

## Interactions with systemic antifungal agents

All systemic antifungal agents have the potential to interact with other pharmacotherapy, primarily through interactions with the cytochrome P450 enzyme (CYP450) system. This bulletin discusses the major drug interactions with the triazoles (fluconazole, itraconazole and voriconazole) and terbinafine.

### Background

An interaction occurs when the effect of one drug is modified by the previous or concurrent administration of another drug (or drink, herb etc). In general, interactions may be divided into two main categories *pharmacokinetic* (modification of absorption, distribution, metabolism or elimination) or *pharmacodynamic* (potentiation or antagonism of a pharmacological effect).

### Azole antifungals

#### Pharmacokinetic interactions

*Impaired itraconazole absorption:* Itraconazole capsules (& ketoconazole tablets) require an acidic GI tract for optimal dissolution and absorption. The oral availability of itraconazole capsules is halved when given with acid suppressants (antacids, H<sub>2</sub>-antagonists and proton-pump inhibitors) increasing the risk of treatment failure. There are several options for managing this interaction including:

- stopping the acid suppressant temporarily (antacids may be continued but should be dosed at least two hours apart from itraconazole)
- using an alternative antifungal (eg. terbinafine)
- giving itraconazole capsules with a glass of Coca-Cola™ or Pepsi™ which are acidic (pH 2.0 – 2.5) and temporarily reduce gastric pH sufficiently to allow itraconazole absorption

*Inhibitory effects on CYP450 enzymes:* Fluconazole, itraconazole and voriconazole inhibit CYP450 2C9, 2C19 & 3A4 and may increase the concentrations of many drugs [see the PML ("pink book") for a list of substrates for these enzymes p.137-143]. The impact is often profound eg. itraconazole increases triazolam concentrations by up to 30-fold, simvastatin by 10- to 20-fold and felodipine by 6-fold. Management of these interactions may involve:

- temporarily stopping a drug eg. 'statin'
- monitoring clinical effect with dose reduction if necessary
- use of a safer drug combination eg. temazepam is preferred over triazolam with triazoles as it has minimal CYP metabolism
- using an alternative antifungal

*Enzyme induction:* Itraconazole and voriconazole are hepatically metabolised and enzyme inducers eg. carbamazepine may reduce antifungal concentrations to subtherapeutic.

Table: Some pharmacokinetic data on antifungals

Drug	Elimination	Effect on CYP450
Fluconazole	80% renal	Inhibits 2C9, 2C19 & 3A4*
Itraconazole	Mainly 3A4	Inhibits 3A4*
Voriconazole	2C19, 3A4, 2C9	Inhibits 2C9, 2C19 & 3A4
Terbinafine	Multiple CYPs	Inhibits 2D6

\*Itraconazole has greater inhibition of CYP3A4 than fluconazole

#### Pharmacodynamic interactions

Itraconazole has negative inotropic effects and is suggested to cause or exacerbate heart failure in some individuals. This potential may be increased with concomitant use of other drugs with negative inotropic effects eg. verapamil.

#### Terbinafine

Terbinafine inhibits CYP2D6, which is involved in the metabolism of 25% of all drugs. This may result in loss of efficacy of codeine (because of inability to produce the active metabolite, morphine), and elevated concentrations of drugs such as haloperidol, metoprolol, nortriptyline and perhexiline. These interactions may be managed using a similar approach to the triazole interactions. Strong enzyme inducers may reduce terbinafine concentrations to ≈ 50% of 'normal'.

#### Other antifungals (in brief)

- *Amphotericin's* main drug interaction is increased nephrotoxicity with other nephrotoxic drugs eg. diuretics, aminoglycosides & NSAIDs.
- *Ketoconazole* is used rarely nowadays because of the availability of safer agents with greater efficacy, less toxicity and lower interaction potential.
- *Miconazole* inhibits CYP3A4 and CYP2C9 and sufficient drug (about 30%) is available systemically from the oral gel to inhibit drug metabolism. In particular, substantial increases in INR (up to 18) have occurred in warfarinised patients. Alternative antifungals (eg. nystatin) should be used with warfarin.

Contact your ward pharmacist or Drug Information (ext. 80900) if you need assistance with management of these interactions.