New Antifungals Boast Fewer Drug Interactions

The echinocandins' lower potential for interactions makes them 'ideal' for combination therapies.

BY DAMIAN McNAMARA
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MIAMI — The echinocandin antifungal agents appear to have little significant toxicity and may ultimately prove to be safer than the azoles or amphotericin B in terms of potential interactions, according to Paul O. Gubbins, Pharm.D.

"Echinocandins are an exciting new class. To date, there are few significant drug-drug interactions," Dr. Gubbins said at a meeting on fungal infections sponsored by Imedex.

The echinocandin caspofungin (Cancidas) has "no significant interaction" with cytochrome P-450 (CYP450) metabolism or P-glycoprotein, according to product labeling. The most abundant enzyme in the CYP450 system, CYP3A4, metabolizes about 50%-60% of all medicines.

In addition, the recently approved echinocandin micafungin (see accompanying story) is not a substrate or inhibitor for P-glycoprotein, a transmembrane efflux pump in the liver, intestine, kidneys, and blood-brain barrier.

With a lower potential for interactions, the echinocandins may be ideal for combination therapy, said Dr. Gubbins, chair of the department of pharmacy practice, University of Arkansas, Little Rock.

Toxicity is another important consideration, and it can relate to drug interactions. Traditional formulations of amphotericin B have renal toxicity that can produce additive drug interactions. "We're all familiar with the toxicities of amphotericin B. They are subtle and, in most cases, unavoidable. Consider renal-sparing alternatives" such as lipid amphotericin B or caspofungin, he suggested.

When prescribing traditional amphotericin B, monitor serum levels of drugs that have a narrow therapeutic index and are eliminated by the kidneys. Examples include aminoglycosides and 5-flucytosine.

Physicians are much more aware of drug interactions now than they used to be, and not just for antifungals, but for all drug classes, Dr. Gubbins said in response to a meeting attendee's question.

Some patients, such as organ transplant recipients, require closer monitoring. They often use drugs they cannot avoid, such as immunosuppressants, which increase the risk of fungal infections, he added.

The azoles have a complicated set of interactions. They can interact through multiple mechanisms, including CYP450 metabolism, gastric pH–dependent effects, and P-glycoprotein activity. "Interactions can be managed with alternative drugs in the affected class or by switching agents," Dr. Gubbins said.

Itraconazole leads the azole class in terms of potential interactions. The antifungal interacts through the CYP450 system with statins, especially lovastatin, simvastatin, and atorvastatin (Lipitor), and this can lead to skeletal muscle toxicity. Other affected agents include benzodiazepines, anxiolytics, immunosuppressants, and corticosteroids. With corticosteroids, he said, "The key is, it doesn't matter if you give these orally or IV, or if they're inhaled, you can get interactions."

Itraconazole can also have significant pH interactions. Dissolution depends on gastric pH, meal composition, and gastric emptying. Dr. Gubbins suggested that patients take the tablets with a high-fat meal that is dense in calories in order to slow gastric emptying or with a meal that contains enough protein to buffer the stomach contents. Other techniques for reducing pH interactions include spacing the administration of tablets, considering itraconazole oral solution, or switching to another agent. P-glycoprotein interactions are significant only for itraconazole, not for voriconazole (Vfend), or fluconazole, Dr. Gubbins said.

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Although several agents lower serum levels of itraconazole, including phenytoin, phenobarbital, rifampin, and rifabutin (Mycobutin), "remember that itraconazole affects other medications more than other medications affect itraconazole," he said. "The ones we're worried about are the ones with a narrow therapeutic index, such as digoxin."

Fluconazole affects more CYP450 enzymes than does itraconazole. "It's a whole different ball game," Dr. Gubbins said. Interactions depend largely on fluconazole concentration and are typically seen with doses greater than 200 mg.

Of particular concern are interactions between fluconazole and phenytoin or warfarin. "With phenytoin, if you do not see a response, it could be that [phenytoin] is inhibiting fluconazole."

"We also worry about the anticoagulant warfarin. … This interaction is almost guaranteed." Decreasing the warfarin dose might help, but "you almost always need to move to another antifungal."

Three CYP450 enzymes metabolize voriconazole extensively. Two have genetic polymorphisms that make interactions more likely in certain populations. For example, a CYP2C19 polymorphism is present in 2%-5% of whites, 12%-23% of Asians, and 38%-79% of South Pacific populations.

Drugs that affect voriconazole include phenytoin, rifampin, and rifabutin. Other potential interactions include carbamazepine, protease inhibitors, nonnucleoside reverse transcriptase inhibitors, benzodiazepines, and statins.

"How do we get around this? There are drugs we just don't use with voriconazole, such as rifampin or rifabutin," Dr. Gubbins said. He also suggested increasing the voriconazole dosage cautiously with phenytoin and monitoring patients taking warfarin closely. ■

Micafungin Approval Strengthens Antifungal Armamentarium

BY DAMIAN McNAMARA
Miami Bureau

MIAMI — Approval of micafungin by the Food and Drug Administration in March added another option for combatting infections caused by *Candida* or *Aspergillus* species, John R. Perfect, M.D., said at a meeting on fungal infections sponsored by Imedex.

Micafungin (Mycamine), an echinocandin antifungal agent, is indicated for prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation and for treatment of esophageal candidiasis. The echinocandin class also includes caspofungin (Cancidas), approved in 2001. Two more drugs in this class, anidulafungin and aminocandin, are in development.

"My suspicion is, [drugs in this class] will have a significant impact on how we manage patients," said Dr. Perfect, professor of medicine at Duke University Medical Center, Durham, N.C.

However, "candins lack any significantly good data for any fungal infections outside *Candida* or *Aspergillus*," he added.

One possible drawback is that the echinocandins are available only for intravenous infusion. Other considerations are the low urinary and brain concentrations achieved by these drugs, but Dr. Perfect added that "these things are not necessarily bad."

Dr. Perfect disclosed an affiliation with PLIVA, a company that manufactures generic fluconazole, ketoconazole, and metronidazole.

Both caspofungin and micafungin are effective in treating esophageal candidiasis. The echinocandins also have a long half-life and low toxicity, and require little dosage adjustment for patients with renal or liver dysfunction. And the agents have a low potential for drug interactions, which means they can be used in patients taking many other drugs, he said.

Although prevention of *Aspergillus* infections would be an off-label use of micafungin, the drug does have activity against these organisms, said Dr. Perfect. He predicted that the echinocandins would have a role in preventing *Aspergillus* infections in the future. "Candins for aspergillosis are trendy in combination, but no one has any data to support that today."

The "paradigm-changing study" for the echinocandins, Dr. Perfect said, was a randomized, double-blind, multicenter comparison between caspofungin and amphotericin B for patients with invasive candidiasis (N. Engl. J. Med. 2002; 347:2020-9). The patients were stratified by neutropenic status and Apache score, and there was no difference between the two drugs in outcome. The study design was practical, he added, because after 10 days of intravenous therapy, patients were switched to oral fluconazole. Intravenous therapy is very expensive, he noted.

Dr. Perfect and his colleagues examined caspofungin efficacy for 109 episodes of invasive candidiasis at Duke University Medical Center. The clinical cure rate was 83% (55/66) for bloodstream infections and 88% (23/26) for intraabdominal infections. "This drug performed very, very well with intraabdominal infections."

The failure rate for invasive candidiasis at Duke decreased from 26% in 2001 to 11% in 2003. "In this population, there are few ways you are going to improve on that success rate," he said.

Some people point out that echinocandins are very expensive, compared with the azoles, which are available as generics in many cases, Dr. Perfect said. "But there are a number of candins coming out, so hopefully the market will help with that.

"You have to look at your patient population and the flora you have in your hospital to see what is best," he said. For example, he would prescribe caspofungin if he had four patients with breakthrough *Candida glabrata* infections while on azole therapy. ■

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'We all hear that pregnancy is a time of joy, a natural high, and that pregnancy-related hormones are protective. The data, however, collide with these truisms.'

Brad D. Pearce, Ph.D., p. 49