Antagonistic or opposing interactions. One medicine may counteract or oppose the desirable actions of another. Examples are[1–3]:

- Vitamin K opposes the anticoagulant activity of warfarin.
- Oral hypoglycaemics and glucocorticoids have opposing effects on blood glucose levels.
- Caffeine antagonises the sedative effects of benzodizepines.
- Beta-blockers with beta-receptor agonists.
- Metoclopramide with dopaminergic agents in Parkinson's disease.

Interactions due to disturbances in fluid and electrolyte balance. Examples are[1–3] :

- Diuretics causing potassium loss sensitise the myocardium to the effects of digoxin.
- ACE inhibitors plus potassium supplements or potassium-sparing diuretics (e.g. spironolactone) may lead to hyperkalaemia.
- NSAID-induced fluid retention may oppose the desirable actions of antihypertensive, diuretic or heart failure drugs.
- Lithium carbonate with thiazide diuretics may increase serum lithium levels and increase the risk of lithium toxicity.

Drug or neurotransmitter uptake interactions. Some drugs that act on adrenergic neurons can be prevented from reaching the sites of action by the presence of other drugs. Examples are[1,3]:

- Non-selective beta-blockers (e.g. propranolol) may antagonise the effects of beta-agonist bronchodilators (e.g. salbutamol).
- Drugs with alpha2-adrenergic receptor blocking properties (e.g. phentolamine) may abolish the alpha2-adrenergic receptor mediated effects of clonidine.

Pharmacokinetic interactions

Pharmacokinetic interactions occur when one drug alters the absorption, distribution, metabolism or excretion of another, thus modifying the concentration of the drug at the effector-site. In assessing the potential importance of a pharmacokinetic interaction, several factors need to be considered:

- Only a small percentage of theoretical pharmacokinetic interactions actually lead to adverse outcomes.
- Clinically important interactions are more likely to be encountered when the affected medicine has a narrow therapeutic index or a steep dose–response curve.
- Only a relatively small number of medicines consistently inhibit or induce hepatic metabolism to a significant extent.
- Any medicine that has the potential to adversely affect kidney function may influence the pharmacokinetics of other medicines that are renally excreted.
- Adverse outcomes from interactions are more likely in older patients, in those with liver or kidney dysfunction and in those who are taking a large number of medicines.

Although thousands of pharmacokinetic interactions have been reported in the literature, most are of doubtful clinical importance. Moreover, those that are important tend to involve a relatively small number of medicines.

By considering the mechanisms by which one medicine may influence the pharmacokinetics of another, rational thinking can be applied to such issues as the likelihood of a pharmacokinetic interaction, the potential significance of such an interaction and how a potential interaction can be avoided.

Absorption

One medicine may alter the absorption of another via a number of mechanisms:

- *Modification of gastric pH.* Gastric pH is increased by antacids and antisecretory agents (PPIs, H2-receptor blockers). This may lead to an increase in the solubility (in gastric contents) of a poorly soluble weak acid, a decrease in the solubility of a weak base, an increase in the stability of an acid-labile drug, and an enhanced release of drug from enteric-coated formulations. Each of these effects can modify the onset, rate and/or extent of absorption. However, the absorptive surface area of the small intestine is sufficiently large that most drugs will be well absorbed even if gastric pH conditions are not ideal. Ketoconazole is an example of a medicine that is less soluble in alkaline conditions and for which the rate and extent of absorption are decreased substantially when gastric pH is elevated.
- *Complexation and adsorption*. Compounds that can form poorly soluble complexes with medicines include metal ions (such as those present in antacids, ferrous sulfate, sucralfate and dairy products), ion exchange resins (cholestyramine) and non-digested substances (such as kaolin, pectin and dietary fibre). Medicines that are susceptible to these interactions include tetracyclines, fluoroquinolones, some anticonvulsants, thyroxine, warfarin and digoxin. Complexation and adsorption interactions can normally be avoided by careful planning of dosage