Clinically important drug interactions

Medication interaction and medication-food interaction can have a significant negative impact on the quality use of medicines.

There is a clear need for pharmacists to keep up to date with their knowledge of interactions. Pharmacists should also be able to make informed recommendations on how to proceed when a patient has been prescribed two or more medicines that are known to interact.

The importance of interactions in terms of incidence, clinical significance and cost to society is difficult to assess. What is known is that in the majority of cases where an interaction leads to hospitalisation, generally the interaction could have easily been avoided with appropriate management and early intervention. Pharmacists must therefore be capable of identifying which interactions are likely to be clinically important in a particular setting. In recent years there has been an exponential growth in the number of published 'potential' interactions, and there is a danger that the relatively small number of well-established and clinically significant interactions can become buried within exhaustive interaction tables.

There is significant inter-patient variability in response to drug interactions. An interaction might manifest clinically with adverse outcomes in one patient and have no consequences in another. In general, the elderly will be more susceptible to the effects of drug interactions, as their homeostatic reflexes are less able to respond to additive pharmacological effects and they have reduced renal function.

This section provides background information that should enable pharmacists to place published information about interactions in a clinical context. It is not intended to provide an exhaustive list of possible interactions. Furthermore, the section does not specifically cover herb–drug interactions (see 'Complementary medicines monographs', Section C).

Just as interactions can lead to an increased pharmacological effect, and therefore risk of toxicity, they can also result in a reduction in pharmacological effect, leading to a possible sub-therapeutic outcome. In both cases the interaction may never come to the attention of the health care team if no medication review is conducted. Thus, an assessment of the concomitant use of interacting medicines is a vital component of the medication review, as are the ensuing recommendations on how the interaction can be avoided (e.g. change in medication) or on how the potential clinical impact of the interaction can be minimised (e.g. dose change, change in timing of doses).

It is important to note that drug interactions can also be clinically beneficial and intended (e.g. combining antihypertensive drugs, the use of diltiazem in combination with cyclosporin to reduce the dosage and cost of the latter, and the treatment of benzodiazepine overdoses with flumazenil).

What follows is a discussion of the mechanisms of potential medicine interactions. Understanding the mechanism of an interaction provides an insight into the interaction management and potential clinical significance. Interactions are generally classified as being pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions

Pharmacodynamic interactions are those in which the clinical effects of one medicine, given a particular effector-site concentration, are modified by co-administration of another. Undesirable pharmacodynamic interactions, which can often be predicted if the pharmacological properties and mechanisms of action of the individual medicines are understood, include the following.

Additive or synergistic interactions. If the observed effect is **equal** to the sum of the two medicines' individual effects the interaction is **additive**; if the combined effect is **greater** than the sum of the individual effects it is **synergistic**. Synergistic interactions have the potential to be more harmful than additive interactions. Examples of interactions leading to additive or synergistic toxicity are[1-3]:

- Alcohol with central nervous system depressants—increased central nervous system depression.
- Verapamil with beta-blockers—additive cardiodepressant effects.
- Anticholinergics with tricyclic antidepressants or some antipsychotics—increased anticholinergic effects.
- Nonsteroidal anti-inflammatory drugs with angiotensin-converting enzyme inhibitors—increased risk of renal impairment and hyperkalaemia.
- NSAIDs with anticoagulants—increased risk of bleeding.
- Methotrexate with co-trimoxazole—additive antifolate activity and increased toxicity.
- Tramadol with selective serotonin reuptake inhibitors—increased risk of serotonin syndrome.