

DRUG INTERACTIONS

SUMMARY

- + A drug interaction occurs when the effect of one drug is altered by the presence of another drug, food, drink or environmental agent.
- + Risk factors for drug interaction occurrence include drugs with a narrow therapeutic index, patient age and genetic characteristics.
- + Information sources on drug interactions include the BNF, Stockley's Drug Interactions and the NMIC.

INTRODUCTION

A drug interaction is a pharmacological response which cannot be explained by the action of a single drug but may be due to two or more drugs acting simultaneously but The effects of a drug may also be changed by the presence of food, drink or by some environmental chemical agent. The outcome of a drug interaction may be harmful if the interaction results in increased efficacy or toxicity of one or more drugs. However, reduction in efficacy due to a drug interaction can sometimes be just as harmful.^{1,2} The clinical relevance of drug interactions is evident when one considers that up to 8% of hospital admissions are due to adverse drug reactions and over 20% of these are due to drug interactions.³ The incidence of drug interactions is difficult to quantify as this may depend on the "clinical significance" of the interaction.¹ However the greater the number of drugs taken inevitably increases the risk of a drug interaction occurring.¹

RISK FACTORS FOR DRUG INTERACTIONS

Several factors may increase the likelihood of a clinically significant drug interaction and include:

- a) **Drugs with a narrow therapeutic index** i.e where a small margin exists between therapeutic and toxic drug levels. (**Table 1**) For other drugs with a wide therapeutic index e.g penicillins and many benzodiazepines, a 20-50% change in concentration may not have clinical sequelae.

Table 1: Commonly Prescribed Drugs With a Narrow Therapeutic Index⁴

Drug	Initial Signs of Toxicity
Digoxin	Nausea, vomiting, loss of appetite
Lithium	Drowsiness, slurred speech, tremor, loss of appetite, nausea and vomiting, diarrhoea
Phenytoin	Unsteadiness, blurred vision, dizziness, drowsiness, stuttering, slurred speech
Theophylline	Nausea, loss of appetite, tremor - less severe effects don't always precede more serious effects e.g. tachycardia, seizures, ventricular arrhythmias

Warfarin	Bruising, bleeding
Tricyclic antidepressants	Fast, slow or irregular heartbeat

- b) High risk patients.** The patient characteristic which has the most bearing on drug interactions is age. Certain patient groups e.g. the elderly may have an increased risk of suffering a clinically significant drug interaction due to polypharmacy. It is estimated that for patients taking 2-5 drugs daily the incidence of a potential drug interaction is 19%. This rises to over 80% for those taking 6 or more drugs.⁵ Renal or in particular, hepatic impairment, either age-related or otherwise may affect the ability to metabolise drugs.^{4,6,7} Patients with severe underlying disease may be less tolerant of changes in plasma concentration of their therapy.⁴ The disease being treated and any concomitant diseases may also influence drug interactions as can the patients pre-existing clinical status.²
- c) Genetic characteristics** relating to approximately 10% of the population, may affect some drug interactions e.g. grapefruit juice and terfenadine resulting in an increased risk of cardiotoxicity. This appears only to be important in the small number of patients who are poor metabolisers of terfenadine.² This risk factor may also explain the propensity of warfarin and tricyclic antidepressants to cause problems.

CLASSIFICATION AND MECHANISM OF DRUG INTERACTIONS

Drug interactions may be classified by their mechanism and usually involve one of two processes namely pharmacodynamic or pharmacokinetic.⁴

Pharmacodynamic Interactions

Pharmacodynamic interactions occur when two drugs have either equal (additive) pharmacological effects e.g. alcohol and tricyclic antidepressants or opposing (antagonistic) pharmacological effects e.g. beta-blockers and beta-2-agonists. These interactions may also occur if electrolyte levels are altered e.g. diuretics and digoxin.^{2,4,6,8,9} Pharmacodynamic interactions may manifest without alterations in the serum concentration or pharmacokinetics of the interacting drugs. These interactions can often be predicted and monitored successfully by the clinician provided that they have knowledge of the drugs mechanism of action and pharmacological effects.

Pharmacokinetic Interactions

Pharmacokinetic drug interactions are the drug interactions most often reported in the literature. These drug interactions are more complicated and may not be as easily predicted. Many of them affect only a small proportion of patients taking a combination of drugs.^{4,9} Pharmacokinetic drug interactions occur when one drug alters the absorption, distribution, metabolism or excretion of another drug, this can either decrease or increase plasma concentration of the interacting drug(s). As a result therapeutic failure or enhancement or emergence of toxic effects may occur.^{2,6,7,8,9} Pharmacokinetic drug interactions which occur with one drug cannot be assumed to occur with drugs in the same class unless their pharmacokinetic properties are similar.⁹ Pharmacokinetic interactions may be of the following types:

- Absorption interactions e.g. binding interactions may result in a reduction in the rate and/or the extent of absorption e.g. formation of a complex between quinolone antibiotics and antacids or between tetracycline and sodium bicarbonate antacids.^{1,2,6} Delayed absorption is rarely of clinical significance unless high peak plasma concentrations are required e.g. in analgesia.⁹ Most of these interactions can be managed by separating the administration of the interacting drugs.
- Distribution interactions involve competition between two drugs for binding sites on plasma proteins or tissues. One or both may be displaced resulting in an increase in the concentration of free (active) drug. These interactions are uncommon and are likely to produce only a detectable increase in effect if the drug is extensively protein bound (more than 90%) e.g. warfarin and aspirin.^{2,8,9}
- Pharmacokinetic interactions through metabolic processes occur primarily in the liver. Many drugs are metabolised in the liver mainly by the Cytochrome (CY) P450 enzyme system. It is now appreciated that the CYP450 system comprises a family of isoenzymes with at least fifteen human liver isoenzymes involved with CYP1A2, CYP3A, CYP2D6, CYP2C9 and CYP2C19 responsible for the metabolism of the majority of drugs¹⁰ (**Table 2**). Some drugs activate this enzyme system (induction) e.g. carbamazepine, phenytoin, rifampicin thus increasing the metabolism of other drugs e.g. oestrogens, cyclosporin. This may result in a reduced effect. The converse may occur with drugs which are enzyme inhibitors e.g. cimetidine, ciprofloxacin, erythromycin, ketoconazole.^{1,2,8,9} If two drugs metabolised by the same isoenzyme are co-administered then the concentration of one or both drugs may be increased e.g. patients receiving theophylline or carbamazepine may experience drug toxicity when co-prescribed cimetidine.

Table 2: Some Drugs that are Metabolised by, Inhibit or Induce Cytochrome P450 isoenzymes^{1,11,12,13}

Cytochrome P450 Isoenzyme	Drugs Metabolised	Inhibitors	Inducers
CYP1A2	Theophylline Imipramine	Cimetidine Ciprofloxacin Fluvoxamine Grapefruit juice	Phenytoin
CYP2D6	Fluoxetine Codeine Venlafaxine	Haloperidol Paroxetine Thioridazine	Phenobarbitone
CYP2C9	Diclofenac Phenytoin Warfarin	Fluconazole Fluvoxamine Fluoxetine Ritonavir	Barbiturates Rifampicin
CYP2C19	Diazepam Omeprazole	Fluoxetine Fluvoxamine Omeprazole	Phenytoin
CYP3A4	Carbamazepine Cyclosporin Cisapride Erythromycin Terfenadine	Cimetidine Erythromycin Itraconazole Fluvoxamine Ritonavir	Carbamazepine Phenytoin Rifampicin Barbiturates

		Miconazole	
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- Pharmacokinetic drug interactions by renal excretion mostly involve reduced excretion of one drug leading to increased plasma levels and possible toxicity e.g. methotrexate and NSAIDs, lithium and diuretics.² The precise mechanism is often unknown but may involve competition between those drugs that share active transport mechanisms in the proximal tubule.^{8,9}

WHEN ARE DRUG INTERACTIONS MOST LIKELY TO OCCUR?

The possibility of a drug interaction should be considered when a drug is being introduced and when it is being withdrawn. The time course of the interaction is variable depending on factors such as the half life of the drugs involved (especially the half-life of the drug whose metabolism is inhibited), dosage, route and presence of active metabolites. The mechanism of an interaction can also have an effect on its time course.⁶ Enzyme inducers e.g. phenobarbitone, warfarin, stimulate the production of new metabolising enzymes and it frequently takes one to three weeks before their effects are at a maximum. In contrast enzyme inhibitors may have an effect on hepatic metabolism within 24 hours.² Some interactions therefore occur almost immediately while others may take days, weeks or even months to develop. Other interactions tend to dissipate with time even when therapy is continued with the two interacting drugs e.g long term broad spectrum antibiotics and the oral contraceptive pill. Thus if the drug interaction is evaluated at the wrong time one may falsely conclude that an interaction does not exist e.g amiodarone interaction with warfarin.^{1,8} The time course of interactions becomes even more complex when drugs are given on an “as required” basis since the frequency and timing of doses can be highly variable between patients.⁶

Table 3: Commonly Encountered Drug Interactions^{1,9,14,15}

Interacting Drug	Interacting Drug	Mechanism of Interaction	Outcome/Action
Erythromycin	Theophylline	Possible inhibition of theophylline metabolism	↑theophylline levels. May take several days to manifest
Erythromycin/ Clarithromycin	Cisapride	Inhibition of cisapride metabolism via CYP3A4	Prolongation of QT interval. Risk of arrhythmias. Concurrent use should be avoided
Warfarin	NSAIDs	Unknown but possibly involves drug displacement	↑risk of bleeding. Unpredictable & occasionally serious ∴ monitor concurrent use
Warfarin	Antibacterials	Effects on warfarin metabolism e.g.erythromycin, independent effects on clotting systems or effects on Vit.K synthesising bacteria in gut e.g. broad spectrum antibiotics	↑ anticoagulant effects of warfarin ∴ increased risk of bleeding

Combined Contraceptive	Oral	Broad antibiotics ampicillin	Spectrum e.g	Impairment of bacterial flora responsible for recycling oestrogen	↓ contraceptive efficacy. Observe “7 day rule”
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HOW TO MANAGE DRUG INTERACTIONS?

Four steps are involved in managing a drug interaction.

- Avoid the combination - if the potential hazards of the interaction outweigh the benefits then choose an alternative drug if available.
- Adjust the dose - if the effects of the interaction are an increase or decrease in the drug's effect then a dosage modification may compensate for this. This may be needed when starting and stopping two interacting drugs.
- Monitor the patient - if interacting drugs are used the patient should be closely monitored for signs of toxicity, adverse effects, reduction in efficacy or where possible plasma concentration.
- Continue medication as before - if interacting drugs are the optimal therapy for a condition or if the interaction is not clinically significant.^{2,6,7}

SOURCES OF INFORMATION ON DRUG INTERACTIONS

Table 4 provides examples of some of the more commonly encountered drug interactions. Further information on clinically significant drug interactions can be obtained from the following sources:

- British National Formulary (BNF)
- Summary of Product Characteristics / Data Sheet Compendium
- Martindale - The Complete Drug Reference
- Drug Interactions, Stockley
- National Medicines Information Centre (NMIC)

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