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AN OVERVIEW OF AZOLE ANTIFUNGALS

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ABSTRACT

As the number of individuals with immune system suppression has grown in recent years, the danger of human fungal infections has significantly increased. Fortunately, there has been a rapid advancement in the treatment of fungal infections. It was discovered that combining already available azoles with additional antifungals is probably going to increase their efficacy. But after receiving antifungal medication, a number of circumstances might cause therapeutic failure or recurrence. These variables relate to the various properties of the antifungal(s) employed. Therefore, professionals should thoroughly research the various properties of antifungals in order to prevent these issues and further to make the best use of the antifungals. The goal of the current study was to identify variations in the pharmacology, pharmacokinetics, spectrum of activity, toxicity, and possible medication interactions of the related azoles. The azoles of interest are sufficiently diverse in terms of their pharmacology, pharmacokinetics, spectrum of activity, safety, toxicity, and potential drug interactions, according to the current review, which enables medical professionals to distinguish between these agents based on their individual properties when designing a patient's therapy.

Keywords: Human fungal infections, Azoles of interest, Different characteristics and development in the antifungal chemotherapy.

1. INTRODUCTION

Infectious disease is a condition in which the infecting agents do cause the body to react, which results in clinically manifest signs and symptoms. Humans and the surrounding microorganisms coexist peacefully, but an infection may arise from the microorganisms when the defence system is compromised or the concentration of pathogens reach an exceptionally high density. Infectious illnesses have been brought on by bacteria, viruses, parasites, fungus, prions, worms, and parasitic organism among others. Infections brought on by bacteria were formerly the most dreaded, but as methods of treating bacterial infections in patients became more effective, fungus have now replaced bacteria as the most dangerous pathogens [1]. Molds and yeasts are the two most common types of fungi. Mold colonies are made up of filamentous threads called hyphae, whereas yeasts are normally made up of a single, tiny, oval cell. Some fungi are dimorphic; depending on the external environment, such as temperature, they may either exist as yeasts or molds. Molds and yeasts are the two most common types of fungi. Mold colonies are made up of filamentous threads called hyphae, whereas yeasts are normally made up of a single, tiny, oval cell. Some fungi are dimorphic; depending on the external environment, such as temperature, they may either exist as yeasts or molds. [2, 3] Even while fungi are common in the environment, only a few species are frequently discovered in close proximity to people who might spread illness. The majority of fungi that primarily affect immunosuppressed people are frequently categorised as opportunistic pathogens (Candida and Cryptococcus), while a small number of fungi that are responsible for causing disease in healthy people are considered to be true pathogens (Histoplasma and Paracoccidioides) [4]. But it's clear that some opportunistic fungal infections can also lead to illness in otherwise healthy people (Candida vaginitis or Cryptococcus gattii outbreaks) [5,6] High morbidity and mortality are characteristics of invasive fungal infections, which are still challenging to identify, prevent, and treat despite becoming increasingly prevalent. [7]

2. TYPES OF FUNGAL INFECTIONS

1. Topical/superficial disease caused by fungal pathogens:

The outermost layers of the skin, nails, hair, and mucous membranes can develop superficial fungal infections. [8]

Dermatophytosis- Organisms that consume keratin are called dermatophyte fungus [9].

The stratum corneum of the epidermis and tissues made of keratin, such as the hair and nail, are infected by dermatophytes. Most superficial fungal infections are caused by Trichophyton spp., Microsporum spp., and Epidermophyton spp., while some yeast and other non-dermatophyte moulds can also be the culprits. [10]

Tinea pedis- The primary pathogens responsible for tinea pedis are Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum. Tinea pedis is a dermatophyte infection of the foot that mostly affects the toes and sole. This infection, which is the most prevalent dermatophyte fungal illness to afflict men [11], affects between 5 and 30 percent of the population. People who have tinea pedis may be more prone to subsequent bacterial infections, such as those caused by Group a streptococcus. [12]

Tinea corporis- T. rubrum and T. mentagrophytes, which affect the neck, trunk, and extremities, are two of the main causal organisms for tinea corporis. A finely defined circular lesion with erythema, scaling, and tiny blisters or pustules

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at the border is the characteristic of a tinea corporis lesion. The lesion typically has a diameter of 5 cm. Domesticated animals including cats, dogs, hamsters, and guinea pigs frequently transfer the fungus to people [11].

Tinea capitis- Trichophyton tonsurans is the most common cause of this illness, which often affects children and manifests as baldness and scaling on the scalp [13, 14].

Tinea unguium or onychomycosis (nails)

The main causes of onychomycosis are T. rubrum and T. mentagrophytes dermatophytes, which account for over 90% of toenail infections and 50% of fingernail infections [15–16].

1. **Malassezia infection**
   Malassezia spp. are widespread surface commensals of oily skin, including the scalp and chest, and they are linked to folliculitis, seborrheic dermatitis, and pityriasis versicolor [17].
2. **Malassezia folliculitis**
   A rash on the upper back and shoulders caused by Malassezia folliculitis can itch and look like acne [18].
3. **Subcutaneous Infection**
   Although they can spread, subcutaneous mycoses typically only affect the dermis and subcutaneous tissues.

Sporotrichosis- The most common subcutaneous infection is sporotrichosis, which is brought on by the dimorphic fungus Sporothrix schenckii . The fungus is present in soil and plants, and it typically injures farmers and gardeners, particularly those who take care of roses. It is a small cutaneous or subcutaneous lesion that has the potential to grow and spread through the lymphatic system. The condition known as lymphocutaneous sporotrichosis is not life-threatening [19].

Chromoblastomycosis- The Dematiaceae family of fungi, which includes Fonsecaea pedrosoi, Cladosporium carrionii, Fonsecaea compacta, Phialophora verrucosa, and Rhinocladiella aquaspersa, are responsible for the chronic cutaneous or subcutaneous fungal infection known as chromoblastomycosis [26]. They can be found in wood, vegetable waste, and soil. Raised, crusty skin lesions are the symptoms.

Chronic mucocutaneous candidiasis- A uncommon illness called chronic mucocutaneous candidiasis involves persistent C. albicans infection of the mucous membranes, which may spread to the skin and nails. Though the underlying problem is still not well understood, the disorder is linked to defective cell-mediated responses to Candida [27,28]. White fissured lesions, hyperkeratotic, granulomatous, and vegetative lesions, as well as an autosomal recessive characteristic linked to endocrine problems such hyperparathyroidism are some of the signs.

Systemic fungal infections- The endemic or dimorphic mycoses are two separate categories of systemic fungi diseases. Unlike opportunistic mould and yeast infections, which are saprophytes and only invade an immunocompromised host, these infections are brought on by real pathogenic fungi [36,37]. These infections pose a serious risk to health and are frequently fatal. Patients with solid organ transplants who use immunosuppressive drugs to reduce the risk of rejection are more vulnerable to systemic fungal infections [2,3].

3. CLASSIFICATION OF AZOLE GROUP

According to fig. 1, the azoles are subclasses of five-membered nitrogen heterocyclic ring compounds that contain at least one additional nitrogen, sulphur, or oxygen atom. The parent compounds have two double bonds and just one ion pair of electrons from each heteroatom in the ring, and they are aromatic. In azoles, the heteroatom that is not a component of a double bond is numbered first, immediately by the other heteroatom [20].

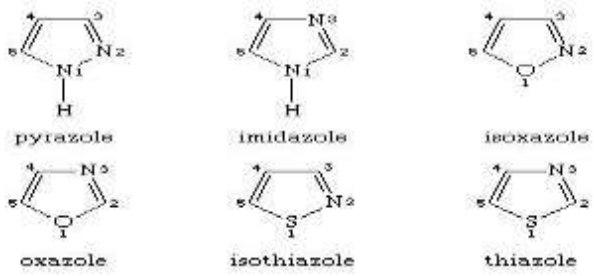

Fig. 1: The different basic structural rings of azoles

Azoles are classes of fungi static substances having wide-ranging action. Imidazole's and triazoles are the two groups into which they are divided. Each group's members are structurally related, and changes to side-chain structure determine both the antifungal activity and level of toxicity.[21]

4. PHARMACOLOGY OF AZOLE

Mechanism of action- Fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole are some of the azoles with systemic action. By inhibiting CYP-dependent 14-demethylase, which is required for converting lanosterol to ergosterol, the azoles have a fungistatic action. The stability of the fungal cell membrane depends on ergosterol, and

inhibiting its production compromises membrane integrity [22]. Additionally, the triazoles indirectly target several stages of the process for ergosterol production. For instance, in C. albicans that is fluconazole-sensitive, fluconazole only partially inhibits the synthesis of ergosterol and totally blocks the synthesis of obtusifoliol, but voriconazole completely inhibits the production of both ergosterol and obtusifoliol 5. The enzyme 3- ketoreductase, which C. neoformans uses to convert the 3-ketosteroid obtusifolione to obtusifoliol, may likewise be inhibited by itraconazole and fluconazole. [23]

Spectrum of activity- Azoles have a wide range of action against moulds and yeasts. However, as this therapeutic class grows, variations in the distinct medicines' activity spectra become apparent. The discrepancy in the spectrum of action may be explained by the different ways that different species inhibit 14-demethylase and secondary targets. Although they are infrequently employed for this purpose, azoles also have some antibacterial properties. The majority of important fungi and yeasts are resistant to miconazole's broad antifungal range.[24] Sensitive organisms include Blastomyces dermatitidis, Coccidioides immitis, Paracoccidioides, Histoplasma capsulatum, Candida species, including (C. Krusei, C. Inconspicua, C.Albicans, C. Lusitaniae, C. Glabrata, C. Guilliermondii, C.Tropicalis, C. and C. Parapsilosis), Cryptococcus neoformans, and Aspergillus fumigatus [24] Similar to miconazole in terms of its antifungal range, ketoconazole is more potent against C immitis and a few other yeasts and fungi. [25] C. neoformans and Coccidioides immitis are both susceptible to fluconazole, while Aspergillus species are not species of Fusarium and the zygomycosis agents. [25] Itraconazole is typically fungistatic to numerous yeasts and exhibits fungicidal action against filamentous fungi and some strains of C. neoformans. When used against the majority of fluconazole-susceptible and fluconazole-resistant Candida species, it has moderate to high activity (except C. Glabrata). [25]

5. PHARMACOKINETICS OF AZOLE

Absorption, distribution, biotransformation and excretion [29, 30]-The azoles are weak lipophilic bases chemically. After oral administration, they have an excellent relative or absolute bioavailability (except the capsule form of itraconazole). A reduction in stomach acidity might decrease the bioavailability following delivery via oral route of the azoles, with the exception of fluconazole, which requires an acidic environment to dissolve. There are contradicting accounts, however it seems that taking the medication with food speeds up absorption. Elevated gastric pH has a considerable impact on how well the solid oral dose forms of itraconazole and ketoconazole dissolve in the stomach [31]. Fluconazole requires substantially less biotransformation to be removed from the body than the other azoles since it is hydrophilic and highly soluble in water. Itraconazole and voriconazole have a low solubility in aqueous solution and are very lipophilic [32]. The main oxidative drug-metabolizing enzyme in humans, CYP3A4 is inhibited by azoles [33]. The affinities of the azoles for this enzyme vary. Additionally, fluconazole and voriconazole both inhibit CYP2C9/19, and fluconazole also blocks the UGT2B7 pathway [34]. The main method of removal is by hepatic metabolism [32] To be excreted from the body, azoles need a lot of oxidative (CYP) metabolism [32]. Only 2-4% of a dosage given orally shows up in urine unaltered. Itraconazole undergoes active metabolite metabolism, which may greatly increase the drug's antibacterial effectiveness. 20% of the metabolites are removed in the urine, and the biliary route accounts for the majority of excretory pathways (>80%) [34]. Several transport proteins, which are expressed in tissues all across the human body, help with drug disposition. The interactions of the azoles with transport proteins differ [35, 36]. With measurable amounts in saliva, milk, and cerumen, the azoles seem to be broadly dispersed throughout the body. With the exception of fluconazole, which reaches 50–90% of plasma concentrations, cerebral spinal fluid penetration is relatively low. With the exception of fluconazole, the majority of azoles are strongly protein-bound in the bloodstream (>95%), mostly to albumin [35, 36]. The liver, adrenal glands, lungs, and kidneys have the largest quantities of azoles. The most well-known efflux transport protein, P-glycoprotein, interacts with itraconazole and ketoconazole [35, 37]. Itraconazole and ketoconazole interact with the breast cancer resistance protein (BCRP), a different transporter [35, 36]. Although the relevance of these interactions with BCRP has not yet been fully clarified, they may help to partially explain several interactions that cytochrome P450 interactions alone were previously unable to effectively explain [35, 36]. The half-life of the azoles' rate of elimination appears to be dose-dependent: the higher the dosage, the longer the half-life [35, 36]. A biphasic elimination pattern is also seen, with fast clearance in the first 1-2 hours and a gradual drop during the next 6–9 hours. Time to effectiveness may take longer than with medications like amphotericin B because of the extended half-life and mode of action (impaired production of the fungal cell membrane).

6. ADVERSE EFFECT AND TOXICITY

The azoles administered orally have a number of adverse effects. Cardiopulmonary (hypotension, peripheral/pulmonary edema), CNS (dizziness, headache, seizure), dermatologic/hypersensitivity (anaphylaxis, eosinophilia, pruritus, rash), electrolyte disturbances (hypokalemia), gastrointestinal (abdominal pain/dyspepsia, diarrhea, disguise, nausea/vomiting), hematological (anemia, myelosuppression (alopecia, fever). But it's possible to develop nausea,

vomiting, and hepatic impairment, especially with ketoconazole [38].nParticularly with ketoconazole, altered testosterone and cortisol metabolism has been documented [38]. Ketoconazole medication may cause reproductive issues in dogs. Vision disturbances are one of the side effects of voriconazole that can occur in people [39]. Congestive cardiac failure has been linked to the use of itraconazole [40].

7. INTRACTION

Since many azoles are lipophilic, interactions involving their biotransformation and disposal are involved. Several diverse processes contribute to the azoles' drug interactions. Through a variety of mechanisms, including pharmacodynamic, pH, complexation and electrostatic interactions, CYP and P-glycoprotein, these substances can interact with medications [41]. The azoles' pharmacokinetic interactions are a result of their physicochemical characteristics. Itraconazole and ketoconazole are susceptible to metabolic and pH-based interactions. Agents that are cationic, elevate stomach pH, or are lipophilic CYP3A4 substrates with low oral bioavailability are drugs that are likely to interact with these azoles [41]. All azoles are weak bases, and weakly basic substances dissolve more slowly at higher pH levels. As a result, changes in stomach pH can affect how well azoles like itraconazole capsules are absorbed. [43]. Concurrent use of cimetidine, ranitidine, anticholinergic drugs, or stomach antacids reduces the absorption of all azoles except fluconazole. [43]

8. CONCLUSION

In recent years, there has been an accelerated growth in the field of fungal infection treatment. The majority of clinically significant Subcutaneous Infection, topical infection, Malassezia folliculitis have responded exceptionally well to treatment using drugs from the azole group. To utilise these drugs effectively, clinicians must be aware of the variations in toxicity and the possibility of drug-drug interactions.

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