Organic Chemistry: An Indian Journal

Commentary | Vol 15 Iss 9

Azole Antifungals: An Update

Emily Brown*

Editorial Office, Organic Chemistry: An Indian Journal, UK

***Corresponding author:** Emily Brown, Editorial Office, Organic Chemistry: An Indian Journal, UK; E-mail: organicchem@journalres.com

Received: September 2, 2021; **Accepted:** September 2, 2021; **Published:** September 2, 2021

Commentary

Imidazoles and triazoles are two types of azole antifungals that have the same mechanism of action. Imidazoles have a two-nitrogen azole ring and are mostly used topically; triazoles, which have three nitrogens in the azole ring, have largely replaced them for systemic delivery. Triazoles have a better pharmacokinetic profile than imidazoles and do not impede human sterol production appreciably. They've been around for almost 30 years. Fluconazole, itraconazole, voriconazole, and posaconazole are among triazoles that will be reviewed in depth. The first azoles used in clinical practise were fluconazole and itraconazole. Newer azoles like voriconazole and posaconazole have been developed to overcome fluconazole's low efficacy against Aspergillus and other moulds, as well as to improve itraconazole's absorption, tolerability, and drug interaction profile. The structural similarities between voriconazole and fluconazole and posaconazole and itraconazole are striking. The cytochrome P450 enzyme 14-asterol-demethylase is inhibited by triazoles. This enzyme is involved in the biosynthesis of ergosterol, an important component of the fungal cell membrane. The inhibition of this enzyme causes a buildup of 14-a-methylsterols on the fungal surface, which stops the growth of the fungus. Fungistatic triazoles are commonly used. There are multiple clinically significant medication interactions with triazoles. Itraconazole and posaconazole are also inhibitors of gastric P-glycoprotein, but not fluconazole or voriconazole. P-glycoprotein is a transmembrane efflux pump that inhibits GI absorption and so limits systemic exposure to many medicines. As a result, inhibiting Pglycoprotein azoles may result in increased systemic exposure of medicines that are transported by this route. Because itraconazole-induced interactions have been widely researched, and both itraconazole and posaconazole inhibit CYP3A4, medications that have been shown to interact with itraconazole should be taken with caution in patients who are taking posaconazole. Drug interactions with triazoles include cyclosporine, tacrolimus, and sirolimus, as well as most calcium channel blockers, benzodiazepines, numerous statins and steroids, warfarin, and rifabutin. Carbamazepine, phenobarbital, phenytoin, rifampin, and rifabutin all reduce azole concentrations considerably. Terfenadine, astemizole, cisapride, pimozide, and quinine have been shown to extend Q-Tc and predispose to torsades de pointes. Finally, simultaneous treatment with triazoles (excluding fluconazole) with vinca alkaloids, cyclophosphamide, vinorelbine, and busulfan can result in enhanced cytotoxic chemotherapy-related damage. If an interaction is detected, using an azole should be done with caution. The lack of evidence for an interaction does not rule out the possibility of one, especially with the newer azoles.

Posaconazole is effective against most Candida and Aspergillus species in vitro. Scedosporium spp., Fusarium spp., Histoplasma spp., Coccidioides spp., Penicillium marneffei, Sporothrix schenckii, Blastomyces dermatitidis, Trichosporon spp., Cryptococcus neoformans, and various dematiaceous moulds are also susceptible. The enhanced action of posaconazole

Citation: Brown E. Azole Antifungals: An Update. Org Chem Ind J. 2021;15(9):37

© 2021 Trade Science Inc.

against zygomycetes is its most distinguishing feature when compared to other azoles. Posaconazole is licenced for the prevention of infections in highly immunocompromised patients, such as those who have had a Hematopoietic Stem Cell Transplant (HSCT) and have Graft Versus Host Disease (GVHD), as well as those who have hematologic malignancies and neutropenia due to chemotherapy. This recommendation was based on the results of two trials that compared posaconazole to fluconazole, fluconazole, and itraconazole, respectively. The first was a randomised, multicenter, double-blind, and double dummy trial in HSCT patients with GVHD who were given either 200 mg posaconazole three times per day or 400 mg fluconazole daily. The incidence of proved or probable fungal infections in the intention to treat population between randomization and day 112 was the major effectiveness end measure. Posaconazole was equally efficient as fluconazole in preventing invasive fungal infections, but it outperformed fluconazole in preventing aspergillosis. The second research was a multicenter, randomised, unblinded trial in patients undergoing chemotherapy for acute myelogenous leukaemia or myelodysplastic syndrome. Evaluators were uninformed of the treatment assignments. Patients were given 200 mg of posaconazole three times a day or 400 mg of fluconazole suspension or 200 mg of itraconazole solution twice a day. The treatment was given for the duration of neutropenia or for 12 weeks after randomization, whichever happened first, until invasive fungal infection occurred. In the intention-to-treat population, the primary end point was the occurrence of proved or probable fungal infection during prophylaxis. The use of galactomannan to diagnose the majority of aspergillosis breakthrough cases is still a point of contention in these two investigations. Posaconazole was found to be superior to the comparator in the prevention of invasive fungal infections with this caveat. Posaconazole is also licenced to treat oropharyngeal candidiasis in patients who have failed to respond to fluconazole or itraconazole. For this condition, the dose is 100 mg once daily or up to 400 mg twice daily for patients who have failed to respond to previous treatments. Posaconazole was found to be equally efficacious as fluconazole in treatment-naive patients and to have a decent response in refractory patients in the studies. Finally, despite the fact that posaconazole has not been approved for the treatment of refractory fungal infections, several uncontrolled case studies have shown a promising response rate for zygomycosis, histoplasmosis, fusariosis, coccidioidomycosis, or patients with chronic granulomatous disease in this setting.