Drug interactions

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Abstract

Drug–drug interactions (DDIs) arise when the effects of one drug are altered by the co-administration of another. The clinical response depends on many factors, including individual patient characteristics such as age, co-morbidities and pharmacogenetics. The number of potential DDIs is extensive, but the incidence in published studies implies that many of these are not clinically relevant. Interactions are classified as pharmacokinetics-related, where drug absorption, distribution, metabolism or excretion is affected, or pharmacodynamics-related, when drugs with similar pharmacological actions are co-prescribed. The mechanism underlying drug interactions are now better understood, notably those involving the family of cytochrome P450 isoenzymes, as well as those related to P-glycoprotein and organic anion transporter polypeptides, which act as drug transporters in the liver and kidneys. These molecules exhibit genetic polymorphisms that influence the likelihood of clinically relevant DDIs following drug co-administration. With an ageing population, an increasing number of new drugs and more polypharmacy, increasing efforts are needed to avoid DDIs. Although computerized programs can reduce the number of DDIs, a risk–benefit evaluation by the prescribing physician is also required. This article outlines the main mechanisms involved in clinically relevant DDIs.

Keywords Cytochrome P450; drug interactions; P-glycoprotein; pharmacodynamics; pharmacokinetics; polypharmacy

Key points

- Drug–drug interactions (DDIs) account for around a sixth of all adverse reactions to drugs
- Many potential DDIs are involved, although only a small proportion are relevant in clinical practice
- Pharmacokinetic interactions occur when one drug alters the handling of another by altering its absorption, distribution, metabolism or excretion
- Pharmacodynamic interactions occur when two drugs act on the same drug target (e.g. cell surface receptor, enzyme) or physiological system (e.g. blood clotting, blood pressure, central nervous system, plasma electrolyte concentration)
- DDIs can be minimized if prescribers are aware of them (especially when prescribing high-risk drugs), avoid polypharmacy where possible, use appropriate reference resources, monitor drug therapy appropriately, take advice from clinical pharmacists and use decision support systems where available

Introduction

Drug–drug interactions (DDIs) represent a significant problem for prescribers and, with ever more drugs available and guidelines recommending multiple drug therapies for common conditions, the potential for interactions increases. Many theoretical DDIs are not clinically relevant as they do not result in a clinically significant adverse outcome (see Table 1 for classification by severity). Although some adverse drug reactions, such as first-dose anaphylaxis, can be unpredictable, DDIs can often be identified and prevented. Clinically relevant adverse outcomes are more likely if DDIs involve drugs with a low therapeutic index and patients who are more vulnerable because of age or disease (e.g. renal impairment). With an ageing population, more polypharmacy and an increase in the number of people taking alternative therapies, there is an increasing potential for drug interactions. Therefore, there is a growing need for clinical vigilance, surveillance and reporting of adverse reactions to the relevant drug safety authorities.

Frequency of drug interactions

The number of potential DDIs far outweighs the number of adverse reactions related to them that are actually encountered in clinical practice. The proportion of clinically relevant DDIs ranges from 3% to 20% and is related to the number of drugs taken by the patient. In a large prospective study of 18,820 patients, 6.5% of hospital admissions were related to an adverse drug reaction, of which one in six was caused by a DDI. In a recent analysis of community prescribing in Scotland between 1995 and 2010, the proportion of adults prescribed ten or more medications tripled, while the proportion of potentially serious DDIs more than doubled.[1] These figures are likely to increase without preventive measures including prescriber education and clinical decision support tools.

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Classification of drug interactions by severity

A life-threatening or contraindicated combination
Dosage adjustment or close monitoring is needed
Give guidance about possible adverse effects and/or consider some monitoring
No interaction, or no interaction of clinical significance

Source: Stockley's Drug Interactions, 11th ed. Claire Preston (Ed.) London: Pharmaceutical Press; 2011.

Table 1

New approaches to identifying DDIs involving translational bioinformatics are under investigation.[2] These novel methods involve computational techniques such as data-mining of adverse reaction databases and text-mining of medical records, online literature repositories and internet search logs to identify data signals. Results of interest can then be further examined using more traditional methods. These approaches should identify a large proportion of adverse events caused by DDIs that are currently unknown, missed or unreported. Common examples of DDIs are shown in Table 2.

Principal mechanisms underlying drug interactions

There are three mechanisms by which drugs interact with each other.

Pharmaceutical interactions

These are uncommon and occur when drugs are mixed inappropriately in syringes or infusion fluids before administration (e.g. phenytoin precipitates if mixed with a glucose solution before administration). Most DDIs are related to altered pharmacokinetics and/or pharmacodynamics.

Pharmacokinetic interactions

These account for most commonly encountered DDIs and occur when one drug affects the absorption, distribution, metabolism or excretion of another. This results in an increased or decreased exposure to one or other drug. Most involve impaired drug elimination because of interference with hepatic metabolism, renal excretion or transcellular transport.

Drug interactions commonly leading to hospital admission

Drug combination	Adverse event
Warfarin and aspirin	GI bleeding
NSAIDs and aspirin	GI adverse effects
Warfarin and interacting drugs	Bleeding (GI and non-GI)
Diuretic combinations	Renal failure
Diuretics and ACE inhibitors	Renal failure
Digoxin and interacting drugs	Digoxin toxicity

ACE, angiotensin-converting enzyme; GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug.

Table 2

Absorption: although altered stomach acidity or binding of a drug to another substance in the stomach can affect drug absorption, most drug absorption interactions occur in the small intestine, because of a change in intestinal blood flow or intestinal motility, or an alteration in the bacteria that reside in the intestine. Common examples include the following:

- metoclopramide increases stomach emptying and the rate of delivery of co-administered drugs (e.g. ciclosporin, modified-release theophylline) to the small intestine
- colestyramine and other binding agents can impair the bioavailability of other drugs (e.g. furosemide), and ferrous sulphate can chelate levothyroxine.

Distribution: alterations in blood flow caused by, for example, reduced cardiac output or vasoconstriction can affect drug distribution. Many medications bind extensively to plasma proteins such as albumin in the bloodstream and can be prevented from reaching their site of action. However, a drug bound in this way can be displaced from its binding site by another with greater binding affinity, increasing the amount of (unbound) drug available to cause an effect. For example, diazepam displaces phenytoin from plasma proteins, resulting in an increased plasma concentration of unbound phenytoin and an increased risk of adverse effects. The effects of protein displacement are usually of limited clinical significance as the metabolism of the affected drug usually increases in parallel with the increased concentration of unbound drug, so that any effects of the interaction are normally short-lived.

Hepatic metabolism: DDIs related to hepatic metabolism are common. This is because many drugs are broken down by specific microsomal isoenzymes of cytochrome P450 (CYP). CYP3A4 is responsible for most DDIs, and its activity can vary by >50-fold in the general population. These enzymes are subject to relatively specific induction or inhibition by other drugs; examples of common substrates and their inducers and inhibitors are shown in Table 3.

The metabolism of a substrate drug can be altered by a second, interacting drug. The interacting drug can induce the formation of new isoenzymes, leading to increased activity of that pathway and metabolism of the substrate drug. This in turn reduces the plasma concentration and activity of the substrate drug. For example, the plasma concentration of novel oral anticoagulants (NOACs) apixaban, dabigatran and rivaroxaban is reduced by 50% when co-administered with carbamazepine, phenytoin or rifampicin, increasing the risk of thromboembolism.

Alternatively, the activity of cytochrome enzymes can be inhibited, reducing the elimination of the substrate drug and increasing its activity, with resulting exaggerated effects. For example, terfenadine, a non-sedating antihistamine, is metabolized by CYP3A4 to fexofenadine. Ketoconazole inhibits the metabolism of terfenadine, leading to its accumulation and the blockage of potassium channels in the heart, with consequent QT prolongation and potentially fatal arrhythmia known as torsade de pointes. Another common CYP3A4 interaction is inhibition by macrolide