concentration ranges', Section D). Pharmacists should be alert whenever another medicine is added to (or removed from) the regimen of patients taking a narrow therapeutic index medicine.

As noted, interactions are also important if the affected medicine has a steep dose–response curve. In practical terms, these are medicines that do not elicit a graded response: either they elicit the desired effect or they do not. For example, combination oral contraceptives work in part by blocking ovulation. If they do not achieve this effect then the therapeutic objective has not been met. The critical issue for such a medicine is that a reduction in blood levels due to an interaction may render it completely ineffective.

The magnitude of the change in plasma concentration

If the magnitude of the change in the plasma concentration of medicine is small relative to the changes normally observed within an individual, the consequences of the interaction will probably be negligible. For example, a 20% reduction in the rate of absorption will not in itself be of significance if there is normally a twofold variation in the absorption rate. Similarly, if there is normally a twofold to threefold variation in the plasma concentrations among different individuals, anything leading to a 20% reduction in clearance would not normally be expected to be clinically important. In contrast, for a narrow therapeutic index agent, such as digoxin, for which dosages are normally individualised, any interaction leading to a 20% reduction in clearance may be enough to precipitate toxicity.

Temporal considerations

The consequences of a pharmacokinetic interaction between two medicines may depend on the sequence in which they are commenced and/or ceased. For example, if an enzyme inhibitor is commenced in a patient stabilised on phenytoin for epilepsy, the plasma concentration of phenytoin is likely to increase and this may lead to phenytoin toxicity. However, if a medicine that inhibits the metabolism of phenytoin is withdrawn from the dosage regimen of a patient already stabilised on phenytoin, the outcome may be a reduction in plasma phenytoin levels and an associated loss of seizure control. Therefore, the impact of an interaction should be considered not only when a new medicine is started but whenever a patient's regimen is altered.