Drug interactions and drug metabolism

Drug interactions

Drug interactions are a common cause of adverse drug events. There are too many to list, but the principles behind drug interactions and some examples follow.

Pharmacokinetic

- Drugs can interact outside the body before administration. For example, when morphine and cyclizine solutions are mixed in patient-controlled analgesia infusion devices, cyclizine can precipitate as crystals.
- The absorption of drugs in the intestine is altered by drugs that influence gastric emptying, for example opioids that slow emptying or metoclopramide that promotes it.
- Distribution of drugs can be altered if they are displaced from protein-binding sites by other compounds. Warfarin is liberated from serum albumin by aspirin.
- Metabolism of drugs by the liver can be altered by drugs that induce or inhibit hepatic cytochrome P450 enzymes.
- Elimination of some drugs from the kidneys can be altered by others, for example probenecid decreases the excretion of penicillin.

Pharmacodynamic

Different classes of drugs may act by different mechanisms but have the same physiological effect. For example, beta-blockers, ACE inhibitors and nitrates can all reduce systemic blood pressure. The additive effect of each drug can be summative (net effect equals the sum of the individual drug effects), or there may be synergism (net effect exceeds sum of individual drug effects) or potentiation (one drug increases the effect of another).

Alternatively, drugs may antagonise each other. Interactions may also be indirect, for example the hypokalaemia induced by diuretics, increasing the risk of digoxin toxicity.

Drug metabolism

Enzymes metabolise drugs to make them more water-soluble and allow them to be eliminated from the body. The first phase is biotransformation, which occurs by the processes of oxidation, hydroxylation, reduction and/or hydrolysis. In the second phase, a new functional group may be conjugated to the drug.

Cytochrome P450 (CYP) enzymes

CYP isoenzymes are responsible for the oxidative metabolism of many drugs. They are located mainly in hepatocytes, but are also present to a lesser extent in the small intestine, kidney, lung and brain. There are many CYP isoenzymes. Six CYP isoenzymes are responsible for the vast majority of drug oxidation: 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4. Patients may have different levels of expression of certain isoenzymes, for example 5–10% of Caucasians express low levels of CYP2D6, so are more likely to develop adverse effects or toxicity from high levels of unmetabolised drugs.

Certain drugs may induce or inhibit one or more isoforms, altering the metabolism of other
drugs. Phenytoin, for example, induces CYP3A4 and increases the metabolism of digoxin, thyroxine and tricyclic antidepressants. On the other hand, fluoxetine and paroxetine inhibit CYP2D6, and as a result the plasma levels or tricyclics may become toxic. There are very many other examples, and detailed tables are available online: P450 Drug interaction table

Drugs taken orally are absorbed into the hepatic portal vein through the small intestine, where CYP enzymes begin to metabolise them before the drug has entered the systemic circulation – a phenomenon known as “first pass metabolism”. Some drugs, for example morphine, are subject to extensive first pass metabolism so their oral bioavailability is much less than their parenteral bioavailability.