New Antifungals

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Increasing use of antibiotics & immunosuppressives has encouraged the emergency of fungal infections.

New antifungals are introduced to widen the antifungal spectrum, to increase drug potency and to improve drug tolerability. These include

1. Azoles such as voriconazole (Vfend) and posaconazole (Noxafil).
2. Echinocandins such as caspofungin (Cancidas), micafungin (Mycamine) and anidulafungin (Eraxis).

Azoles

Like amphotericin, azoles target ergosterol in fungal cell membrane. Unfortunately there is cross-inhibition of some cytochrome dependent enzymes in humans by azoles, which contribute to drug toxicity & drug interaction potentials. Voriconazole is fungistatic against Candida, but fungicidal against Aspergillus. Posaconazole is the only azole active against zygomycetes.

The azoles have the advantage of oral administration. Intravenous formulation of voriconazole is made possible by the addition of a chemical called SBECD, which may accumulate in those with severe renal impairment and is potentially nephrotoxic. There is no intravenous preparation for posaconazole.

Oral absorption of voriconazole is reduced when taken with food. Voriconazole is metabolised in the liver and its dose should be reduced with hepatic impairment. Its pharmacokinetics is also affected by CYP2C19 enzyme genetic variability. Nineteen percent of Asians & 2% of Caucasians have poor CYP2C19 activity, resulting in high drug blood levels.

Voriconazole is usually well tolerated. Common adverse events include

1. Transient & reversible visual changes (photopsia). Patients should be advised to use with caution when driving a motor vehicle.
2. Hepatotoxicity which, on occasion, can be serious.
3. Prolonged treatment leads to photosensitivity.
4. Visual hallucinations are more common with intravenous formulation.

Oral absorption of posaconazole is increased with food, especially with fatty meals and is not affected by antacids. Oral absorption is even better with multiple dosing e.g. qid. Posaconazole is metabolised in the liver through glucuronidation & is excreted in the bile.

However, it inhibits liver CYP3A4 system, resulting in high blood levels of those drugs using the same system. Posaconazole also inhibits gastric P-glycoprotein, leading to unopposed GI absorption of those drugs using this pathway.

The safety profile of posaconazole seems to be better than voriconazole. Common adverse reactions include headaches & gastrointestinal complaints.

Echinocandins

Unlike amphotericin & azoles, they act specifically on fungal cell walls by inhibition of D-glucan synthase which is absent in mammalian cells.

Echinocandins are fungicidal against Candida & fungistatic against Aspergillus. Micafungin & anidulafungin have lower MIC90 for Candida than caspofungin.

They are only available as intravenous preparations due to their large molecular structures and poor bioavailability.

Infusion related reactions due to histamine release may occur with all echinocandins.

No dosage adjustment for caspofungin and micafungin is necessary for renal insufficiency. For patients with moderate hepatic impairment, a lower dose of caspofungin is advisable; but no adjustment is needed for micafungin.

Co-administration of cyclosporine with caspofungin may increase risk of hepatotoxicity (much less with micafungin and anidulafungin).

Enzyme inducers (e.g. phenytoin, rifampicin) may increase clearance of caspofungin; dose of caspofungin should then be increased.

Micafungin may raise sirolimus or nifedipine level.

Anidulafungin seems to have the least adverse effects among echinocandins.

Indications (Table 1)

Oesophageal Candidiasis

Fluconazole (Diflucan) remains the first choice. New
Azoles are indicated for fluconazole-resistant Candida. New echinocandins, though effective, are less preferred due to lack of oral formulation.

**Candidemia**

Fluconazole is indicated if there is no neutropenia and there is no prior exposure to azole. Otherwise, new echinocandins are preferred.

New antifungals are also indicated for non-albicans Candida, which are usually resistant to fluconazole, with the exception of posaconazole as it may take up to 1 week to achieve a steady drug level.

### Prophylaxis Against Invasive Fungal Infection

In USA, posaconazole is approved for prophylaxis against fungal infections in severely immunocompromised patients such as haematopoietic stem cell transplant patients (HSCT) with graft versus host disease (GVHD) and neutropenic patients with haemic malignancy. It was demonstrated to be better than fluconazole. However, the probability of breakthrough infections with posaconazole increased with low posaconazole blood levels. Therefore, monitoring posaconazole plasma concentrations is warranted in high-risk populations.

### Empirical Treatment of Invasive Fungal Infection in Patients with Febrile Neutropenia

Intravenous voriconazole, caspofungin or micafungin is preferred.

Salvage therapy with posaconazole may be considered for those refractory diseases.

### Treatment of Known Invasive Aspergillus Infection

Voriconazole has replaced amphotericin as the treatment of choice for invasive aspergillosis because of better tolerability & outcome. If Aspergillus is resistant to voriconazole, it is not certain whether change into another class of drugs (e.g. amphotericin or caspofungin) or combination therapy will work.

### Conclusion

These new antifungals are promising. However, they should be administered with prudence in view of their high cost and potential for emergency of resistant strains if abused.