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COMPETING INTERESTS
None declared.

Clinically important drug–drug interactions and how to manage them

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This article is designed to be read in conjunction with the A3 table of drug interactions provided as an insert in this issue of the *Journal of Primary Health Care* and also available on the journal website.

Background

The more medicines a person requires, the increased risk of a drug–drug interaction. Unfortunately it is not possible to simply stop potentially offending medicines, but the medicines interactions need to be managed as safely as possible.

There are two types of medicine interactions—pharmacodynamic and pharmacokinetic. Pharmacokinetic interactions are relatively straightforward and are relatively predictable if the actions of the medicine are known. These involve the additive effect of similar medicines, or a cancelling effect, for example:

- Increasing risk of hypotension with:
  - Two antihypertensives
  - An antihypertensive + tricyclic anti-depressants
  - An antihypertensive + isosorbide mononitrate
- Increasing renal impairment with:
  - ACE inhibitor, diuretic and NSAID.

Pharmacodynamic interactions are more complex and usually involve interference with absorption, e.g. tetracycline and food, calcium or metabolism by enzymes such as the cytochrome P450 enzymes, p-glycoprotein and other less common enzyme systems.

Twenty years ago we talked of 'liver enzymes' and competition through protein binding. This has become more sophisticated now, with many types of enzymes, but the main ones are a large

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group of cytochrome P450 enzymes that are located in membrane, not just of the liver, but also small intestines, with smaller concentrations in the kidney, lung and brain.

Although there are numerous cytochrome P450 (CYP) enzymes, the dominant ones for medicine metabolism are CYP3A4, which is responsible for metabolising approximately 36% of medicines, and CYP2D6, which metabolises approximately 19% of medicines. Some drugs are substrates, some inhibitors and some inducers of the enzyme groups—but are not necessarily a substrate for the enzymes they inhibit or induce.

There is also a wide variation of enzyme activity between individuals, with a five- to eightfold variation in CYP3A4 activity between individuals, and greater than 50% variation between individuals for CYP2D6 activity. This variation is in the normal population. Five to 10% of Europeans and less than 1% of Asian people are poor metabolisers of medicines metabolised by CYP2D6.

P-glycoprotein (PGP) is another recent discovery. It is a protein associated with cell membrane and involved in cell transport and has evolved to 'pump out' toxic agents. There appears to be a co-ordinated interaction between PGP and CYP3A4.

Absorption from the gastrointestinal tract is usually passive or assisted, but PGP in the lumen side of the intestinal epithelium actively transports substances back into the intestinal lumen, e.g. digoxin, a PGP substrate. Quinidine is a PGP inhibitor and so quinine inhibits the expulsion of (oral) digoxin back into the intestine, and so increases digoxin serum concentrations (less interaction if digoxin given IV). Conversely, rifampicin stimulates PGP and so decreases serum digoxin.

In the kidney there is a similar effect with PGP enhancing clearance of substances. Quinidine and cyclosporin inhibit PGP, so clearance of digoxin is inhibited. In the central nervous system PGP inhibits the passage of some medicines across the blood–brain barrier, such as loperamide. A PGP inhibitor allows greater passage across the blood–brain barrier.

Identification and management of drug–drug interactions

The A3 table included with this journal provides information on the management of some common medicine interactions. The potential for an interaction is often predictable, but there are usually many variables involved in whether the interaction will be clinically significant. Also not all medicines in the same class interact to the same extent, e.g. simvastatin versus atorvastatin.

Risk assessment

- How common is the interaction?
- How severe will the interaction be if it occurs?
- Is it a dose-related interaction?

Management

- Prescribe an alternative, non-interacting drug
- Stop the target interacting drug temporarily
- Monitor
  - with investigations—INR, blood pressure, liver function tests
  - clinically—dizziness, muscle aches.

Once dosage of two interacting medicines is established clinically, interaction is considered managed, unless the interacting medicine is stopped or has a dosage change.

SIMVASTATIN

There are increasing reports to the Centre for Adverse Reaction Monitoring (CARM) of rhabdomylitis due to interactions with simvastatin, resulting from serum concentrations of simvastatin increasing over 200 times. Important medicines to be wary of:

- **Itraconazole**
  - Serum concentration may increase up to 200-fold
  - Avoid combination.
- **Erythromycin and clarithromycin**
  - Serum concentrations may increase up to 80-fold
  - Avoid this combination
  - Limited data for roxithromycin. If used, ensure the patient is very aware to report **any** muscle aches.
- **Diltiazem and verapamil**
  - Serum concentrations may increase up to 60-fold
  - A relatively common combination, but many reports to CARM of simvastatin-induced rhabdomylitis have the combination of simvastatin and diltiazem
  - Ensure the patient knows to report any muscle aches immediately
  - Check the lipid profile 4–6 weeks after the combination (plus ALT) and consider down titrating the simvastatin if the lipid profile is particularly low.
- **Amiodarone**
  - There are increasing reports that this is a significant interaction for some people.

WARFARIN

- **Erythromycin, clarithromycin and roxithromycin**
  - Increasing reports of high INR results, some resulting in hospitalisation
  - If the combination is really necessary, monitor the INR in 3 days.
- **Tramadol**
  - Increasing reports
  - If tramadol is used, it should be used consistently and monitor INR in 3 days, then 1 week if there was no change.
- **Amiodarone**
  - 20–60% increase in warfarin
  - Monitor INR weekly for 4 weeks (onset usually seen in 2 weeks).

SSRIS

- **Tricyclic antidepressants**
  - May get 40-fold increase in tricyclic antidepressant
  - Warn the patient about symptoms of serotonin syndrome / toxicity.
- **Tramadol**
  - The Australian Adverse Drug Reaction Centre has had an increasing number of reports of serotonin toxicity with the combination of tramadol and an SSRI, especially if in combination with a tricyclic antidepressants or an antipsychotic medicine.

TRIPLE WHAMMY

This is the combination of an **ACE Inhibitor (or angiotensin II antagonist)** plus **diuretic (or dehydration)** plus **NSAID (or COX-2 Inhibitor)** and is an important risk factor for renal failure, especially in the older person.

DRUG INTERACTIONS THAT MATTER

AND HOW TO MANAGE THEM

INTRODUCTION

Drug interactions can be broadly categorised as pharmacokinetic or pharmacodynamic. In pharmacokinetic interactions there is a change in the plasma concentration of the interacting drug which can lead to toxicity or sub-therapeutic effect. In a pharmacodynamic interaction there is a modification of pharmacological effect without a change in plasma concentration; for example, additive anticholinergic effects seen with amitriptyline and oxybutinin or serotonin syndrome which can occur with an SSRI and tramadol. This resource mainly focuses on major pharmacokinetic drug interactions that may be seen in general practice and their management. It is not a comprehensive resource.

TABLE OF COMMONLY USED MEDICINES THAT INTERACT

The table has **interactions that are relatively common or carry a high risk of toxicity in red**, **moderate interactions in blue**, **minor interactions in green** and **interactions to be aware of in black**. The table quantifies the potential interaction by reporting what are generally the maximum potential increases in serum concentration. Where the percentage increase is given, e.g. 300% increase, then this means that the serum concentration may be increased threefold, which is similar to giving three times the dosage of the target medicine. Hence many of the interactions are dependent on the initial dosage of the target medicine. As an example, the interactions with simvastatin have become more significant with the higher dosages of simvastatin being used.

Because of the variability in individual metabolism, many interactions will not be obvious in most individuals, but when an interaction occurs, it may lead to considerable morbidity, or mortality. The usual way to manage the potential interaction is through conscientious monitoring and general awareness of the clinical symptoms of toxicity. If a new medicine has been added and a new symptom occurs, be suspicious of an interaction, not just an adverse effect.

MANAGING INTERACTIONS

Questions to ask when about to prescribe a potentially interacting medicine:

- Is the combination really necessary—what are the alternatives?
- What are the likely adverse effects of high dosages of the target medicine (how hazardous)?
- What clinical monitoring does the patient need to know about to report back to you?
- What objective monitoring needs to be done, and when?

THE RED ALERT DRUGS AND INTERACTIONS

The following medicines should ‘ring alarm bells’ as having important interactions:

• Warfarin	
• Statins	particularly simvastatin (not pravastatin)
• Macrolide antibiotics	particularly erythromycin, clarithromycin (less with roxithromycin, minimal with azithromycin)
• Calcium channel blockers	particularly diltiazem and verapamil
• Azole antifungals	particularly itraconazole
• SSRIs	particularly fluoxetine, paroxetine; less so citalopram
• Amiodarone	
• Digoxin	
• Cyclosporin	
• Antiepileptic medicines	particularly carbamazepine, phenytoin; less so valproate, gabapentin

REFERENCES

As well as searching the primary literature, the David Flockhart Interaction website was used for the cytochrome P450 enzyme table (www.drug-interactions.com) and Stockley’s Drug Interactions textbook.

This table was developed for the Goodfellow Unit Symposium (2007) by Drs **Linda Bryant** (Clinical Advisory Pharmacist, Department of General Practice and Primary Health Care, University of Auckland; East Health PHO; and Comprehensive Pharmaceutical Solutions Ltd) and **Tana Fishman** (Senior Lecturer, Department of General Practice and Primary Health Care, University of Auckland), and further developed with assistance from **Robert Buckham** (Chief Drug Information Pharmacist, Christchurch Hospital) and **David Woods** (BPAC).

INTERACTING CLASS	INTERACTING DRUGS	Statins (not pravastatin) Atorvastatin	Statins (not pravastatin) Simvastatin	Calcium channel blockers Amlodipine	Calcium channel blockers Diltiazem	Calcium channel blockers Felodipine	Calcium channel blockers Verapamil	Combined oral contraceptives	Tricyclic antidepressants	Cyclosporin Tacrolimus	Digoxin	Tramadol	Triazolam	Warfarin
Macrolides Erythromycin is the most potent inhibitor. Roxithromycin has less inhibitory activity. Azithromycin minimal.	**Erythromycin**	30–40% increase. **Monitor** for muscle aches.	400–600% increase. **Avoid** combination.	Isolated cases. **Monitor** BP, swollen ankles.	150% increase. **Monitor** BP, swollen ankles.	250% increase. **Monitor** BP, swollen ankles.	Isolated cases. **Monitor** BP, swollen ankles.	Breakthrough bleeding reported. **Avoid** or take extra precautions	Unlikely interaction.	500–700% increase. **Avoid** combination. If unavoidable, reduce dosage to 35% and monitor cyclosporin.	200–400% increase. Unpredictable (~10% of patients). **Avoid** or **monitor** digoxin in 5–7 days.		Possible increase in serum concentration. **Avoid** or **warn** of increased sedation.	Small number of patients have increased INR. **Avoid** or **monitor** INR at 3–5 days.
	Clarithromycin	200–400% increase. **Monitor** for muscle aches.	1000% increase. **Avoid** combination.	No published reports but **monitor** BP, swollen ankles.	No published reports but **monitor** BP, swollen ankles.	No published reports but **monitor** BP, swollen ankles.	No published reports but **monitor** BP, swollen ankles.	Although low risk, high consequences. Use extra precautions.	Unlikely interaction.	200–1200% increase. **Avoid** combination.	200–400% increase. Unpredictable (~10% of patients). **Avoid** or **monitor** digoxin in 5–7 days.		Up to 500% increase in serum concentration. **Avoid** combination.	Small number of patients have increased INR. **Avoid** or **monitor** INR at 3–5 days.
	Roxithromycin	Limited reports and information. Less likely to interact. **Monitor** for muscle aches.	Limited reports of an interaction. **Monitor** muscle aches.	No published reports. Least likely macrolide to interact but **Monitor** BP, swollen ankles.	No published reports. Least likely macrolide to interact but **monitor** BP, swollen ankles.	No published reports. Least likely macrolide to interact but **monitor** BP, swollen ankles.	No published reports. Least likely macrolide to interact but **monitor** BP, swollen ankles.	Although very low risk, high consequences. Use extra precautions.	Unlikely interaction.	50–60% increase. **Avoid** or **monitor** cyclosporin in 3–5 days.	200–400% increase. Unpredictable (~10% of patients). **Avoid** or **monitor** digoxin in 5–7 days.		Small increase in serum concentration.	Small number of patients have increased INR. **Avoid** or **monitor** INR at 3–5 days.
Calcium channel blockers Diltiazem and verapamil are potent inhibitors. Amlodipine, felodipine and nifedipine less so.	**Amlodipine**	No apparent interaction. **Monitor** muscle aches.	No apparent interaction. **Monitor** for muscle aches.		Expected additive action. Effect may be greater due to enzyme inhibition.	Not a rational combination.	Expected additive action. Effect may be greater due to enzyme inhibition.	Unlikely interaction	Unlikely interaction.	40% increase. **Monitor** cyclosporin, renal function, BP.		Unlikely interaction.	Unlikely interaction.	No apparent clinical effect.
	Diltiazem	Not reported, but potential increase. **Monitor** muscle aches.	200–500% increase. **Monitor** ALT (6 weeks) and muscle aches.	Expected additive action. Effect may be greater due to enzyme inhibition.		Expected additive action. Effect may be greater due to enzyme inhibition.	Expected additive action. Effect may be greater due to enzyme inhibition.	Unlikely interaction	Case reports of up to 200% increase. **Monitor** for increased sedation, blurred vision, postural hypotension.	150–300% increase **Monitor** cyclosporin, renal function, BP.	150–300% increase possible. **Monitor** digoxin in 7–10 days.		200–300% increase. **Warn** about sedation and risk of driving.	No apparent clinical effect.
	Verapamil	400% increase. **Monitor** ALT (6 weeks) and muscle aches.	400–600% increase. **Monitor** ALT (6 weeks) and muscle aches.	Expected additive action. Effect may be greater due to enzyme inhibition.	Not a rational combination.	Expected additive action. Effect may be greater due to enzyme inhibition.		Unlikely interaction	Case reports of up to 200% increase. **Monitor** for increased sedation, blurred vision, postural hypotension.	150–300% increase **Monitor** cyclosporin, renal function, BP.	150–300% increase possible. **Monitor** digoxin in 7–10 days.		Unlikely interaction.	No apparent clinical effect.
Azole antifungals Itraconazole is a particularly potent inhibitor. Fluconazole is a less potent inhibitor.	**Fluconazole**	Potential for an interaction. **Be alert** for muscle aches.	Potential for an interaction (has been reported). **Be alert** for muscle aches.	Unlikely to be clinically important. **Be alert** for swollen ankles.	Unlikely to be clinically important. **Be alert** for swollen ankles.	Unlikely to be clinically important. **Be alert** for swollen ankles.	Unlikely to be clinically important. **Be alert** for swollen ankles.	Contradictory information. High consequences. Use extra precautions.	Limited reports. **Monitor** for TCA adverse effects.	200–300% increase. **Reduce** dosage 70–80% and **monitor**.	Potential interaction. **Monitor** digoxin in 7–10 days.		200% increase in some cases. **Warn** about sedation, driving.	Increased INR in a number of people. **Monitor** INR after 3–5 days.
	Itraconazole	200–300% increase. **Monitor** ALT (6 weeks) and muscle aches.	1000–2000% increase. **Avoid** combination.	An interaction is likely. Also negative inotropic effect noted, **Monitor** BP, swollen ankles and cardiac function.	Significant increase plus negative inotropic effect. Reduce diltiazem. **Monitor** BP, swollen ankles, and cardiac function.	Significant increase plus negative inotropic effect. **Monitor** BP, swollen ankles and cardiac function.	An interaction is likely. Also negative inotropic effect. **Monitor** BP, swollen ankles and cardiac function.	Isolated cases of contraceptive failure. **Avoid** or use extra precautions.	Limited reports. **Monitor** for TCA adverse effects.	200–300% increase. **Reduce** dosage 70–80% and **monitor**.	200–400% increase but unpredictable. **Monitor** digoxin in 7–10 days.	Potential interaction – may increase tramadol concentrations. **Monitor** for ↑ ADRs, including serotonin toxicity.	200–300% increase in some cases. **Warn** about sedation, driving.	Only isolated cases reported. **Monitor** INR after 3–5 days.
SSRIs Fluoxetine and paroxetine are the most potent inhibitors. Citalopram is less likely to interaction, although there have been cases.	**Fluoxetine**	Unlikely interaction.	Small potential for an interaction. **Monitor** for muscle aches.	Isolated cases of interaction. **Be alert** for swollen ankles.	Isolated cases of interaction. **Be alert** for swollen ankles.	Isolated cases of interaction. **Be alert** for swollen ankles.	Isolated cases of interaction. **Be alert** for swollen ankles.	Unlikely interaction.	400%* increase. Dose dependent. **Warn** about serotonin toxicity, increased seizure risk.	Isolated reports of interactions. **Avoid** and use an alternative antidepressant.	Isolated reports. **Monitor** for any gastrointestinal disturbances.	May increase seizure risk and reduce analgesia. **Warn** about serotonin toxicity. Care if also on a TCA.	No apparent interactions.	Unpredictable increase in INR. **Monitor** INR. Potential additive antiplatelet effect.
	Paroxetine	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	Unlikely interaction.	400%* increase. Dose dependent. **Warn** about serotonin toxicity, increased seizure risk.			May increase seizure risk and reduce analgesia. **Warn** about serotonin toxicity. Care if also on a TCA.	No apparent interaction.	Isolated reports of increased INR. **Monitor**. Potential additive antiplatelet effect.
Antiepileptics Carbamazepine and phenytoin are potent enzyme inducers. Valproate, gabapentin and lamotrigine are less likely to cause an interaction.	**Carbamazepine** **Phenytoin**		Probable reduction in simvastatin concentration. **Monitor** lipid profile.	Potential reduction in amlodipine concentration. **Monitor** blood pressure.	40–400% increase in carbamazepine and phenytoin possible. **Monitor** serum concentrations in 7 days. Effect of diltiazem can be reduced. **Check** blood pressure.	Felodipine concentrations reduced. **Check** blood pressure control.	40%* increase in carbamazepine and phenytoin possible. **Monitor** serum concentrations in 7 days. Effect of verapamil can be reduced. **Check** blood pressure.	Pregnancy risk. Spotting occurs in > 60%. Estimate failure rate 3.1 / 100 women years. **Avoid** or increase contraceptive dosage.	Concentration of the tricyclic antidepressant can be reduced but not usually clinically significant. (NB TCAs increase seizure risk)	Concentration of cyclosporin reduced. May need a 2- to 5-fold increase in dosage. **Monitor** serum cyclosporin or use alternative antiepileptic.	Unlikely interaction.	Interaction unlikely but tramadol can lower seizure threshold.	No apparent clinical effect.	INR is reduced. Dose increase of warfarin often required. **Monitor** INR in 5–7 days.
	Amiodarone	Potential interaction. **Monitor** for muscle aches.	Cases of rhabdomyolysis reported. Statin-dose dependent. **Monitor** for muscle aches, and ALT in 6 weeks.	No reported interactions, but **be alert** for swollen ankles.	Possible additive effect on myocardial contractility.	No reported interaction, but **be alert** for swollen ankles.	Possible additive effect on myocardial contractility.	Unlikely interaction.	Unlikely interaction.	Significant increase. **Monitor** cyclosporin. Be aware of long half-life of amiodarone.	Double digoxin concentration. **Monitor** digoxin in 2 weeks.		Potential interaction. May prolong sedation. **Avoid** combination (temazepam likely to be less problematic).	Increase in INR seen in most patients. **Monitor** INR weekly for 4 weeks (onset seen in ~2 weeks).
	Grapefruit juice	150–250% increase. **Avoid** combination.	1500% increase. **Avoid** combination.	Can increase concentrations. **Avoid** combination.	Can increase concentrations. **Avoid** combination.	Up to 1200% increase. **Avoid** combination.	150% increase. **Avoid** combination.	Unlikely to be important but spotting has been reported.	Unlikely interaction.	Up to 150% increase. **Avoid** combination.		Unlikely interaction.	150% increase. **Avoid** combination.	Unlikely interaction.
	Rifampicin		Probable reduction in simvastatin concentration. **Monitor** lipid profile.	Potential interaction. **Monitor** blood pressure.	Diltiazem concentrations markedly reduced. **Monitor** blood pressure and pulse rate.	Limited information, but possible interaction. **Monitor** blood pressure.	Verapamil concentrations markedly reduced. **Monitor** blood pressure and pulse rate.	Spotting occurs and 50–70% have menstrual disturbances. Use extra precautions for 4–8 weeks after stopping rifampicin.	Isolated reported of decreased TCA concentrations.	Cyclosporin concentrations likely to be reduced. **Monitor** cyclosporin.	Serum digoxin concentration can be reduced by 50%. **Monitor** digoxin concentration in 7–10 days.		Triazolam concentration may be decreased but not temazepam.	INR can be reduced and a dose increase of warfarin required. **Monitor** INR in 5–7 days.
	St Johns Wort		Probable reduction in concentration – **monitor** lipid profile.	Potential interaction. **Monitor** blood pressure.	Potential interaction. **Monitor** blood pressure.	Potential interaction. **Monitor** blood pressure.	Potential interaction. **Monitor** blood pressure.	Interactions reported. **Avoid** combination.	Serotonin toxicity risk. **Avoid** combination.	Reduced cyclosporin concentrations. **Avoid** combination.	Digoxin may be reduced by up to a third. **Avoid** combination.	Potential risk of serotonin toxicity and increased seizure risk.		Limited cases of reduced INR. **Avoid** combination.

The coloured text in the table relates to the importance of the interaction:
RED=Major
BLUE=Moderate
GREEN=Minor, if at all
BLACK=To be aware of

Potential interactions not in the table:

'Dangerous Trio' – Diuretics, ACE inhibitor (or Angiotensin II antagonist) plus NSAID (or COX-2 inhibitor).	Increased risk of renal failure.	**Avoid** or **monitor** renal function in 7–10 days, then in 1 month.
Warfarin and tramadol	Increased INR is reported.	**Avoid** combination. **Monitor** INR in 3–5 days. Regular tramadol is preferable to prn.
Lithium and ACE inhibitors or diuretics or NSAIDs	Increased lithium concentrations possible.	**Monitor** lithium weekly for 2 weeks (NSAID), 6 weeks (ACE Inhibitor), 4 weeks (NSAID).
Allopurinol and azathioprine	Increased azathioprine concentrations.	**Avoid** combination.
Antibiotics and oral contraceptives	This interaction is very unlikely but due to the consequences using extra precautions is suggested (equates to 7-day rule). Probably more risk with broad spectrum.	