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DRUG INTERACTIONS I: HOW THEY OCCUR

-  Drug interactions occur more often via pharmacokinetic than pharmacodynamic processes
-  Most clinically important interactions involve altered metabolism of the affected drug(s) in the liver
-  Older patients and / or those with chronic illness are at increased risk of drug interactions
-  The potential for interaction (with a drug, herb or food) should always be considered before writing a prescription

INTRODUCTION

Medication use is extensive in developed countries: it has been estimated that approximately four fifths of US adults use at least one medication (prescription medicine, over-the-counter (OTC) drug, herbal remedy) per week, and this rate increases with age.¹ A recent US survey reported an average of 2.3 medications prescribed or provided per patient visit.² A study carried out in Ireland noted that, during 2001-2002, up to 45% of patients ≥ 70 years were receiving ≥ 5 concomitant medications.³ The concomitant use of more than one medication leads to the potential for **drug interaction which is said to occur when the response of a patient to a drug is changed by the presence of another drug, food/drink, herbal substance or some environmental agent.**⁴

This is the first of 2 bulletins on drug interactions; it will explain the various ways that a drug interaction may occur, and describe ways of preventing or minimising their impact on the patient.

EPIDEMIOLOGY

Reviews of various prescription databases have reported incidences of potential drug-drug interactions in up to 6% of patient records, and potentially serious drug-drug interactions in up to 1% of cases.^{5,6} In a study of 458 US Veterans' Administration (VA) patients, **197 people reported taking dietary supplements in addition to prescription medicines, of which 45% showed a potential for interaction, mostly non-serious.**⁷

The importance of drug interactions to the clinician primarily involves knowing or predicting those occasions when a potential interaction is likely to have significant consequences for the patient i.e. might lead to (a) reduced or increased efficacy of the drug(s) involved, (b) increased adverse drug reactions (ADRs) or (c) might even require withdrawal of one of the drugs.^{4,8}

There are well-known risk factors for developing drug interactions (see Table 1).

Table 1: Drug characteristics associated with a high risk of interaction^{4,9}

Characteristic	Examples
Narrow Therapeutic Index	Digoxin, warfarin, ciclosporin, aminoglycosides, lithium
Steep Dose-Response Curve	Sulphonylureas, verapamil, levodopa
Saturable hepatic metabolism	Phenytoin, theophylline
Dosage dependent on patient response	Immunosuppressives, anti-epileptics

Co-prescription with drugs that have a narrow therapeutic index (i.e. where a small margin exists between the therapeutic and toxic drug levels) has an increased chance of a clinically significant drug interaction occurring, as has the use of drugs with a steep dose-response curve (i.e. a small rise in drug levels leads to a large increase in effect). Drugs with a saturable metabolism are more likely to accumulate in the presence of a drug interaction (Table 1). Careful attention is required when co-prescribing these drugs.

The patient characteristics associated with high risk of drug interactions are outlined in Table 2.

Table 2: Patient characteristics associated with high risk of drug interactions^{4,10}

Increasing age	Genetic predisposition
Chronic illness	Critically ill patient/ Presence of renal or hepatic dysfunction
Number of prescribing physicians	Use of multiple co-prescribed +/- OTC drugs (polypharmacy)

Increasing age is a major risk factor for drug interaction; many of the other high-risk patient characteristics listed in Table 2 are associated with older age. It is now recognised that polypharmacy (concomitant use of ≥ 5 drugs) is often necessary to properly manage specific diseases.¹¹ However, **the greater the number of co-prescribed medicines, the greater the risk of potential drug interaction:** the risk of potential drug interaction in patients taking 2 - 5 drugs has been estimated to be 19%, but the risk rises to $> 80\%$ for those taking ≥ 6 drugs.¹² Patients with chronic or critical illness may be more prone to adverse sequelae from potential drug interactions since the underlying illness has impaired their homeostatic mechanisms. A recent large study reported that patients were more likely to suffer adverse events, including drug interactions, with increasing numbers of prescribing physicians involved in their care.¹⁰

MECHANISMS OF DRUG INTERACTIONS

Drug interactions are usually caused by either pharmacodynamic or pharmacokinetic processes.

Pharmacodynamic interactions: These interactions generally involve additive, synergistic or antagonistic effects of drugs acting on the same receptors or physiological systems.⁴ Pharmacodynamic interactions are common but not always recognised. Table 3 outlines some examples. The effects of pharmacodynamic interactions can usually be predicted and managed when the pharmacology of co-administered drugs is known.

Table 3. Common pharmacodynamic interactions^{4,12}

Type of interaction	Examples	Pharmacological Effect
Additive/synergistic	NSAID + warfarin Verapamil + β -blockers	Increased risk of bleeding Bradycardia and asystole
Antagonistic/opposing	β -agonists + β -blockers	Interference with therapeutic effect of one/both drugs
Alterations in electrolyte/fluid balance	ACE inhibitor + spironolactone Digoxin + loop diuretic	Hyperkalaemia Digoxin toxicity at therapeutic doses

Pharmacokinetic interactions occur when one drug affects the other in terms of its absorption, distribution within the body, metabolism or elimination / excretion. This results in altered plasma concentrations of the affected drug (increased or decreased) or altered duration of effect (enhanced clearance or accumulation) with the potential for subsequent reduced efficacy or enhanced toxicity.¹² Table 4 outlines potentially clinically relevant pharmacokinetic interactions.

Table 4: Pharmacokinetic (PK) interactions commonly encountered in clinical practice^{4,13,14}

PK Parameter*	Mechanism of effect	Result	Management**
Absorption*	Chelation / complexing mechanisms (e.g. antacids + tetracyclines/ quinolones) Interference with gut flora (e.g. by antimicrobials) Changes in GI pH (eg PPIs + ketoconazole) Changes in GI motility (uncommon)	Formation of poorly-soluble complexes \downarrow enterohepatic circulation reabsorption (e.g. of oral contraceptive pill) Reduced absorption Can \uparrow or \downarrow absorption	Alter administration times Rare but unpredictable - may affect efficacy Alter administration times Check SPC for details
Distribution*	Interference with plasma protein binding (e.g. phenytoin displaced by valproate)	Rise in the plasma level of displaced drug	Usually temporary and not clinically significant
Metabolism*	Induction / inhibition of cytochrome P450 isoenzymes in liver [see text for further details]	Can \downarrow or \uparrow drug levels resulting in \downarrow efficacy or \uparrow toxicity of either / both drugs	Need to be aware of potential for interaction: may need to alter dosage (as per SPC directions)
Elimination / Excretion*	Change in active renal tubular excretion (e.g. NSAIDs + Methotrexate (MTX); NSAIDs / loop diuretics + lithium)	\downarrow excretion of MTX \downarrow excretion of lithium	May need to reduce dose of MTX May need to reduce dose of lithium

* P-glycoprotein induction / inhibition may \downarrow or \uparrow concentration of affected drug in cells at several stages in the pharmacokinetics of a drug *in vivo*

** the Summary of Product Characteristics (SPC) for each medicine gives information on potential for drug interactions (www.medicines.ie; www.imb.ie)

Problems with **absorption** usually involve more than one of the mechanisms outlined in Table 4. Interference with **plasma protein binding** was previously thought to have potentially serious consequences, however it is now understood that most drugs, extensively bound to plasma proteins and subject to displacement reactions (e.g. warfarin, phenytoin, methotrexate), have a compensatory clearance system, therefore any increase in free drug is temporary.^{4,9} The commonest type of interaction affecting **elimination** involves change in **active renal tubular excretion** of one drug by another (Table 4). Drug interactions tend not to interfere with **biliary excretion** mechanisms.

Most clinically important drug interactions involve alteration in the rate of metabolism of the affected drug(s).⁴ The majority of drugs used clinically are lipophilic (lipid soluble) which allows their passage through biological (lipid) membranes and subsequent access to their site of action.¹³ However, lipid solubility hinders excretion and therefore the drugs require conversion to more water-soluble (“polar”) products to enable elimination via the bile or urine.⁸ Metabolism involves a sequence of enzymatic steps (phase I and phase II reactions) that make the drug substance more water-soluble.¹⁵

The cytochrome P-450 (CYP) family of enzymes plays a critical role in metabolism. It comprises a large number of oxidative enzymes involved in the biosynthesis and degradation of many endogenous substances (e.g. lipids, vitamins, steroids).¹⁵ These enzymes also metabolise ingested substances such as drugs and foodstuffs. The liver is the major site of CYP activity but enzymes are also found in the gut (where they can influence bioavailability), kidneys, skin, lung and placenta.⁴ Four main sub-families, thought to be responsible for >80% of drug metabolism, have been identified (CYP 1 - 4), within which a small number of sub-groups (“isoforms”) are understood to be the principal enzymes involved in drug metabolism (Table 5).^{4,8}

Table 5. Examples‡ of common substrates, inducers, inhibitors of CYP isoforms^{4,8,15,19}

CYP isoform	Substrate	Inhibitor	Inducer
CYP 3A group (includes 4,5,7)	Atorvastatin, simvastatin Clarithromycin, erythromycin Diltiazem, verapamil, nifedipine Indinavir, ritonavir, nelfinavir Ciclosporin, tacrolimus Losartan, sildenafil, methadone Oestradiol, progesterone	Itraconazole*, ketoconazole* Clarithromycin*, erythromycin* Diltiazem, verapamil Indinavir, ritonavir, nelfinavir Grapefruit juice	Rifampicin Carbamazepine Phenytoin Phenobarbitol Efavirenz St John’s Wort
CYP 2D6	Carvedilol, metoprolol, timolol Fluoxetine, paroxetine, venlafaxine Tricyclic antidepressants Codeine, dextromethorphan	Bupropion*, quinidine* Fluoxetine*, paroxetine* Cimetidine, amiodarone, sertraline Duloxetine, terbinafine, clomipramine	Rifampicin
CYP 2C9	Diclofenac, ibuprofen, naproxen Glipizide, glibenclamide Warfarin, diazepam	Fluconazole* Amiodarone Isoniazid	Rifampicin
CYP 2C19	Proton pump inhibitors Diazepam, amitriptyline Citalopram, warfarin	Proton pump inhibitors Cimetidine, ketoconazole Chloramphenicol	Carbamazepine Rifampicin
CYP 1A2	Amitriptyline, imipramine Clozapine, theophylline Warfarin	Fluvoxamine*, ciprofloxacin* Fluoroquinolones Cimetidine, amiodarone Erythromycin	Omeprazole Tobacco smoke Broccoli, brussel sprouts

‡ Full details on CYP metabolism are given in the Summary of Product Characteristics (SPC) for each medicine (www.medicines.ie / www.imb.ie)
* denotes a strong inhibitor, i.e. one that causes a > 5-fold increase in the plasma levels or more than 80% decrease in clearance.

Each individual enzyme generally has a substrate specificity, i.e. drugs metabolised by CYP 3A4 may interact with each other but not with CYP 2D6 drugs. **The activity of CYP enzymes is modulated by genetic factors**; polymorphisms (i.e. an alteration, usually a reduction, in the expected enzyme activity) have been identified for many of the major isoforms, resulting in altered drug response.¹³ Genetic polymorphisms resulting in reduced activity of CYP 2C9 and 2D6 enzymes have been noted in approximately 6% and 10% of Caucasian populations respectively;^{16,17} this may make the carrier more prone to drug toxicity.¹⁶ **However, other factors such as age, ethnic origin, gender, diet, use of alcohol or tobacco as well as chronic illness have also been implicated in modulating activity.**⁴ Because CYP function is so crucial in determining the way a drug is handled by the body, each new drug must undergo a process of evaluation to determine which, if any, CYP enzymes are involved in its metabolism.¹⁸

The importance of the CYP system of metabolism for drug interactions lies in the fact that the **activity of CYP enzymes can be blocked (inhibited) or increased (induced) by certain drugs or exogenous substances.** This results in an alteration of the predicted plasma level of an affected drug, whenever it is used in association with the inhibiting / inducing substance. Table 5 gives examples of drugs (“substrates”) that are normally metabolised by the major isoforms and commonly used inducing and inhibiting substances for each isoform. **CYP 3A and CYP 2D6 are responsible for >50% of known drug metabolism activities** therefore drug interactions are frequently seen when drugs are co-administered from within each of these groups. **Enzyme inhibition usually occurs rapidly** and results in accumulation of the affected drug and the risk of toxicity (e.g. increased levels of theophylline with use of cimetidine).

Enzyme induction may take days or weeks to achieve maximum effect and usually reduces efficacy of the affected drug (e.g. reduced oral contraceptive efficacy with phenytoin) for some time after discontinuation of the inducer drug.¹⁵ However, if active metabolites are responsible for the drug's effect, the reverse may occur (e.g. CYP 2D6 converts codeine to the active morphine, therefore CYP 2D6 inhibitors reduce codeine efficacy).¹⁵ [The Indiana School of Medicine has developed a Cytochrome P450 drug interaction table, which divides medicines into CYP substrates, inhibitors and inducers and which is updated regularly (check out: <http://medicine.iupui.edu/clinpharm/DDIs>)]¹⁹

P-Glycoprotein (PGP) is a transport system that is present in many cells throughout the body, including intestinal, renal tubular, biliary canalicular systems and those making up the blood-brain barrier.^{13,20} It is thought that PGP may also contribute to drug interactions at several possible sites (see Table 4). Studies have shown that several inhibitors and inducers of CYP 3A also appear to have the same effect on the PGP system.²⁰ The true significance of the PGP and other transport systems is still being investigated.

OTHER TYPES OF DRUG INTERACTION

Table 5 outlines some foodstuffs that interact with the CYP system. One **food-drug interaction** known to be clinically relevant is **grapefruit juice** (inhibitor of CYP 3A especially in gut) and drugs metabolised by CYP 3A.²¹ This results in higher than anticipated blood levels of certain drugs, e.g. nifedipine which gives a greater than expected response. Patients need to be told that the effect may last up to 3 days after taking grapefruit juice. **Tobacco** is known to induce CYP1 A2 activity. This may result in lower than expected blood levels of affected drugs.²² For example, when theophylline is prescribed to a smoker, there is a risk of toxicity when the patient discontinues smoking unless the dose is reduced, because the plasma levels of theophylline will increase.

In recent years, the risk of **herb-drug interactions** has been brought to the fore with **St John's Wort**, which is a known inducer of CYP 3A4 (see Table 5). Patients taking drugs metabolised by this system, run the risk of reduced efficacy if St John's Wort is used concomitantly. This has been shown to have catastrophic consequences for patients with HIV²³ or in post-transplant patients.²⁴ In addition, there have been reports of increased bleeding with concomitant use of warfarin with either **gingko biloba** or **garlic**.²⁵ **Ginseng** also has been reported to affect the INR when used with warfarin but the outcome depends on the extract of ginseng used.^{25,26}

Finally, **alcohol** is known to **potentiate the sedative effect of CNS depressants** and **the hypotensive effect of many anti-hypertensive agents** (e.g. ACE inhibitors, β -blockers, calcium channel blockers).²⁷

HOW TO MINIMISE DRUG INTERACTIONS

It is very difficult to remember all the known clinically important interactions and how they occur.⁹ However, there are some broad general principles that may be helpful for prescribers in order to minimise risk to the patient:^{4,9,12,26,28}

- Be alert for drugs known to have a narrow therapeutic window (e.g. anticoagulants, anticonvulsive agents, digoxin). Take care when initiating such a drug or co-prescribing another drug with it
- Be aware of commonly used drugs known to be enzyme inducers or inhibitors (Table 5)
- Be familiar with the metabolism of the drugs you prescribe frequently and their potential to interfere with other drugs – full details available at www.medicines.ie / www.imb.ie
- Consider the pharmacology of the drugs you prescribe in order to avoid potential pharmacodynamic interactions with other drugs, herbal remedies or foodstuffs
- Avoid using a combination (especially those involving NSAIDs) if the potential hazards appear to outweigh the benefits
- If no alternative combination is possible, monitor the patient closely for signs of toxicity or reduced efficacy, measure drug levels (e.g. phenytoin, lithium) or outcome (e.g. INR) if possible, and adapt the relevant dosage(s) according to individual response
- Remember that the elderly and chronically ill patients are at increased risk of drug interactions

Finally always ask about use of over-the-counter (OTC) medicines and herbal or alternative remedies before writing a prescription.

SUMMARY

Most clinically important drug interactions involve alteration in the CYP system of metabolism of one drug substance by another.⁴ Guidance is available in the Summary of Product Characteristics on the metabolism of each marketed drug and the potential, if any, for clinically relevant drug interactions. The clinical impact of CYP-mediated drug interactions at an individual patient level will also depend on genetic and environmental factors. Pharmacodynamic drug interactions may be predicted and avoided by remembering the mechanism of action of the drugs being co-prescribed.^{4,9}

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