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POSACONAZOLE: A PROMISING BREAKTHROUGH FOR MUCORMYCOSIS TREATMENT

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Abstract

Posaconazole, a novel triazole antifungal medication, shares the same active mechanism as other azoles by inhibiting lanosterol-14a-demethylase, a key enzyme involved in ergosterol synthesis. This mechanism is effective against most fungi, except Pneumocystis and Pythium. Posaconazole exhibits a strong affinity for this target due to its distinct chemical structure, which allows it to combat even modified forms of fluconazole and voriconazole. It is widely distributed in the body, with a particular affinity for the liver, and has shown excellent tolerance in long-term studies. Adverse events associated with posaconazole treatment are generally mild and include minor gastrointestinal and neurological complaints. Posaconazole has demonstrated promising clinical efficacy in treating fungal infections that are often resistant to existing therapies, such as aspergillosis, fusariosis, and emerging Zygomycosis. Common side effects reported during posaconazole treatment include fever, diarrhea, nausea, vomiting, and headaches. Clinical trials have also noted elevated liver enzyme levels, hyperbilirubinemia, and hepatocellular damage, indicating the importance of monitoring these parameters during posaconazole therapy. This review aims to consolidate current knowledge on Posaconazole's pharmacokinetics, pharmacodynamics, toxicity, resistance, clinical experience in specialized populations, and novel treatment strategies to provide a comprehensive understanding of the drug's clinical utility.

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Introduction:-

The term Mucormycosis, also known as Zygomycosis, was coined by RD Baker, an American pathologist. It is a deceptive fungal disease characterized by rapid progression. Mucormycosis is caused by fungi belonging to the Mucorales order and the Mucoraceae family, first described by Paultauf in 1885. It is the third most common invasive fungal infection, following candidiasis and aspergillosis. Typically, it affects individuals with weakened immune systems, rarely occurring in healthy individuals. The infection occurs when rapid growth and invasion of fungal species follow tissue damage in immunocompromised individuals (57,59,60). These fungi are found in various

ecosystems and primarily affect individuals with underlying health issues or those taking antiretroviral drugs. Inhalation of fungal particles from the air can lead to sinus or lung infections, while skin damage such as cuts or burns can result in skin infections. Controlling these diseases is challenging due to difficulties in diagnosis, similarity to aspergillosis, and limited diagnostic tools. Prompt treatment, including surgery and antifungal therapy, is essential. Resistance to certain antifungal drugs limits treatment options, but the approval of new triazole antifungal drugs like saavoncole by regulatory agencies has expanded the treatment arsenal. However, comparative clinical data and appropriate use of different antifungal agents and strategies need further discussion. [1-10,53]

History:

The initial documented case of Mucormycosis dates back to 1885 when Paultauf, a German pathologist, described it as Mycosis Mucorina. In subsequent years, there has been a significant increase in the incidence of Mucormycosis, particularly among individuals with compromised immune systems, observed mainly during the 1980s and 1990s. A study conducted in France focused on the prevalence rate, revealing an annual increase of 7.4%. Furthermore, reports have indicated the possibility of seasonal variation in Mucorales occurrence, with cases documented worldwide. [2,11-14, 61]

Posaconazole drug:

Posaconazole is an azole antifungal medication that shares a similar chemical structure with itraconazole but differs significantly from fluconazole (58) and voriconazole (15, 16) (Fig. 1). It belongs to the class of systemic triazole antifungal drugs and operates through the same antifungal mechanism as other azole derivatives (17, 18). Posaconazole has demonstrated effectiveness against various fungi, including Candida spp., Aspergillus spp., Cryptococcus, and certain agents of Mucormycosis and fusariosis in adults (19-23).

Currently, there are four approved classes of antifungal drugs for treating fungal infections: polyenes (e.g., amphotericin B)(62) azoles (e.g., ketoconazole, itraconazole, fluconazole, and voriconazole), flucytosine, and echinocandins (e.g., caspofungin) (24-26). The existing antifungal armamentarium comprises formulations of amphotericin B (AmB), echinocandins, flucytosine, and triazole antifungals (27).

Posaconazole is available in three forms: oral suspension (40 mg/mL), delayed-release tablets (100 mg), and intravenous administration (18 mg/mL). The oral suspension and delayed-release tablets are approved for patients aged 13 years and older in the USA, or adults aged 18 years and older in Europe, while intravenous administration is limited to patients 18 years and older. Posaconazole is licensed for prophylaxis against fungal infections (IFD) in two patient populations: (1) patients undergoing remission induction therapy for acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) who are expected to develop chronic neutropenia and are at high risk of developing IFD, and (2) recipients of allogeneic hematopoietic stem cell transplantation (HSCT) who receive high-dose immunosuppressive drugs for graft-versus-host disease and are at high risk of developing IFD (17, 28). Additionally, posaconazole is approved for the treatment of oropharyngeal candidiasis, for patients intolerant to first-line treatment for IFD, and salvage treatment of IFD caused by rare pathogens such as fusariosis, chromoblastomycosis, mycetoma, and coccidia (29, 30).

Posaconazole, marketed as Noxafil by Schering Corporation in Kenilworth, NJ, has received approval from the Food and Drug Administration (FDA) as a prophylactic agent against Aspergillus and Candida infections in immunocompromised patients. This includes patients undergoing hematopoietic stem cell transplantation with graft-versus-host disease and patients with hematological malignancies undergoing chemotherapy (27, 30). Studies have demonstrated its promising efficacy in the treatment of fungal infections. (54,55)

Chemical Structure:

Posaconazole is derived from itraconazole through the substitution of chlorine atoms with fluorine atoms in the phenyl ring and hydroxylation of the triazolone side chain. These modifications enhance its potency and broaden its spectrum of activity (41, 42). Figure 1 depicts the structural formulas of posaconazole and itraconazole (41, 18).

Naturally, posaconazole is known as 4-[4-[4-[4-[[[(3R, 5R)-5-(2,4-difluorophenyl)tetrahydro-5-(1H-1,2,4-triazol-1-ylmethyl)-3-furanyl]methoxy]phenyl]-1-piperazinyl]phenyl]-2-[(1S,2S)-1-ethyl-2-hydroxypropyl]-2,4-dihydro-3H-1,2,4-triazol-3-one. Its chemical formula is C37H42F2N804, and it has a molecular weight of 700.78 (41, 30)

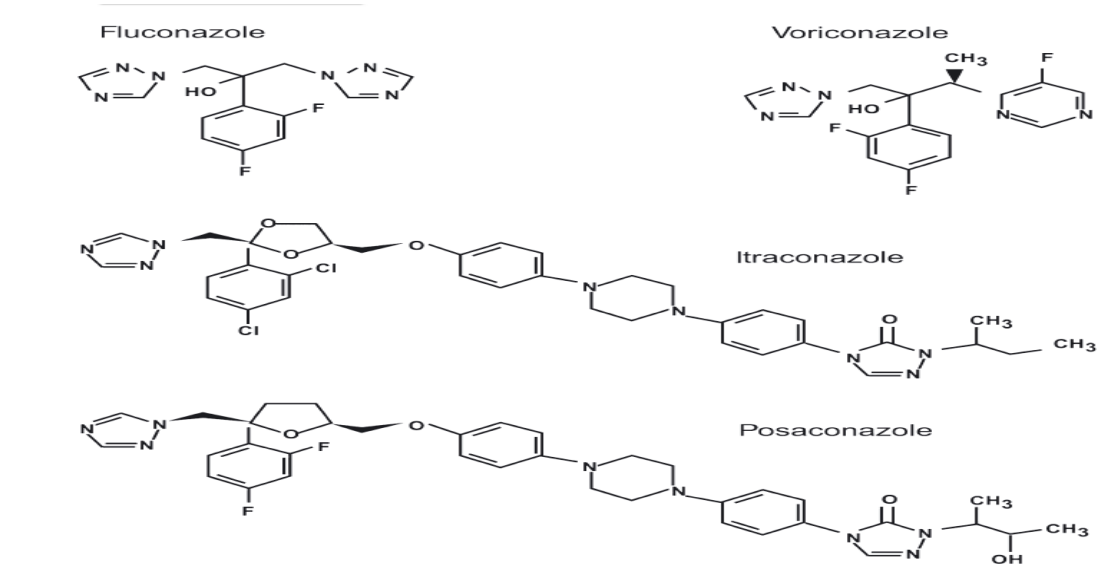

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Fig No 1:- Chemical structure of Fluconazole, Voriconazole, Itraconazole, posaconazole.

Basis of discovery:-

Azole antifungals, discovered nearly 30 years ago, currently represent the largest group of antifungal agents used in clinical practice. Their primary mode of action is the inhibition of lanosterol 14α-demethylase, a fungal cytochrome P450 enzyme involved in the synthesis of ergosterol (43, 44). Ergosterol is a crucial component of the fungal cell membrane, and its depletion can impede fungal growth and result in cell death (43, 44, 45).

Modifications to the azole class led to the development of triazole-containing agents, which exhibit enhanced binding to fungal P450 enzymes in the spine (43, 44). The first-generation triazoles, fluconazole, and itraconazole, significantly improved the treatment of various serious fungal infections, including candidiasis. However, these earlier agents have limitations in terms of efficacy and tolerability. Consequently, efforts have been made to develop new triazoles to address these limitations, leading to the introduction of voriconazole (Vfend; Pfizer) and more recently, posaconazole (Noxafil; Schering-Plow).

Drug properties:-

Posaconazole is an antifungal drug belonging to the triazole class, similar in formulation to itraconazole. It possesses a range of fungicidal properties and is effective against various fungal pathogens like Candida and Aspergillus. [42,43,45,56]

The first generation of azoles	Imidazole	Ketoconazole
		Clotrimazole
		Bifonazole
		Miconazole
The second generation of azoles	Triazoles	Itraconazole
		Fluconazole
The third generation of azoles	Triazoles	Posaconazole
		Voriconazole

Table 1:- Some azoles used in medicine (used topically and/or systematically).

Synthesis of Posaconazole drug:-

A well-established method for synthesizing posaconazole involves the enzymatic desymmetrization of a homochiral diol (33) using Novo SP 435 hydrolase and vinyl acetate. This step is followed by iodocyclization, resulting in the formation of compound 34 (Figure 2). Researchers have tested 169 different hydrolases to improve the efficiency of this initial step. In the subsequent transformation, the iodine in the 34th position is substituted by a 1,2,4-triazole

group, and the acetate group is replaced with tosylate, yielding compound 35. Under specific conditions, compound 35 reacts with compound 36, while simultaneously removing the benzyl group, forming the desired product, posaconazole. These procedures have been documented in references [47,48,49,50,51].

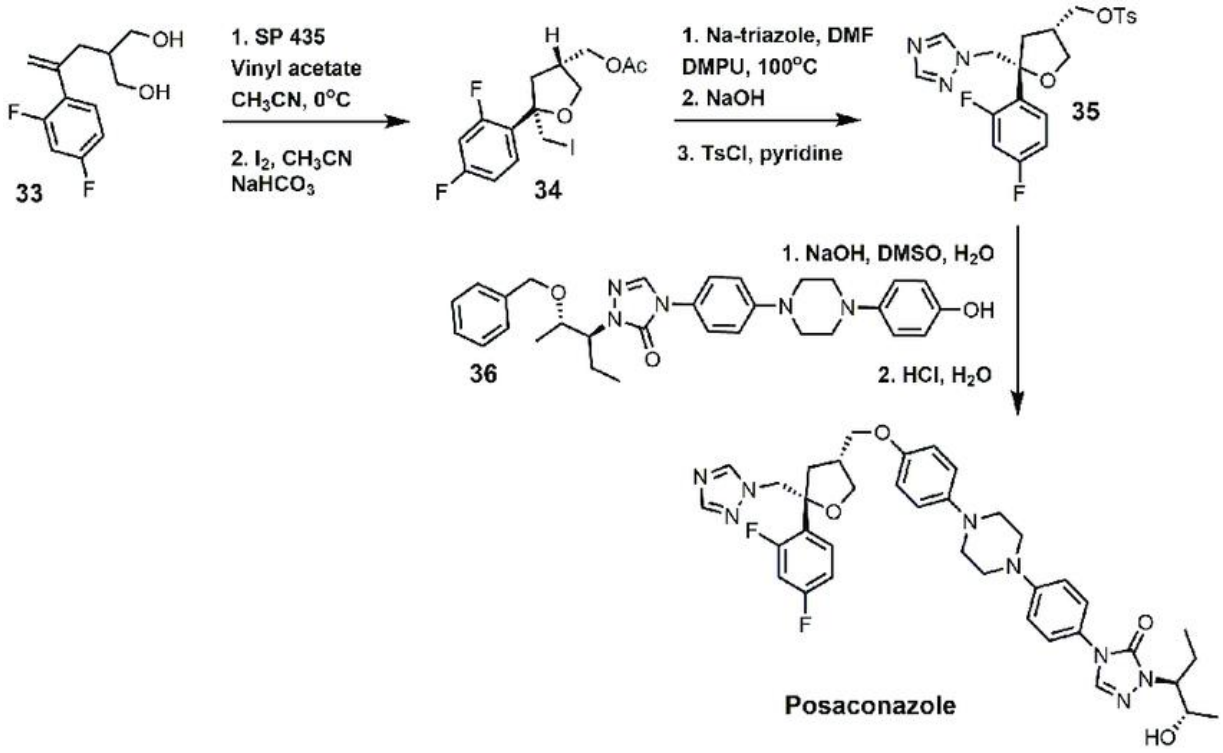

Figure 2:- Synthesis of posaconazole.

Pharmacology:-
Similar to other triazole antifungal drugs, posaconazole acts by inhibiting the activity of lanosterol-14-alpha-demethylase (30-32), an enzyme found in fungi. By targeting this enzyme, posaconazole interferes with the synthesis of ergosterol, a crucial component of the fungal cell membrane. Consequently, the depletion of ergosterol disrupts the integrity of the cell wall, resulting in cell death or impaired growth (27).

Mechanism of Action:-
Posaconazole, similar to other azole compounds, exerts its antifungal effects by inhibiting the enzyme lanosterol 14α-demethylase. This inhibition disrupts the biosynthesis of ergosterol, a critical component of the fungal cell membrane (refer to Fig. 1). Consequently, the levels of methylated sterol precursors increase while the presence of ergosterol decreases within the fungal cell membrane. This disruption hampers the formation and proper functioning of the fungal membrane, which is believed to be the mechanism responsible for the fungicidal activity of posaconazole (17, 28).

Pharmacodynamics: -
Researchers incorporate factors such as in vivo drug availability and in vitro antimicrobial susceptibility (MIC) of the pathogen as predictors of Posaconazole's in vivo antimicrobial efficacy. These factors are considered within the framework of pharmacokinetics /pharmacodynamics (PK/PD). The aim is to establish a correlation between the drug exposure of posaconazole and its consistent antifungal response against the pathogen, as indicated by the MIC.

Multiple studies, specifically involving maternal subjects, have confirmed the relationship between posaconazole exposure and its antifungal activity against the pathogen, as determined by the MIC. [17]

Pharmacokinetics:-

Property	**Posaconazole**	
	Value	**Comments**
Absorption $C_{max,}$ ng/ml cave, ng/ml AUC, ng.ml/h	 851 723 9093	Large in volume, large in volume, No effect on stomach pH (20)
Bioavailability	Variable	
Protein binding	>90%	
Volume of distribution	1774 L	Working in the CNS, bone and eye infections
Time to maximum concentration	4 To 5 hrs.	
Metabolism	Hepatic: glucuronidation to inactive metabolites	
Elimination half-life	25–35 hours	
Elimination route	<1% removed unchanged from urine; 66% removed unchanged along the way	

Table 2:- Summarizes the pharmacokinetic properties of posaconazole [27, 30–32, 38-40].

Composition of posaconazole with other anti-fungal:-

In vitro studies investigating the combination of posaconazole with other antifungal agents, such as flucytosine, amphotericin B, or echinocandins, have yielded mixed results and have not provided clear contraindications. The combination showed indifference in some cases, meaning no significant interaction or effect was observed. However, in certain instances, a synergistic effect was observed, indicating that the combination of posaconazole with these agents resulted in improved antifungal activity.

These findings suggest that posaconazole may have superior effects compared to other azoles in certain situations. However, it is important to note that the efficacy and safety of combination therapy should be evaluated through clinical studies and individual patient considerations. [15,37]

Indications:-

The FDA has approved the use of posaconazole as a prophylactic treatment in patients aged 13 years and older who have a high risk of developing Aspergillus and Candida infections. This high risk is typically associated with severe immunosuppression, such as that resulting from hematopoietic stem cell transplantation and graft-versus-host disease.

Dosing:-

The posaconazole suspension has been demonstrated to be administered in different dosing regimens for prophylaxis or treatment of invasive fungal diseases (IFDs). For prophylaxis, it can be given as 200 mg three times daily (TID). In the treatment of IFDs or in cases where patients do not tolerate first-line treatment, the suspension can be given as 400 mg twice daily (BID) or 200 mg four times a day (QID).

In addition to the suspension, a delayed-release tablet formulation of posaconazole is available. The recommended dosing for this tablet is a loading dose of 300 mg twice daily (BID) on the first day, followed by a maintenance dose of 300 mg once daily (QD) thereafter.

It is important to note that these dosing regimens have been supported by research and are cited as examples. The specific dosage and duration of posaconazole treatment should be determined by healthcare professionals based on individual patient factors and the targeted fungal infection.[17]

Drug & Food Interactions:-

A randomized, open-label, four-way crossover study was conducted in 20 healthy men to investigate the impact of meal status and fatty foods on the bioavailability of posaconazole suspension and delayed-release tablet. The results indicated that the bioavailability of posaconazole suspension was significantly higher compared to the tablet formulation. Furthermore, the presence of high-fat diets significantly increased the bioavailability of posaconazole suspension.

In summary, the study findings demonstrated that the absorption and availability of posaconazole were influenced by the formulation (suspension vs. tablet) as well as the prandial status and the consumption of fatty foods. The suspension form exhibited superior bioavailability compared to the tablet, and the presence of high-fat meals further enhanced the bioavailability of posaconazole suspension.[52]

Drug-Drug Interactions:-
Drug-drug interactions of Posaconazole drug are described in the summarized way in Table No. 3

Concomitant drug	**Interaction**	**Recommendation**
Cyclosporine	Increase in cyclosporine concentrations	Reduce cyclosporine dose by 25%, monitor levels frequently
Tacrolimus	Increase in tacrolimus concentrations	Reduce tacrolimus dose by 33%, monitor levels frequently
Midazolam	Increase in midazolam concentrations	To monitor the side effects of benzodiazepine, adjust the dose as needed
Sirolimus	Increase in sirolimus concentrations	Monitor sirolimus levels regularly, adjusting the dose as needed
HMG-CoA reductase inhibitors (statins) metabolized by CYP3A4	Increase in statin concentrations	Consider reducing the dose of statins to reduce the risk of rhabdomyolysis
Calcium channel blockers metabolized by CYP3A4	Increase in concentrations of these agents	To monitor hypotension, reduce the dose if necessary
Rifabutin	Increase in rifabutin concentrations Decrease in posaconazole concentrations	Avoid simultaneous use unless the benefits outweigh the risks
Phenytoin	Increase in phenytoin concentrations Decrease in posaconazole concentrations	Avoid simultaneous use unless the benefits outweigh the risks
Cimetidine	Increase in posaconazole concentrations	Avoid simultaneous use unless the benefits outweigh the risks
Vinca alkaloids (vincristine, vinblastine)	Increase in vinca alkaloid concentrations	Consider a reduction in the amount of vinca alkaloids to reduce the risk of neurotoxicity
Ergot alkaloids)	Increase in ergot alkaloid concentrations	Opposed (due to increased QT power
Terfenadine, astemizole, pimozide, tiapride, quinidine	Decrease in concentrations of these agents	Disputed (due to increased QT power)

Table 3:- Drug interactions with posaconazole [27, 30-32]

Toxicity:-
To date, no definitive correlation has been established between posaconazole exposure and treatment-related toxicity (17, 33, 34). In the development of a delayed-release tablet, plasma toxicity levels above 3.75 mg/L were selected based on the 90th percentile of exposure observed in previous clinical studies where the oral suspension of posaconazole was safely administered (17, 33).

Commonly reported adverse events (AEs) associated with posaconazole treatment include gastrointestinal disorders such as nausea, diarrhea, vomiting, hypokalaemia, and fever. These AEs can typically be managed through clinical observation (17, 28, 35, 36).

In the subsequent sections, we will discuss two major concerns in clinical settings related to posaconazole: hepatic toxicity and cardiotoxicity.

Conclusion:-

Posaconazole exhibits a broader spectrum of activity compared to other azole antifungal medications, making it effective against a wider range of fungal species, including zygomycetes. Moreover, posaconazole demonstrates a lower susceptibility to common mechanisms of resistance, such as efflux pumps and genetic mutations in the target enzyme. This attribute contributes to its ability to combat fungal strains that may have developed resistance to other azoles.

The introduction of posaconazole in the treatment of systemic fungal diseases has marked significant advancements. Its broader spectrum of activity and reduced susceptibility to resistance mechanisms have expanded the options available for treating these conditions, providing improved outcomes for patients.[15]

Conflict of Interest:-

The authors have declared no conflict of interest.

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