Antifungal Pharmacology: Current Concepts
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ABSTRACT:
Drug toxicity is no longer the primary limiting factor in the management of invasive mycoses thanks to the development of new antifungal drugs during the past ten years, such as echinocandins and second-generation triazoles. However, a lot of these more recent antifungal medications have significant restrictions on their range of activity, pharmacokinetics, and special propensity for pharmacokinetic drug-drug interactions and peculiar toxicities brought on by prolonged usage. In order to increase the safety and effectiveness of systemic antifungal therapy, this article discusses essential pharmacological characteristics of systemic antifungal drugs as well as developing methodologies, such as pharmacokinetic-pharmacodynamic optimization and therapeutic drug monitoring.

Keywords: cytochrome, gastrointestinal, inhibitory concentration, therapeutic drug monitoring

INTRODUCTION:
Squibb Laboratories' introduction of amphotericin B-deoxycholate in 1958, following arduous efforts to create orally bioavailable formulations of more than 200 polyene macrolide antibiotics produced by the soil actinomycete streptomycyes [1], effectively marked the beginning of the era of systemic antifungal chemotherapy.

Despite the fact that amphotericin B was to become the gold standard treatment for serious fungal infections for more than 40 years, adverse infusion effects and dose-limiting nephrotoxicity prompted the ongoing search for equally effective but less toxic substitutes that could be given both intravenously and orally.

With the invention of fluconazole in 1990, this objective was finally attained more than three decades later. Fluconazole, in contrast to earlier azoles like miconazole and ketoconazole, had excellent oral bioavailability, predictable linear pharmacokinetics with wide distribution into many tissues, including the cerebral spinal fluid and vitreous chamber of the eye, and a significantly lower risk of drug interactions and toxicity in critically ill patients. [2]
Patients with AIDS who had oropharyngeal candidiasis responded well to fluconazole treatment; however, resistance may develop in long-term patients with diminishing CD4+ cell counts. [3] For mucosal and systemic yeast infections, fluconazole soon rose to the top of the list of antifungal medications most frequently recommended.

However, there hasn't been much done to combat opportunistic moulds, such as "QFSHJMMVT, Mucorales, and"VTBSJVNspecies) and inherent resistance among some $BOEJEB species (such as Can EJEBHMBCSBUB, $BOEJEBLSVTFJ) led to the need for broader-spectrum substitutes. Fluconazole's drawbacks were partially addressed by the drug itraconazole (1992), which had improved activity against endemic fungi and "QFSHJM MVTspecies, but oral dosing formulations were hampered by inconsistent absorption (capsules) [4] or unfavourable gastrointestinal (GI) effects (solution formulation) [5], which reduced its efficacy in cancer patients who had mucositis or nausea and vomiting. [6]

Voriconazole (2002) and posaconazole (2006), two broader-spectrum triazoles, revolutionised the treatment of invasive mould infections in critically immunocompromised patients. While posaconazole had a spectrum of activity that included several Mucorales in addition to "Aspergillus and 'VTBSJVN species, Fusarium was demonstrated to be more effective than traditional amphotericin B for the treatment of invasive aspergillosis [7]. Both medications could be taken orally, opening the door to their use not only for the treatment of known or suspected mould infections but also for prophylaxis in patients with severe immunodeficiencies. [9-13] Triazole antifungal drugs unfortunately frequently have higher pharmacokinetic variability and danger of medication interactions as a trade-off for their wider spectrum of efficacy. Isavuconazole, one of the more recent triazoles being studied, appears to exhibit a range of activities similar to voriconazole and posaconazole, but with reduced medication interactions and pharmacokinetic variability. [4] Many of the drug's pharmacokinetic issues could be resolved by current efforts to better orally and intravenously administer the posaconazole solution.

The identification and development of echinocandin antifungal medicines was the last significant development in the discovery of antifungal drugs in the 20th century. Semi-synthetic lipopeptides called echinocandins harm the fungal cell wall by preventing the formation of -1,3-d-glucan in sensitive fungus. These drugs were predicted to be efficient antifungal drugs with very little collateral toxicity in mammalian cells because a glucan-rich cell wall is a target not found in mammalian cells. Clinical trials of patients with invasive candidiasis15–17 and aspergillosis have shown that this prediction was accurate. [18] However, several common opportunistic yeasts Cryptococcus species) and less common moulds (i.e., Fusarium, Scedosporium, and Mucorales) that frequently manifest as breakthrough infections in highly immunocompromised individuals still have no action against echinocandins.

Therefore, despite the fact that systemic antifungal therapy has come a long way since its inception in the 1950s, the present antifungal arsenal is still far from ideal. Due to patient-
specific comorbid conditions, hypersensitivities, drug interaction risks, immunosuppression, the site of the infection, and the possibility of infection with pathogens that are more inherently antifungal-resistant, no single antifungal agent is suitable for all patients with a given mycosis. The clinical pharmacology of older vs. newer antifungal drugs is reviewed in this article, with a focus on pharmacokinetic difficulties that arise with newer agents and newly available information on toxicity with longer-term therapy.

**OVERVIEW OF ANTIFUNGAL PHARMACOLOGY:**

Fungi are metabolically similar to mammalian cells despite having a cell wall and a different cell membrane composition, and they don't offer many pathogen-specific targets. Generally speaking, systemic antifungal medications can be categorised according to the pathogenic fungi where they work. The primary cell membrane sterol of many pathogenic fungus, ergosterol, is the target of the antifungal actions of azoles and polyenes. Azole antifungal agents cause growth arrest and eventual fungal cell death by inhibiting the fungal cytochrome P450 (CYP)-dependent enzyme 14-demethylase (lanosterol demethylase), which reduces the amount of ergosterol in cell membranes, compromises membrane fluidity, and accumulates toxic 14-methylated sterols. However, this inhibition is not wholly specific to fungi; in fact, pharmacokinetic drug-drug interactions are frequently caused by collateral inhibition of human CYP enzymes by azoles.

The pocket on the 14-demethylase enzyme that contains heme is the fungal target for azole binding. [20] The shape of each drug's binding pocket for 14-demethylase and its azole structure, as well as the possibility for cross-resistance among triazoles in some fungal species, significantly determine its binding affinity. [20] Extension of the nonpolar side chains for compounds generated from ketoconazole (such as itraconazole and posaconazole) improves azole binding to the 14-demethylase apoprotein, resulting in an expanded range of mold-fighting activities. [21] An o-methyl group on the fluconazole derivative voriconazole confers action against Aspergillus species and other filamentous fungus. [21,22] Most frequently, azole binding pocket mutations of 14-demethylases and/or overexpression of MDRI efflux pumps that expel fluconazole or the multidrug adenosine triphosphate-dependent efflux pumps CDR1 and CDR2, which expel all triazoles, result in resistance to triazole antifungal drugs. [3] Newer triazoles with improved affinity to the enzyme maintain effectiveness against fluconazoleresistant bacteria like C. Krusei because intrinsic resistance in C. Krusei is caused by impaired fluconazole binding to 14-demethylase. [23] Fluconazole resistance in C. glabrata, however, is typically caused by the development of multidrug efflux pumps; as a result, cross-resistance with all azole antifungal medications may be seen. [24]

The allylamine terbinafine inhibits ergosterol manufacture similarly to azole antifungal drugs by blocking squalene monoxygenase, an enzyme in fungi that converts squalene to squalene epoxide, a precursor to lanosterol in the ergosterol synthesis pathway. [20] Although allylamines do not appear to have the same adverse effects on human CYP enzymes as azole
antifungal medicines, terbinafine metabolism will be accelerated by medications like rifampin that highly activate CYP metabolism in mammals. [25] Terbinafine accumulates in the skin and nail beds after oral administration and has comparatively low bloodstream concentrations. [26] As a result, onychomycosis and cutaneous fungal infections are the main conditions for which it is used as a systemic antifungal drug. [26]

The only other antifungal that specifically targets the membrane of the fungus cell is the broad-spectrum polyene amphotericin B. Amphotericin B directly binds to ergosterol and forms complexes with it that intercalate the cell membrane, causing pores to develop and intracellular contents to flow out. [27] When the medication builds up to large concentrations in organs like the kidney, where it directly damages distal tubular membranes, such as the kidney, amphotericin B may lose its affinity for ergosterol-rich fungal cell membranes compared to cholesterol-rich mammalian cell membranes. [28] Nephrotoxicity is so frequently a dose-limiting side effect of amphotericin B therapy. During medication infusion, amphotericin B also directly increases the release of proinflammatory cytokines by mononuclear phagocytic cells, which frequently causes fever, rigours, and chills. [29,30] Amphotericin B can be reformulated into lipid carriers to decrease this infusion effect to variable degrees. The main benefit of lipid amphotericin B formulations, however, is the reduced distribution of amphotericin B to the kidneys, which lessens but does not completely eradicate amphotericin B's nephrotoxicity. [31] Amphotericin B is now routinely used in two forms—a lipid complex and a liposomal formulation—to treat a variety of invasive fungal infections. Alternative cell wall sterols [3,32] and improved resistance to oxidative damage in the cell membrane through increased production of neutralising enzymes, notwithstanding the rarity of amphotericin B resistance developing during therapy. Clinical isolates with inherent or acquired resistance to amphotericin B have been found to have 2 pathways.

Echinocandins are the only antifungal medications now being used in clinical settings that specifically target the fungal cell wall by competitively blocking the production of 1,3-d-glucan polymers, which are essential for cross-linking some pathogenic fungi's cell walls. [34] In fungi that are susceptible, echinocandins attach to the 1,3-d-glucan synthase enzyme complex, resulting in a glucan-depleted cell wall that is vulnerable to osmotic lysis, particularly in quickly developing cells. [35] This antifungal class's spectrum is largely determined by the level of 1,3-d-glucan polymerization in the fungal cell wall and the expression of the enzyme target glucan synthase, which is typically thought to have fungicidal activity against $BOEJEB species and fungistatic activity against "Aspergillus species". [36] Genuine echinocandin resistance is still a relatively uncommon clinical phenomenon, but it has been shown that mutations in specific "hot spot" regions of the ,4 and ,4 catalytic subunits of glucan synthase are linked to decreased echinocandin inhibitory activity against the enzyme, higher MICs, and a higher likelihood of treatment failure. [37]

In general, two classes of antifungal medications are ineffective as monotherapies for systemic mycoses. These medications preferentially target intracellular processes in fungi
through mechanisms similar to those of cancer chemotherapeutic drugs. Flucytosine (5-FC) is transformed to cytostatic 5-fluorouracil in fungal cells, where the active substance inhibits thymidylate synthase and results in RNA miscoding. Flucytosine (5-FC) is selectively taken up by two fungus-specific enzymes, cytosine permease and cytosine deaminase. [28,38] However, the human gut's native intestinal bacterial flora can change 5-FC into 5-fluorouracil, which can cause nausea, vomiting, diarrhoea, and bone marrow suppression. [28,39] Flucytosine is mostly effective against yeasts, but it must be administered in conjunction with other medications to prevent resistance brought on by changes in cytosine permease and cytosine deaminase, which reduces the drug's import and ability to be converted to its active form. [39] A systemic antifungal drug called griseofulvin binds to tubulin and prevents the production of microtubules. The medication is only useful for noninvasive dermatophyte infections since it concentrates in keratinocytes. It's interesting that griseofulvin prevents the growth of numerous cancer cell types in culture, which has rekindled interest in it as a possible breast cancer adjuvant treatment.

**PHARMACOKINETIC CONSIDERATIONS:**

Antifungal pharmacokinetic qualities, rather than spectrum of activity, are frequently the most crucial factor in medication selection since poor GI tract function or decreased renal/hepatic drug clearance can significantly affect the safety and effectiveness of antifungal therapy. Amphotericin B and the echinocandins are two types of antifungal medicines that need to be delivered intravenously since their absorption from the GI tract is insufficient. Triazole antifungal agents were developed to address this issue; however, the degree of absorption varies significantly from drug to drug. Fluconazole and voriconazole both have oral bioavailability levels above 90% and can be administered with or without food (fluconazole), though it is preferable to do so on an empty stomach (voriconazole). [40] Itraconazole oral cyclodextrin formulation is administered on an empty stomach, whereas itraconazole capsules and posaconazole liquid require meals to increase gastric residence time and promote drug dispersion. However, due to GI discomfort and the unpleasant aftertaste of the solution, patients may choose to take itraconazole solution with meals. [41]

In patients with poor appetite, nausea, diarrhoea, and GI dysfunction brought on by cancer chemotherapy (mucositis), organ transplant (graft-vs-host disease affecting the gut, colitis), or in patients receiving acid suppression therapy, especially when combined with potent medications like proton pump inhibitors, the oral absorption of a posaconazole suspension can be unpredictable. [42,43] Posaconazole’s absorption is dose-limited at 800 mg/d, although it can be increased when it’s taken along with a high-fat (>50% of calories from fat) meal or nutritional supplement. [44] When the medication was administered in divided dosages as opposed to a single daily dose, the exposure was improved by 180%. [42,45] Posaconazole is therefore typically started at dosages of 200 mg 3 to 4 times day with food in patients with suspected or confirmed infections until infection stabilises or acceptable serum levels can be confirmed (see Therapeutic Drug Monitoring section). The dosage can then be
increased to 400 mg twice per day. Instead of raising drug doses above 800 mg/d, it is preferable to use clinical strategies that enhance drug breakdown and absorption (e.g., delivery with acidic cola or fruit juice or a highfat meal, termination of acid suppression therapy).

For voriconazole, patient-to-patient pharmacokinetic variability is more variable than it is for posaconazole due to genetic diversity in metabolism. 46 Despite receiving the same fixed daily dose, patients with polymorphisms in the CYP2C19-encoding gene have three distinct patient populations with noticeably different rates of nonlinear voriconazole clearance: homozygous patients who extensively metabolise the drug, heterozygous patients with moderate voriconazole clearance rates, and homozygous patients who poorly metabolise the drug through this pathway and have slow voriconazole clearance rates. [47] Patients with an Asian or Pan-Pacific ancestry are more likely to have the poor metabolism genotype (14%–19%) than patients with an African ancestry or white people (2%), for example. [47] In contrast, voriconazole is often linearly cleared more quickly in juvenile patients, which could lead to low or undetectable serum drug concentrations at recommended adult doses. [48,49] Children should therefore get greater weight-based dosages (7 mg/kg every 12 hours, occasionally raised to 12 mg/kg every 12 hours without a loading dose).

Drug interactions can potentially result in low (fluconazole, caspofungin, posaconazole) or undetectable (itraconazole, voriconazole) bloodstream concentrations of the antifungal agent and a higher risk of treatment failure when any triazole or caspofungin is coadministered with strong inducers of phase 1 (CYP) and phase 2 metabolism (e.g., rifampin, phenytoin). 50 Higher antifungal drug doses may not always be able to overcome interactions with strong CYP3A4 inducers in the cases of itraconazole, voriconazole, and posaconazole. [51-54]

Some antifungal treatments interfere with the metabolism or clearance of other medications, which exacerbates pharmacokinetic drug-drug interactions. The clearance of other renally excreted medications will be reduced by the nephrotoxicity associated with amphotericin B therapy, which is frequently increased by calcineurin inhibitors, aminoglycosides, intravenous radiocontrast agents, foscarin, or aggressive diuresis. [55] However, triazole antifungal medications provide the greatest risk for pharmacokinetic drug-drug interactions because they all differentially inhibit human CYP enzymes. [56,57] Patients taking pharmaceuticals with a restricted therapeutic index, such as chemotherapeutic treatments, immunosuppressants, and several cardiovascular medications, may have hazardous interactions if they are not foreseen. Although it is outside the purview of this review, other recent reviews have been written on the subject of medication interactions. [50,57-59]

Finally, the location of the infection is crucial when choosing an antifungal treatment because some Antifungal substances are only found in anatomically privileged areas like the central nervous system. oral itraconazole and posaconazole, may not achieve significant concentrations in vitreous fluid or, in the case of to treat hematogenous infections, the bloodstream. Central nervous system infections caused by fungi are infamously challenging
to cure, and numerous antifungal medications possess high molecular weights and substantial protein content that prevents them from penetrating the blood-brain barrier barrier. [60,61] Among the antifungal medications now on the market, the three drugs with the best penetration of the cerebral fluid and vitreous chamber are 5-FC, fluconazole, and voriconazole. Liposomal amphotericin B, however, and maybe lipid formulations of amphotericin B, other triazoles, and echinocandins may still reach concentrations in the brain parenchyma that are sufficient for therapeutic effectiveness. [28,63] Echinocandins and more recent triazole antifungal medications have a minimal impact on the management of candiduria. Drugs that are microbiologically active are excreted in concentrations in the feces. [5]

PHARMACODYNAMIC CONSIDERATIONS:
Antifungal agents have various patterns of activity in vivo, much like antibacterial agents (i.e., concentration-dependent or concentration-independent, as defined by the shape of the dose-response curve at clinically achievable doses). [64] These in vivo activity patterns can frequently be connected with medication dose and pathogen MIC to pinpoint optimal dosing regimens that enhance antifungal efficacy while minimising toxicity. Because insufficient distribution results in inefficient drug concentrations, pharmacodynamic data may also be helpful for identifying infection sites where antifungal medications have a higher chance of treatment failure (such as cerebrospinal fluid, vitreous fluid, and urine).

THERAPEUTIC DRUG MONITORING OF ANTIFUNGAL AGENTS:
Recent treatment recommendations and expert assessments are necessary since several antifungal drugs demonstrate substantial variability in bloodstream concentrations that are challenging to anticipate on the basis of dose alone. Therapeutic drug monitoring (TDM) has been advised for various antifungal medications in specific patient populations by the authors 85–88. Because 5-FC is routinely delivered along with nephrotoxic drugs like amphotericin B that induce significant changes in drug clearance, therapeutic drug monitoring has long been crucial in enhancing 5-FC safety. The most frequent dose-limiting toxicities of 5-FC include hepatotoxicity and bone marrow suppression, and both effects have been closely associated with serum peak concentrations of more above 100 g/mL. Only 20% of patients with invasive fungal infections had “therapeutic” serum concentrations, 5% had undetectable levels, and 39% had serum concentrations that are often regarded as toxic (>100 g/mL), according to an examination of 1000 5-FC concentrations from 233 patients. Therefore, personalised weight-based 5-FC dosages (100 mg/kg daily) should be made based on the patient's renal function and serum 5-FC levels, which are assessed two hours after an oral dose is administered. [64] During the first week of treatment, target blood concentrations should be evaluated, and if the patient is on other nephrotoxic medications or experiences fluctuations in renal function, they should be checked once or twice a week after that. [64]
TOXICITIES OF ANTIFUNGAL AGENTS:

A growing number of severely immunocompromised patients are getting systemic antifungal drugs for ever longer treatment courses, despite the fact that the safety and tolerability of systemic antifungal therapy has improved significantly. Therefore, in addition to the more well-known dose-limiting toxicities linked to systemic antifungal agents (e.g., infusion-related toxicities and nephrotoxicity with amphotericin B, hepatotoxicity with triazole antifungal agents), clinicians also need to be aware of longer-term risks, such as repeated drug interactions, organ dysfunction, cutaneous reactions, and malignancies. [31,50].

Itraconazole taken orally may produce nausea and gastrointestinal problems because of the cyclodextrin excipient, making it challenging to stomach for lengthy treatment regimens. In addition, itraconazole has been linked to a rare triad of hypertension, hypokalemia, and edoema that is most commonly seen in elderly persons and may be caused by the medication's unfavourable inotropic effects or adrenal suppression. [66] Itraconazole should not be used for an extended period of time to patients who have a history of heart failure.

CONCLUSION:

The last ten years have seen a change in the way invasive mycoses are treated thanks to the development of novel systemic antifungal medications. It is necessary to be more cognizant of these novel medicines' limitations in terms of their pharmacokinetics, activity spectrum, and potential for pharmacokinetic drug interactions. The bloodstream concentrations of more recent broad-spectrum triazoles, particularly voriconazole and posaconazole, vary significantly from patient to patient, making TDM necessary in some circumstances to regulate drug therapy and dosage. The extended use of antifungal treatments by ambulatory individuals with long-term immunosuppression has raised concerns about long-term toxicity. However, the advantages of safer and more effective antifungal medication far outweigh the tolerable risks of developing toxicity and inadequately treating a potentially fatal systemic fungal infection for the majority of patients.

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