AZOLES FOR THE TREATMENT OF INVASIVE FUNGAL INFECTIONS

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Azoles used for invasive fungal infections include two classes, the imidazoles (**ketoconazole**) and the triazoles (**itraconazole, fluconazole, voriconazole, posaconazole**). A number of agents are available for topical use in different indications but this is beyond the paper's focus. Azoles are usually recognized according to spectrum of activity and safety profiles. The imidazole ring is the synthetic component that confers activity to azoles. Triazoles are obtained by a slight modification of this ring and present similar or improved activity and less adverse effects. Azoles inhibit an enzyme required for the production of ergosterol an essential component of the fungal cytoplasmic membrane. However, since this enzyme is similar to one found in the human liver, drug interactions due to metabolism do occur. Because of important differences in activity and safety it is easier to understand each azole separately.

KETOCONAZOLE

Ketoconazole was among the first antifungal agents available for use. However, because oral absorption varies significantly between individuals according to the level of acidity in the stomach and because of its anti-androgenic properties it is uncommonly used in the fungal world. Ketoconazole remains pertinent in some cases for endocrinologists.

FLUCONAZOLE

Fluconazole, an imidazole, is well absorbed when given orally, distributes widely throughout the body and is mostly eliminated through the kidneys. It has very good activity against *Candida* spp. and is used as first line agent for treatment and prevention of most infections. For treatment of severe infections or in patients with an immune dysfunction, amphotericin B or an echinocandin is usually preferred. Fluconazole is also indicated for treatment of cryptococcal meningitis. Regarding safety, fluconazole is very well tolerated. Short term side effects include mostly headache, nausea, and vomiting. If used chronically, uncommon side effects include hair loss, anorexia, and slight increase in liver enzymes. Fluconazole inhibits human CYP450 3A4 in a dose dependant manner which may lead to drug interactions. Monitoring for efficacy and safety is warranted when fluconazole is administered with a medication known to interact.

ITRACONAZOLE

Itraconazole is a highly lipophilic imidazole. Oral absorption of the capsule formulation is improved with food. Since absorption is sometimes poor with the capsule it has been replaced by an oral solution. Its absorption is more predictable and improved when taken on an empty

stomach. Itraconazole is mostly used for treatment of dimorphic fungi (blastomycosis, histoplasmosis, sporothricosis, coccidioimycosis, paracoccidioidomycosis) and the mold *Aspergillus* spp. The most important adverse effect is the dose limiting nausea and vomiting. In more severe infections, a balance is required between the level of discomfort of the patient and response to therapy. Dividing the dose into twice daily administration and certain antiemetic medication such as prochlorperazine can help attenuate this side effect. Itraconazole is a more potent inhibitor of CYP450 3A4 than fluconazole and therefore has more drug interactions. Expertise in this matter should be considered when concomitant medications are used.

VORICONAZOLE

Voriconazole is considered as a second generation triazole with very good activity against yeast, dimorphic fungi and opportunistic molds including *Aspergillus* spp. Since it has certain affinity for several target sites, it has demonstrated good clinical efficacy in patients with fluconazole resistant *Candida* spp infection. However, its non-linear pharmacokinetic profile complicates dosing for different populations and patient conditions. Interpatient variability and more importantly intrapatient variability of serum concentrations have been associated with decreased efficacy and increased side effects and warrants concentration monitoring in selected patients. The easy to use oral and parenteral formulations of voriconazole offer some advantages for patients and from a cost perspective. The parenteral formulation should not be used in patients with moderate to severe renal dysfunction. Also, it is important to monitor clinical efficacy and adverse effects given the high potential for drug interactions.

POSACONAZOLE

Posaconazole is a highly lipophilic triazole with a broad spectrum of activity which includes yeast (fluconazole resistant strains as well), dimorphic fungi (*Histoplasma capsulatum, Blastomyces dermatidis, Coccidioides immitis, Sporothrix schenckii*), and molds (*Aspergillus* spp, zygomycetes). Posaconazole has a major role as prophylaxis in patients at high risk of filamentous fungal infections and for therapy of zygomycoses. It is only available in oral formulation which should be taken with fatty meals to ensure appropriate absorption. Posaconazole is mostly eliminated through the feces as unchanged drug. However, like other azoles, it does inhibit hepatic CYP450 3A4 and therefore has the potential for significant interactions with drugs metabolized by this pathway. Tolerability is similar to that of fluconazole with gastro-intestinal disturbances and headaches being the most frequent observed side effects.

Selected references:

1. Zonios DI, Bennett JE. Update on azole antifungals. Semin Respir Crit Care Med. 2008;29(2):198-210.