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Fungal infections of the central nervous system: A review of fungal pathogens and treatment

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Abstract

Multiple factors influence the outcome of fungal infection of the central nervous system (CNS). The host and the pathogen in concert with drug delivery across the blood-brain barrier and drug activity are key factors in outcome. Drug costs can be prohibitively expensive. Drug toxicity with standard antifungal agents such as amphotericin B (infusion rate toxicity) can be reduced using simple techniques such as slower infusion and appropriate saline loading. Continuous infusion can allow relatively large doses of amphotericin B (up to 2 mg/kg/day, remaining below 0.08 mg/kg/hour) to be given with toxicity profiles comparable to expensive lipid formulations of amphotericin B. Dedicated peripherally inserted central catheters can remain *in situ* for weeks to months and are safe and relatively inexpensive. Correction of metabolic pathology in the case of mucormycosis and resolution of neutropenia are essential to effective treatment of filamentous fungal infections such as *Mucor, Aspergillus* and *Scedosporium* . The pharmacology and pharmacokinetics of the current major antifungal agents used to treat fungal infections of the CNS are reviewed. Tables that provide information about achievable CNS drug levels, antifungal susceptibilities and the likelihood of intrinsic drug resistance of significant fungal pathogens have been included to help the clinician with therapy. Treatment recommendations for *Cryptococcal* and *Candida* meningitis and for rhinocerebral infection with *Mucor* and *Aspergillus* have been included.

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Full Text

Therapy of fungal central nervous system (CNS) infections is influenced by multiple factors including the pathogen and its drug susceptibility and by drug activity in the CNS, brain and spinal cord. Central nervous system drug levels are affected by the blood-brain barrier and the potential effect of efflux transporters that can modulate drug concentrations in the cerebrospinal fluid (CSF) and neural tissues. [1],[2] Also, efflux transporters have been identified in fungal pathogens that affect their susceptibility to antifungal agents. [3]

Although 70,000 to 1,500,000 fungal species exist and nearly 300 species have been associated with human infection, there are about a dozen yeasts and about 30 molds that are commonly identified as human pathogens. [4] Pathogens encountered in the CNS include yeasts (Candida [neonates], Cryptococcus), moniliaceous molds (Aspergillus spp., Fusarium spp.), dimorphic fungi (Blastomyces , Coccidioides , Histoplasma), zygomycetes (Mucor spp., Rhizopus spp.) and dematiaceous fungi (Pseudallescheria [Scedosporium] spp.).

Fungal cell wall components (ergosterol, chitin, β 1,3 and β 1,6-glucan) have been the major targets of the five classes of antifungal agents in use currently, with the exception of flucytosine (antimetabolic effects). [3] Drugs that affect uniquely occurring fungal cell wall components such as ergosterol (ergosterol binding -polyenes or ergosterol synthesis inhibition-azoles, allylamines) and glucan synthesis inhibitors (echinocandins) are in

current use.

Amphotericin B has been in use for decades and remains an effective agent for most yeasts and molds [Table 1]. The main toxicity is renal impairment via reduction in blood flow to both the renal tubules and glomeruli. Toxicity is infusion rate-related and may be ameliorated by continuous infusion of amphotericin B deoxycholate through a dedicated line such as a peripherally inserted central catheter (PICC) or by use of a lipid-based amphotericin B product. Continuous infusion of amphotericin B deoxycholate may provide an economically preferable alternative to more expensive lipid-based amphotericin B agents (double lumen PICC lines cost about $100 USD and last for weeks to months). Renal toxicity associated with continuous 24-h infusion (up to 2 mg/kg/day, less than 0.08 mg/kg/h) is roughly equivalent to that associated with lipid-based amphotericin B products. [5],[6],[7],[8],[9],[10] Saline infusion prior to amphotericin B infusion is recommended to additionally reduce renal toxicity. [11] Azoles such as fluconazole and voriconazole have been shown to be effective with acceptable toxicity profiles. Newer agents such as the echinocandins are effective antifungals but are expensive [Table 1].

This review will discuss the pharmacology and pharmacokinetics of these agents to treat fungal infections of the CNS. We include a table for likely intrinsic drug resistance to antifungal agents [Table 2], as well as minimal inhibitory concentration data for the most common human fungal pathogens in conjunction with achievable CSF drug levels [Table 3],[Table 4],[Table 5]. We will highlight treatment of Cryptococcal meningitis, Candida meningitis and invasive molds (rhinocerebral mucormycosis).

Mode of Action

Amphotericin B is a polyene antibiotic that is derived from Streptomyces nodosus a soil actinomycete. Amphotericin B binds to ergosterols in the cell wall of fungi and by doing so, disrupts the cell wall integrity leading to increased permeabilty, K + leakage and death of the cell. [3]

Flucytosine is a cytosine analog that enters fungal cells via cytosine permease. It is converted to 5-fluorouracil within the cell. Further enzymatic activity converts this molecule to 5-fluorouridine triphosphate which inhibits thymidylate synthetase (affecting DNA synthesis) or to 5-fluorouridine monophosphate that inhibits proteins' synthesis by interfering with mRNA synthesis.

Allylamines (terbinafine) inhibit squalene epoxidase in the ergosterol pathway. Accumulation of squalene is thought to be toxic to fungal cells. The role for terbinafine in systemic fungal infection is anecdotal. It is used in combination with azoles in the setting of difficult to treat Aspergillus or Scedosporium infections.

Azoles ([imidazoles- ketoconazole, miconazole], [triazoles- fluconazole itraconazole, voriconazole, posaconazole, ravuconazole]) inhibit lanosterol 14 a-demethylase, a cytochrome P-450-dependent fungal enzyme that is necessary for ergosterol production.

Glucan synthesis inhibitors ([echinocandins -caspofungin, anidulafungin and micafungin]) interfere with glucan synthesis leading to osmotically unstable cells (analogous to the effects of penicillin on susceptible gram-positive bacteria). [3],[12]

Pharmacokinetics

Amphotericin B

Amphotericin B is highly protein-bound to human serum albumin and to human a1-acid glycoprotein in vitro (95-99.2%), with the maximum predicted concentration of unbound amphotericin B being 0.774 mg/ml. [13], [14] In vitro experiments suggest that non-protein-bound (free) amphotericin B is the component with antifungal activity. [13],[15],[16] Despite low CSF levels achieved in the rabbit model, sufficient conventional amphotericin B can be detected in brain tissue to have an equivalent anti- Candida effect to liposomal amphotericin B that is dosed at fivefold greater doses. [17] This difference appears to be related to free amphotericin B levels. Lipid-based amphotericin B compounds have less than one-tenth (1/10) the amount of free unbound amphotericin B available compared with the level of free unbound amphotericin B associated with the use of conventional amphotericin B, [13] although a clinical study of the treatment of cryptococcal meningitis found equivalence between lipid and non-lipid-based amphotericin. [18] A recent trial has shown that 10 mg/kg dosing of liposomal amphotericin B is not superior to 3 mg/kg in the treatment of invasive mold infection. [19]

The half-life of conventional amphotericin B is 5.3 days ± 1.25 days, with a volume of distribution at steady state of 1807 ml/kg (virtually all tissue distributed). [15] It appears that conventional amphotericin B is eliminated largely unchanged in urine (20.6%) and feces (42.5%) (via biliary secretion probably) very slowly over a week. Amphotericin B clearance is 50-fold lower than plasma flow to either kidneys or the liver. [15]

Azoles

Fluconazole is a widely used agent with activity against yeasts, particularly species of Candida and Cryptococcus . It has no activity against filamentous fungi. It is available in intravenous and oral preparations. The oral bioavailability is very high and is unaffected by gastric pH or food. Only a small fraction is protein-bound and its elimination is mostly by renal excretion of unchanged drug. The half-life in healthy volunteers is approximately 29.7h, making it suitable for daily dosing. Fluconazole is widely distributed through body tissues, including the CSF.

Fluconazole CSF levels are available from studies in healthy controls and in the setting of CNS infection with Coccidioides, Scedosporium and Cryptococcus in HIV-infected patients. Achieved CSF levels vary between 1.12 -6.2 mg/ml (52-89% of serum levels) and occur within 4h of oral dosing [Table 2]. The CSF half-life appears to be prolonged. Persisting CSF levels between 2.16 - 4.44 mg/ml have been detected in humans with fungal meningitis up to 24h after administration and are higher than concomitant serum levels. [20],[21] The doses used in these studies were lower than the 400 to 800 mg daily which is recommended for CNS infections. The CSF levels are comparable to the levels achieved in a rabbit model. [22] The elimination half-life in the CSF in a rabbit model is approximately 9h. [23] In human studies the ratio of CSF to blood levels appears to be higher in the setting of infection, suggesting increased permeability of the blood-brain barrier related to inflammation.

Itraconazole has a wider spectrum of activity than fluconazole but is more difficult to use due to a complex pharmacokinetic profile. The drug is highly water-insoluble and extensively protein-bound. Oral bioavailability is limited and affected by fasting state and gastric pH. Bioavailability can be improved by administration with food or acids or in capsules or cyclodextrin vehicles and is reduced by H-2 receptor antagonists. Itraconazole has a very high volume of distribution and levels in tissues have been shown to be higher than in plasma. The half-life is long allowing daily dosing. [24]

Although itraconazole has been reported in case series to be successful for some CNS infections, particularly Aspergillus , its penetration into CSF is poor. In rabbit studies peak CSF levels achieved were 0.156 mg/l and the CSF: serum ratio was 9%. Inflammation of the meninges made no difference to the CSF levels. [22]

Voriconazole is a triazole agent with a broader spectrum of activity including yeasts and also filamentous molds Aspergillus spp., Scedosporium spp. and Fusarium spp. Oral bioavailability is reported to be almost 90% and an intravenous preparation is also available. Absorption is affected by fatty meals but not gastric pH. The plasma half-life is 6h allowing for twice daily oral administration. In healthy subjects the volume of distribution is high, suggesting good tissue penetration. In contrast to fluconazole up to 60% of voriconazole is protein-bound and the drug undergoes extensive hepatic metabolism. It is both a substrate and inhibitor of the cytochrome P450 isoenzymes CYP2C19, CYP2C9 and CYP3A4 and has significant interactions with other drugs. The pharmacokinetics are non-linear due to saturation of metabolism. With appropriate loading doses, steady state concentrations can be achieved at 24h. The intravenous preparation contains a vehicle, SBECD, which accumulates in moderate to severe renal impairment, GFR [25],[26]

Cerebrospinal fluid and brain tissue penetration by voriconazole has been reported in human studies of meningitis patients [Table 2]. High CSF levels are achievable rapidly. CSF levels from 0.08 to 3.93 μg/ml are reported (CSF: serum ratios of 0.22-1) [27],[28],[29],[30],[31] and levels of up to 0.72 μg/ml and 2.41 μg/ml have been reported within 2h of intravenous and oral administration respectively. [30] Brain tissue levels appear to be higher than plasma levels and peak tissue levels of 58.3 μg/mg have been reported. [30]

Posaconazole is a broad-spectrum triazole drug that is currently available only as an oral suspension. Less information is available about this agent than the older agents. Its absorption is improved when taken with fatty food. It has a large volume of distribution (Vd=486L) and is extensively protein-bound. It undergoes glucuronidation in the liver to inactive metabolites. [32],[33] It is a substrate for the cytochrome P450 isoenzyme CYP3A4 and is expected to have significant interactions with drugs such as the rifamycins and calcineurin inhibitors. It has a broad spectrum of antifungal activity in vitro including most pathogenic yeasts, Aspergillus spp. and promising activity against zygomycetes and Fusarium spp. Reports and case series demonstrate its clinical activity against Candida spp. (including fluconazole-resistant species), Aspergillus , zygomycetes and Fusarium . The little information available about CNS penetration of this agent suggests that levels are below the limit of detection, [34] but case series suggest that the agent is active against CNS fungal infections. [35],[36]

Ravuconazole is a broad-spectrum triazole drug undergoing evaluation. A rabbit study has shown that the drug

penetrates into brain tissue, [37] but no human data are available at this time.

Echinocandins

Echinocandins are not orally bioavailable and are given by intravenous infusion. All are significantly protein-bound with half-lives compatible with once daily dosing [caspofungin (96.5%, t 1/2 10 hours, Cmax 12 mg/ml), micafungin (99.5%, t 1/2 13 hours, Cmax 7.1 mg/ml), anidulafungin (80%, t 1/2 25.6h, Cmax 7.5 mg/ml)]. Each of these echinocandins achieves maximum concentrations in serum that exceed the MICs of many Candida species and some Aspergillus spp. Clinical studies show efficacy of echinocandins against Candida and some Aspergillus spp. The current role of echinocandins is for salvage therapy of Candida and Aspergillus infections. [12]

Clinical Use of Antifungal Agents

Therapy of cryptococcal meningitis is aimed at CSF sterilization and reduction of intracranial pressure to less than 200 mmH 2 O. Elevated CSF pressures > 350 mmH 2 O can be associated with the clinical signs of papilloedema, decreased visual acuity, decreased hearing, headache and confusion. Focal neurological signs may indicate mass lesions (cryptococcoma).

Therapy is usually given as induction followed by a maintenance course. In HIV-infected individuals, amphotericin B (0.7-1 mg/kg/day) plus flucytosine (100 mg/kg/day divided into four oral doses) is given for two weeks or until the yeast is cleared from the CSF. [38] This is followed by oral fluconazole 400-800 mg/day for up to 10 weeks (until CSF sterile). [39] Chronic suppression follows with fluconazole 200 mg/day. Cessation of therapy may be considered if there has been sufficient immune reconstitution and complete suppression of HIV replication. [40] In HIV-uninfected individuals therapy may be the same or with the combination of amphotericin B and flucytosine being given for 6-10 weeks. In this setting therapy is usually curative without a requirement for further treatment.

Cerebrospinal fluid pressure symptoms can be managed by lumbar puncture to reduce the pressure to 2 O (as often as needed). Ventriculo-peritoneal shunts may be required in patients with sustained increased pressures.

HIV-infected patients with a history of cryptococcosis are at risk for development of immune restoration disease on introduction of antiretroviral therapy. This has been described with lymphadenitis [41],[42],[43],[44],[45] or CNS disease with recurrent meningitis [46],[47],[48],[49] or cryptococcoma. [50] The pathogenesis of this disease process is still being clarified. Optimal therapy has not been defined but case series have reported success with varied management strategies.

Candida meningitis is uncommon, but occurs predominantly in three groups of patients: neonates, neurosurgical patients and immunosuppressed patients. The disease occurs most commonly as a complication of fungemia, but may follow direct inoculation, e.g., after the placement of CNS prostheses. There are no randomized trials to guide therapy. Neonatal Candida meningitis may present in a nonspecific fashion; is a particular risk in extremely low birthweight infants; and series report mortality up to 37.5%. [51],[52],[53], [54]

In neurosurgical patients Candida meningitis occurs after placement of a device such as a shunt or external drain. [55-58] Symptoms vary but usually include lethargy, fever and meningism. Focal neurological abnormalities and seizures may occur. Cerebrospinal fluid pleocytosis is usually observed, however positive gram stains and hypoglycorrhachia are uncommon.

Candida meningitis has been described in a variety of immune deficiency states: chronic granulomatous disease, myeloperoxidase deficiency, IgA deficiency, severe combined immunodeficiency, HIV infection, solid organ transplantation and lymphoma. [59],[60],[61],[62],[63],[64],[65],[66],[67] In the reported HIV-infected patients CSF pleocytosis was universal and hypoglycorrhachia common. In this group of patients all presented with either fever or headache or both.

Amphotericin B and flucytosine in combination are recommended for treatment. [68],[69] Monitoring of flucytosine levels has been recommended, aiming for serum levels 40-60 μg/ml. [70],[71] Fluconazole and flucytosine are known to achieve high levels in the central nervous system. [72],[73],[74] In vitro evidence suggests that amphotericin B and flucytosine act synergistically [75] but no studies confirm clinical superiority of combination therapy for Candida meningitis. Animal data suggest amphotericin B may be more rapidly fungicidal than fluconazole for Candida [76] and there are reports of therapeutic failure of fluconazole in neonatal Candida meningitis. [77],[78] In neurosurgical patients, removal of prosthetic devices is recommended. Duration of therapy is not well defined, but generally a minimum of four to six weeks is

suggested. Intravenous amphotericin with oral flucytosine is commonly employed until the signs and symptoms have resolved, then completion of therapy is with oral fluconazole. The echinocandins and extended-spectrum azoles have been shown to be efficacious in candidemia, and voriconazole is known to penetrate well into the CNS. These agents may be expected to be useful for the treatment of Candida meningitis.

Rhinocerebral infections with Aspergillus spp. or zygomycetes are conditions with high rates of morbidity and mortality. The basis of treatment is to correct the underlying metabolic (ketoacidosis) and hematologic (neutropenia) pathology. These fungal pathogens are angioinvasive and commonly cause tissue infarction (brain/paranasal sinus mucosa/cavernous sinus) by clotting blood vessels. This angioinvasive characteristic promotes tissue invasion at the same time impairing delivery of drugs to the site of infection. Surgical debridement in combination with high-dose amphotericin B (up to 2 mg/kg/day by continuous 24-h infusion or lipid-based alternatives) or voriconazole/posaconazole/echinocandins (if Aspergillus) are the treatments that may alter outcome in an otherwise 100% mortality in untreated patients. These patients usually require multiple surgical procedures that combine otolaryngological and neurosurgical expertise. [31],[79],[80],[81]

Conclusion

A vast amount of literature has been published dealing with treatment of CNS yeast infections such as Cryptococcus neoformans and Candida albicans . Clinical guidelines such as those published by the Infectious Diseases Society of America are a ready reference and clinical guide to therapy and are freely accessible on the internet (http://www.idsociety.org/). MIC tables for the 30 most common fungal species that cause disease in humans are intended as a guide to clinicians. Individual local susceptibility testing is essential in choosing appropriate therapy. Treatment of CNS infections with zygomycetes, on the other hand, is largely based on anecdotal series of cases. Cost of antifungal therapy remains a crucial issue worldwide. Whereas lipid-based formulations of amphotericin B offer lower rates of renal toxicity, their costs may not be affordable. Amphotericin B deoxycholate given as a continuous infusion, with appropriate saline loading, through a dedicated line remains a safe and affordable option with similar toxicity profiles compared with expensive lipid-based compounds. Because it is the free (non-protein-bound) amphotericin B that has antifungal effect, the advantage gained by liposome/lipid formulations (an order of magnitude lower free amphotericin B concentrations) in terms of renal toxicity, can be matched by continuous infusion amphotericin B. More clinical trials that appropriately administer continuous infusions of amphotericin B and measure free amphotericin B concentrations by HPLC (high performance liquid chromatography) could potentially be of great economic and clinical benefit. (Animal models such as the rabbit model of Candida infection [13],[15] have inexplicably not reported or tested continuous infusion amphotericin B treatment arms to date)[95].

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