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. Pharmacodynamic 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

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...
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.
**VERY HOT INTERACTION ISSUES**

**SIMVASTATIN**

There are increasing reports to the Centre for Adverse Reaction Monitoring (CARM) of rhabdomyolysis 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 rhabdomyolysis 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.

**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 oxybutynin 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 is generally the maximum potential increase 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 Cockburn Interaction website was used for the cytochrome P450 enzyme table (www.david-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).
<table>
<thead>
<tr>
<th>INTERACTING DRUGS</th>
<th>INTERACTING CLASS</th>
<th>INTERACTING DRUGS</th>
<th>UNPROVEN</th>
<th>POTENTIAL INTERACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macrolides</strong></td>
<td><strong>Erythromycin</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>30–40% increase.</strong></td>
<td><strong>30–40% increase.</strong></td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td><strong>200–400% increase.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>200–300% increase.</strong></td>
<td><strong>200–400% increase.</strong></td>
</tr>
<tr>
<td><strong>Roxithromycin</strong></td>
<td><strong>Limited reports of an interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>200–300% increase.</strong></td>
<td><strong>200–400% increase.</strong></td>
</tr>
<tr>
<td><strong>Calcium channel blockers</strong></td>
<td><strong>Diltiazem</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Amlodipine</strong></td>
<td><strong>No apparent interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Verapamil</strong></td>
<td><strong>No apparent interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Azole antifungals</strong></td>
<td><strong>Fluconazole</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Itraconazole</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td><strong>Fluoxetine</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Paroxetine</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Antiepileptics</strong></td>
<td><strong>Carbamazepine</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Amiodarone</strong></td>
<td><strong>Potential interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase.</strong></td>
<td><strong>150–200% increase.</strong></td>
</tr>
<tr>
<td><strong>Grapefruit juice</strong></td>
<td><strong>100–150% increase. Avoid combination.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase. Avoid combination.</strong></td>
<td><strong>150–200% increase. Avoid combination.</strong></td>
</tr>
<tr>
<td><strong>Rifampicin</strong></td>
<td><strong>Potential interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase. Avoid combination.</strong></td>
<td><strong>150–200% increase. Avoid combination.</strong></td>
</tr>
<tr>
<td><strong>St Johns Wort</strong></td>
<td><strong>Potential interaction.</strong></td>
<td><strong>Unlikely interaction.</strong></td>
<td><strong>150–200% increase. Avoid combination.</strong></td>
<td><strong>150–200% increase. Avoid combination.</strong></td>
</tr>
</tbody>
</table>

**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:**
- **Dangers:*** Dosage, ACE inhibitor (or Angiotensin II antagonist) plus NSAID (or COX 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. **INR in 3–5 days.** Regular tramadol is preferable to pn.
- **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.