Update

Antifungals

What's New?

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As presented at a University of Toronto CME Conference (November 2003)

Patricia's case

- Patricia, 40, has advanced HIV
- CD4: 30/µL
- Presents with severe odynophagia and oral thrush
- Endoscopy reveals multiple white plaques in the esophagus which bleed when scraped

- Has taken fluconazole, 50 mg to 100 mg daily, on and off over the last five years
- Cultures from the endoscopy show *Candida albicans*

For more on Patricia, go to page 83.

Although many common, superficial, mucocutaneous fungal infections seen in family practice can be successfully managed with topical antifungal drugs, this review focuses on new systemic antifungal treatments.

What advances have occurred in antifungal therapy?

Major advances applicable to general practice include the development of:

1. ***Triazoles***, such as fluconazole. Fluconazole is more selective for fungal versus human sterols and has improved pharmacologic properties, making it more convenient and tolerable for patients.
2. ***Newer azoles***, such as voriconazole. Voriconazole has a broad antifungal activity, including *Aspergillus spp.* It has also shown efficacy comparible to amphotericin B, but with less toxicity. Voriconazole has demonstrated clinical fungicidal activity and toxicity profile superior to amphotericin B in invasive aspergillosis. It will be marketed in both an intravenous and oral form, but is currently not available in Canada.
3. ***Echinocandins***, a newer class of drugs. These drugs are large lipopeptide molecules with low bioavailability and, hence, only available for intravenous use. Caspofungin is

the first drug in this class and is currently available in Canada.

How will the pharmacologic properties and toxicities of antifungals affect use?

Azoles

In contrast to the other azoles, fluconazole has the advantage of not requiring an acidic pH for absorption. Therefore, it is easier to administer without concerns of interactions with H_2 blockers or proton pump inhibitors and has a bioavailability approaching its intravenous form.

Voriconazole's toxicity profile includes hepatotoxicity and rash, as well as transient visual disturbances. Drug interactions are a concern and if concominant drugs, such as cyclosporin, tacrolimus, phenytoin and warfarin are used, levels need to be monitored closely.

Polyenes

Amphotericin B is a parenteral drug and its toxicities relate to both drug and infusion related adverse effects. Nephrotoxicity and electrolyte disturbances are the main consequences of treatment; renal function and electrolytes must be monitored closely.

Caution must be taken when used with other potentially nephrotoxic agents. Intolerability of

Frequently Asked Questions

1. What antifungals are safe during pregnancy?

- Topical and vaginal preparations for the treatment of vaginal candidiasis are safe.
- Prospective studies have not shown any association with adverse pregnancy outcomes or congenital defects for fluconazole and other azoles.

2. My patient has grown yeast in the urine. What does this mean?

- Yeast in the urine in otherwise health ambulatory patients is usually of no significance. (Note: < 10% of patients who develop systemic candidiasis have disseminated from a urinary tract source.)

3. Are there any effective topical treatments for fungal nail disease?

- Topical agents have lower efficacy than oral agents.
- Consideration may be given when patient tolerance or drug interactions are a major issue.
- Topical treatments may also be used for mild disease, disease localized to the lateral nail or to keep patients disease-free.

4. How long should fungal nail disease be treated?

- Treatment of fungal nail disease is prolonged.
- Itraconazole, 200 mg, and terbinafine, 250 mg, daily and orally for 12 weeks have shown similar cure rates; however, terbinafine is more economical.
- Terbinafine, 500 mg, and itraconazole, 400 mg, both taken once daily for seven days one week a month for four months have similar mycologic cure rates of about 80%, which is lower than the 94% seen with continuous therapy.

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A followup on Patricia

In view of her long-standing history of exposure to lower doses of fluconazole, the concern was Patricia might have fluconazole-resistant *Candida albicans*. This is increasingly common in patients with HIV treated for long and intermittent periods of time with azole antifungal drugs.

Resistance was confirmed on lab testing (minimum inhibitory concentration = 64 mg/mL). Patricia was started on caspofungin, 50 mg daily intravenously, with marked improvement of the odynophagia and thrush.

this drug is the main reason for using alternative treatments, such as voriconazole and caspofungin.

Nystatin is another polyene that is still available and primarily used topically in Canada. It has few side-effects.

▶*Allylamines*

The only drug available in this class orally and for clinical use is terbinafine. Terbinafine has a long elimination half-life and accumulates in nails and skin, making it useful for the treatment of fungal nail disease. Hepatitis is a reported side-effect, but is uncommon.

▶*Echinocandins*

Caspofungin is a parenteral agent with poor oral bioavailability. There is no adjustment needed for renal function. Dose adjustment is required for moderate hepatic dysfunction; it is not recommended for use in severe hepatic failure.

Take-home message

- Newer antifungal drugs have been developed that offer more convenience and less toxicity for patients.
- Care and monitoring is warranted since oral antifungal drugs, such as the azoles and allylamines, may be associated with significant drug interactions
- Azole and, in particular, fluconazole-resistant *Candida spp.* continue to emerge in patient populations exposed to azoles over long periods of time (*i.e.*, HIV patients).

Adverse events include elevated liver enzymes and, rarely, hypercalcemia and anaphylaxis. In addition, a histamine-mediated reaction during infusion, with flushing, headache and pruritus, is reported. Drug interactions are not of major concern with caspofungin.

Concommitant use of caspofungin with cyclosporine is not recommended.

Randomized studies comparing caspofungin with amphotericin B for the treatment of systemic and severe mucocutaneous candidiasis have suggested equal efficacy, less drug-related toxicity and less toxicity-associated treatment failures with caspofungin. Dx

References available—contact *The Canadian Journal of Diagnosis* at **diagnosis@sta.ca**.