Drug interactions: principles and practice

SUMMARY

Drug interactions are an avoidable cause of patient harm. Harm may occur due to either increased drug effect causing toxicity or decreased drug effect leading to therapeutic failure.

Drug interactions should be considered both in the differential diagnosis of symptoms (for interactions that have already occurred) and when prescription changes are made (for potential interactions).

Software checkers for drug interactions are widely available, but have limited clinical utility.

Patient harm from drug interactions can be reduced by:

- using a personal formulary – using few drugs and knowing them well

- recognising drugs that are major perpetrators of interactions

- recognising narrow therapeutic index drugs as vulnerable to interactions

- applying clinical pharmacology principles.

Introduction

A drug interaction occurs when a patient's response to a drug is modified by food, nutritional supplements, formulation excipients, environmental factors, other drugs or disease. Interactions between drugs (drug–drug interactions) may be beneficial or harmful. Harmful drug–drug interactions are important as they cause 10–20% of the adverse drug reactions requiring hospitalisation and they can be avoided.[1] Elderly patients are especially vulnerable – with a strong relationship between increasing age, the number of drugs prescribed and the frequency of potential drug–drug interactions.[2] Knowing how drug–drug interactions occur and how to manage them is an important part of clinical practice.

Types of drug–drug interactions

Interactions between drugs may be categorised by the underlying mechanism (see Box):

- *Behavioural* drug–drug interactions occur when one drug alters the patient's behaviour to modify compliance with another drug. For example, a depressed patient taking an antidepressant may become more compliant with medication as symptoms improve.[3]

- *Pharmaceutic* drug–drug interactions occur when the formulation of one drug is altered by another before it is administered. For example, precipitation of sodium thiopentone and vecuronium within an intravenous giving set.

- *Pharmacokinetic* drug–drug interactions occur when one drug changes the systemic concentration of another drug, altering 'how much' and for 'how long' it is present at the site of action.

- *Pharmacodynamic* drug–drug interactions occur when interacting drugs have either additive effects, in which case the overall effect is increased, or opposing effects, in which case the overall effect is decreased or even 'cancelled out'.

Pharmacokinetic drug–drug interactions

Pharmacokinetics is 'what the body does to the drug'. These interactions occur when one drug (the perpetrator) alters the concentration of another drug (the object) with clinical consequences.

Altered bioavailability

This occurs when the amount of the object drug reaching the systemic circulation is affected by a perpetrator drug. For orally administered drugs this occurs when absorption or first-pass metabolism is altered. Drugs with low oral bioavailability are often affected while those with high bioavailability are seldom affected. For example, alendronate and dabigatran have low oral bioavailability. Alendronate co-administration with calcium decreases

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Box **Mechanisms of drug interactions**

Behavioural: altered compliance

Pharmaceutic: outside the body

Pharmacokinetic: altered concentration

    Bioavailability: absorption or first-pass metabolism
    Clearance: metabolism or excretion of active drug
    Distribution: cell membrane transport to the site of action

Pharmacodynamic: altered effect

    Mechanism: molecular signal (e.g. receptor)
    Mode: physiological effect

Pharmacokinetic drug–drug interactions can be managed by recognising drugs with a narrow therapeutic index and the major perpetrators of altered drug metabolism. Any change in prescription should take particular note of these two groups of drugs.

bioavailability and can result in no alendronate being absorbed. Conversely, dabigatran co-administration with verapamil increases bioavailability and can result in an increased risk of bleeding.

Altered clearance

This occurs when the metabolism or excretion of the object drug is affected by a perpetrator drug. Object drugs with a narrow therapeutic index (see Table 1) are particularly vulnerable, as modest changes in concentration may be clinically important. Perpetrator drugs known to strongly affect drug metabolism (Table 2) are more likely to cause large concentration changes and hence clinical consequences.[4] Recognising these potential perpetrators of pharmacokinetic drug–drug interactions is important.

Metabolism

Changes in drug metabolism are the most important causes of unexpected drug interactions. These occur by changing drug clearance or oral bioavailability. There are several enzyme families involved in drug metabolism, and the cytochrome P450 (CYP) enzyme family is the most important (Table 2).

Inhibition of a cytochrome P450 enzyme increases the concentration of some drugs by decreasing their metabolism. For example, clarithromycin is a strong inhibitor of CYP3A-catalysed simvastatin metabolism, thus increasing the risk of myopathy.[5] Drug inhibition of cytochrome P450 enzymes is also used therapeutically. For example, ritonavir, a strong inhibitor of CYP3A, reduces metabolism of other protease inhibitors thus increasing their effectiveness in treating HIV (so called 'ritonavir-boosted' regimens).[6]

Induction of a cytochrome P450 enzyme decreases the concentration of some drugs by increasing their metabolism. For example, carbamazepine is a strong inducer of CYP3A that increases the metabolism of the combined oral contraceptive, thus increasing the risk of unwanted pregnancy.[7]

Prodrugs

Some drugs rely on cytochrome P450 enzymes for conversion to their active form. As this is usually dependent on a single enzyme pathway, prodrugs are particularly vulnerable to changes in metabolism. Inhibition of conversion from prodrug to active drug may lead to inadequate concentrations of the active drug and therapeutic failure. For example, tamoxifen is metabolised by CYP2D6 to its active form endoxifen, and concomitant therapy with the strong CYP2D6 inhibitor paroxetine has been associated with increased mortality in breast cancer.[8]

Excretion

Some drugs are excreted from the body unchanged in the active form, usually in the urine or via the biliary tract in the faeces. Changes in renal drug clearance may occur due to effects on renal tubular function or urine pH. For example, probenecid reduces the renal clearance of anionic drugs such as methotrexate and penicillin.

Altered distribution

This occurs when the concentration of drug at the site of action is changed without necessarily altering its circulating concentration. This is particularly an issue for drugs with intracellular or central nervous system targets. Some drugs cause significant changes in the cell membrane transport of other drugs. For example, verapamil inhibits efflux transporters (e.g. P-glycoprotein) increasing the concentrations of substrates such as digoxin and cyclosporin. Probenecid inhibits anion transporters (e.g. OAT-1) increasing the concentrations of substrates such as methotrexate and penicillins. Drug interactions involving transport are less well understood than drug interactions involving metabolism.

Pharmacodynamic drug–drug interactions

Pharmacodynamics is 'what the drug does to the body'. These interactions occur between drugs with additive or opposing effects. The brain is the organ most commonly compromised by pharmacodynamic interactions.

Pharmacodynamic interactions between drugs with additive effects may be intentional, for example when combining antihypertensives, or unintentional, for example serotonin syndrome caused by adding tramadol to a selective serotonin reuptake inhibitor (SSRI). Conversely, combining drugs with opposing effects can result in loss of drug effect, for example reduced bronchodilation by a beta$_2$ agonist prescribed with a non-selective beta blocker.[9]

Table 1   **Examples of drug classes containing several narrow therapeutic index (object) drugs**

Drug class	Example
Antiarrhythmics	amiodarone
Anticoagulants	warfarin
Antiepileptics	phenytoin
Antineoplastics	sunitinib
Aminoglycoside antibiotics	gentamicin
Immunosuppressants	tacrolimus

The therapeutic index is often easier to recognise than define, as the vulnerability of the patient affects the dose–response relationship. A clinical question which is useful to identify a narrow therapeutic index drug is: would doubling or halving the dose of this drug have a major effect on this patient?

Considering drug effects by organ is a useful way to recognise pharmacodynamic interactions. Ask yourself – might any of these drugs affect the same organ (for example the brain)? This approach allows you to consider interactions between drugs with different modes of action, for example an anticholinergic and a benzodiazepine.[10]

How to avoid unwanted drug–drug interactions in clinical practice

Ensure you have a full drug history including over-the-counter and herbal products. Pharmacodynamic drug–drug interactions can be anticipated based on knowledge of the clinical effects of the drugs involved. The better your pharmacological knowledge, the easier it is! Prescribe few drugs and know them well.

Pharmacokinetic drug–drug interactions are more difficult to anticipate since they are not predictable from the clinical effects of the drugs involved. Recognition of drugs that have a narrow therapeutic index (Table 1) and the major perpetrators of pharmacokinetic interactions (Table 2) will help identify most of these.

We use five 'rules' to manage potential drug–drug interactions in clinical practice:

1. Any *interactions* between existing drugs in a given patient have already occurred. Hence they are part of differential diagnosis.

2. Knowledge of the pharmacological effects of drugs and of patient physiology together allows recognition of potential pharmacodynamic drug–drug interactions.

3. Drugs with a narrow therapeutic index are particularly susceptible to pharmacokinetic drug–drug interactions (Table 1).

4. A small number of drugs are important 'perpetrators' of pharmacokinetic drug–drug interactions (Table 2).

5. Starting or stopping a drug is a prescribing decision that may cause a drug interaction.

Monitoring patients for drug toxicity or loss of efficacy is part of routine care. Checking for changes in symptoms, biomarkers of effect, or drug concentrations soon after prescription changes helps identify drug interactions early and can reduce harm.

Clinical resources for drug–drug interactions

A number of resources are available to help clinicians with drug–drug interactions:

- individual drug monographs in formularies, such as the Australian Medicines Handbook, are a useful starting point for learning about new drugs

- tables listing the major perpetrators of pharmacokinetic drug–drug interactions are available in the Australian Medicines Handbook or online (www.pkis.org)

- prescribing and dispensing software mostly generates alerts from tables of information about drug pairs. The time involved and the amount of irrelevant information retrieved may cause 'alert fatigue' and limit their clinical utility.[11]

- drug information services have access to reference information such as Stockley's Drug Interactions and Micromedex.

Conclusion

Most potential drug interactions can be recognised by applying principles of clinical pharmacology and good clinical care. Increased vigilance by clinicians at the time of changing drugs improves the chance of identifying unwanted drug interactions before they

Prescribe few drugs and know them well

Pharmacodynamic drug–drug interactions can be managed based on anticipating known drug effects and monitoring the patient for those effects. They are often intentional. Unintentional harmful interactions are particularly common with multiple drugs acting on the central nervous system.

Table 2 **Important perpetrators of cytochrome P450 drug–drug interactions** [4]

Enzymes	Inhibitors*	Inducers
CYP1A2	**ciprofloxacin, fluvoxamine,** ethinyloestradiol, interferon alfa-2b	phenytoin, rifampicin
CYP2C9	fluconazole	carbamazepine, rifampicin
CYP2C19	**fluconazole, fluvoxamine, ticlopidine,** fluoxetine, clarithromycin, voriconazole, moclobemide	lopinavir/ritonavir, rifampicin, St John's wort
CYP2D6	**bupropion, fluoxetine, paroxetine, perhexiline,** cinacalcet, doxepin, duloxetine, flecainide, moclobemide, quinine, terbinafine	
CYP3A	**macrolides e.g. erythromycin, clarithromycin** **azole antifungals e.g. voriconazole, itraconazole, ketoconazole,** fluconazole, posaconazole **protease inhibitors e.g. indinavir, ritonavir, saquinavir,** atazanavir, fosamprenavir non-dihydropyridine calcium channel blockers e.g. diltiazem, verapamil **grapefruit juice**, aprepitant, cimetidine, ciprofloxacin, cyclosporin, fluvoxamine, imatinib	carbamazepine, modafinil, phenytoin, phenobarbitone, rifabutin, rifampicin, St John's wort

* bold font indicates very strong inhibitors

Q:

SELF-TEST QUESTIONS

True or false?

5. Drugs with high oral bioavailability are often affected by pharmacokinetic drug interactions.

6. Fluvoxamine is a strong inhibitor of cytochrome P450 2C19.

Answers on page 103

cause significant harm. Knowing a few drugs well and making judicious use of available information is more effective for managing drug interactions than relying solely on electronic decision support. ◄

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Drug interactions

Fatal rhabdomyolysis following voriconazole and simvastatin

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Case

An 85-year-old woman presented with an acute onset of generalised weakness and functional decline. The patient had a history of insulin-requiring diabetes, hypercholesterolaemia, hypertension, glaucoma and chronic kidney disease. She also had longstanding fungal keratitis (>60 days) which had been unsuccessfully treated with topical therapy.

The patient's chronic conditions were managed with multiple medications, including simvastatin 20 mg daily. She had started oral voriconazole, 200 mg twice a day, 32 days before her admission.

The patient was observed in hospital for a few weeks. She was examined by two ophthalmology senior house officers and an infectious diseases physician before a general physician made the diagnosis of rhabdomyolysis.

Blood tests showed a creatine kinase of 23 200 U/L (normal range 34–145), aspartate transaminase 1030 U/L (<31), alanine transaminase 393 U/L (<34) and creatinine 255 micromol/L (<110). Sodium,

potassium, prothrombin time and full blood count were normal.

The rhabdomyolysis was suspected to be the result of a drug interaction between simvastatin and voriconazole.[1] Both drugs were ceased on day 20 of the patient's admission and her blood tests improved. Unfortunately, the woman's clinical symptoms did not resolve and she died of respiratory failure secondary to respiratory muscle weakness 10 days after the concurrent therapy was stopped.

Comment

Simvastatin is a substrate of cytochrome P450 3A4[2] and voriconazole is a known inhibitor of this enzyme.[2] However, their interaction is not documented specifically in key reference sources such as the Australian Medicines Handbook or in the product information, although class interactions are detailed.[2] It is listed as an interaction in dispensing software.[3]

Throughout the admission, the patient's medication was reviewed by three different clinical pharmacists.