Systemic antifungal drugs

John R. Graybill

Infectious Diseases Division, University of Texas Health Science Center, San Antonio, Texas, USA

Summary

In recent years there have been major new developments in systemic antifungal drugs. For amphotericin B there are several lipid formulations recently developed. These clearly reduce infusion and nephrotoxicity, allowing large doses to be administered safely. It remains less clear how much more effective are the lipid formulations as compared to amphotericin B desoxycholate. For the triazoles, itraconazole has been reformulated into a solution which improves oral absorption and can also be given intravenously. The clinical impact of this is still uncertain. Voriconazole and posaconazole are two new broad spectrum triazoles which will compete with itraconazole for activity in fluconazole resistant yeast and mycelial pathogens. Finally, a new class, the echinocandins, is under Phase III study.
Three competitors are highly active against *Candida* and some mycelial pathogens. Their ultimate role has not been defined. All of these developments provide the clinician with an increasing array of choices to use in the expanding word of systemic mycoses.

Key words Polyene, Triazole, Echinocandin, Antifungal, Liposome

In years past the clinical mycoses were conveniently divided into the dermatophytes and those causing systemic mycoses. Dermatophyte infections have been and continue to be extremely common. Systemic mycoses have been rare; although these are still far less common than skin infections systemic mycoses have increased in frequency. At the same time we have appreciated that the usual superficial pathogens can disseminate, and that systemic mycoses have many cutaneous manifestations. The division of pathogens into superficial and deep has begun to blur. Likewise, in the old days there were griseofulvin and potassium iodide as systemic agents for superficial mycoses, but most were treated with topical antifungals. For systemic mycoses the choices were amphotericin B and flucytosine [1,2]. Now we have many more agents for both dermatophytes and systemic mycoses. The appearance of ketoconazole was the first time that we had available a systemically absorbed drug which was effective for both deep mycoses and skin infections, and benign enough to be considered for primary treatment of dermatophytes [3]. Now we have multiple systemically administered drugs which are well tolerated and useful against both deep and superficial pathogens. Finally, we have in terbinafine, a drug developed for superficial pathogens, an agent with a broad enough spectrum that it is being considered for sporotrichosis and even aspergillosis [4]. Our traditional classification of both fungal pathogens and antifungal drugs is much less defined than before, and our therapeutic alternatives are broadening rapidly.

The primary factor which has prompted the search for more systemic antifungal drugs is and has been immune suppression. In the early 1980's this took the form of AIDS, and the mycoses were severe mucosal candidiasis, cryptococcal meningitis, histoplasmosis, and to lesser degrees coccidioidomycosis and aspergillosis [5-9]. These years saw the expansion of azole antifungals to itraconazole and fluconazole. The development of fluconazole resistance in *Candida albicans* prompted a secondary hunt for more broad spectrum triazoles with better pharmacokinetics than itraconazole [10,11]. In the later 1980's and through the present, AIDS has in the US and Europe come under more control with effective antiretrovirals. However, the intensive care units in medicine and surgery have become breeding grounds for candidemia. This has been highly but not universally associated with intravenous, urinary, and other catheters, and broad spectrum antibacterials and corticosteroids [12-14). Unlike AIDS patients, where most of the pathogenic *Candida* are *albicans*, in fungemia more than half of the patients are infected with *C. tropicalis*, *C. glabrata*, and other non-albicans species, which may be fluconazole resistant [15]. In addition to candidemia, the oncology units have had to deal with aspergillosis and zygomycosis in their patient populations [16-23]. Heart/lung transplants also became vulnerable to aspergillosis. Because the mortality has been so high in these patients, efforts to deliver higher doses or new analogues of amphotericin B were the primary areas of interest. However, pathogens such as *Fusarium* and *Trichosporon beigelii*, resistant *in vivo* to amphotericin B, and *Aspergillus terreus* [24], relatively resistant to amphotericin B, have pushed further drug development to new classes of agents [16,18,25]. Also because of devastating outcomes in many of the patients with aspergillosis, there has been serious effort to develop an antigen based diagnostic test for *Aspergillus* antigens in sputum or bloodstream of infected people…to enable screening for disease

Corresponding address:
Dr. John R. Graybill
Infectious Diseases Division
University of Texas Health Science Center
7703 Floyd Curl Drive
San Antonio, TX 78284, USA
Fax: +1 210-6146197
E-mail: JRGraybill@aol.com

earlier, earlier treatment, and hopefully a better outcome [26,27]. Although invasive aspergillosis is not extremely common, the morbidity and mortality of this infection have prompted every development of new antifungals to test against this pathogen and against non-albicans (frequently fluconazole resistant) *Candida* species as the gateway tests for further clinical development.

In the remainder of this article we shall consider the major systemic antifungals by classes, considering first the general mechanisms of action and toxicities, and then consider the specific drugs with their clinical uses and limitations.

Polyene

Mechanism

This is the oldest class of class of systemic antifungals, and polyenes remain the most rapidly acting of the antifungals. The polyenes act within minutes of exposure to fungi, to bind to ergosterol on fungal cell membranes [28]. This binding causes a disruption in steric integrity of the membranes. Initial studies of these drugs determined that the primary action was to reduce osmotic integrity, causing intracellular potassium to leak out and extracellular ions to leak in. This osmotic lesion was thought somehow to kill the fungal cell, but exactly "how" was not clearly elucidated. More recently, there has been evidence that polyenes also disrupt activity of membrane oxidative enzymes. This likely is a major and generally under-appreciated source of fungicidal activity. Another potential for antifungal activity is the ability of amphotericin B to stimulate production of proinflammatory cytokines, such as tumor necrosis factor and interferon gamma. These likely add to the direct antifungal effects, but exactly how much is hard to quantitate.

Toxicities

Polyenes have been sufficiently toxic that amphotericin B has been the only one considered well enough tolerated for systemic administration. Although small rodents absorb amphotericin B orally, for humans the drug must be administered parenterally, usually intravenously. In addition to direct effects on fungi, polyenes act on mammalian cells. The most important toxicities are those to the kidney, and these are threefold. First, amphotericin B causes glomerular vessel vasospasm. This ultimately causes ischemia and death of glomeruli and decrease in creatinine clearance. Second, amphotericin B damages the macula densa, decreasing erythropoietin production and causing a modest anemia[29]. Third, polyenes bind to cholesterol in human cell membranes [1,30]. This also causes an osmotic leak. When amphotericin B is rapidly infused in patients with pre-existing renal failure, the release of potassium combined with the inability to excrete potassium can cause dangerously high serum potassium concentrations. This can cause cardiac arrhythmias [31]. In sharp contrast, when amphotericin B is administered more slowly, in patients with normal renal function, the drug causes a potassium leak in the distal renal tubules. The ion leaches out into the urine, and does not exchange with hydrogen, causing a distal renal tubular acidosis and significant hypokalemia. Thus the antifungal mechanism of amphotericin B, binding to cell membrane sterols, is linked directly to its major nephrotoxicity [1,32-35].

Another form of toxicity is probably mediated through the proinflammatory cytokines. This is the intense inflammation which results when amphotericin B is given parenterally. Most commonly, this is seen as local thrombophlebitis, and systemic chills, fever, nausea, and vomiting. When amphotericin B is administered to other sites, such as intrathecally or intraperitoneally, or subcutaneously, severe inflammation results as well. This can cause arachnoiditis and even cerebrovascular accidents. Thus it is no surprise that amphotericin B has been restricted to systemic mycoses and that dermatologists have had little interest in this drug.

Resistance

In general, resistance to amphotericin B has been uncommon and not well studied. Rare *Candida* species were identified in patients who had become refractory to amphotericin B [36,37]. These isolates were identified as having sharply decreased ergosterol in their fungal cell membranes, and substitution of other sterols which did not bind amphotericin B. Some fungal species, such as *Candida lusitaniae*, had increased though not necessarily absolute resistance. More recently *Aspergillus terreus*, *Fusarium* species, *Trichosporon beigelii*, *Scedosporium prolificans*, and *Pseudallescheria boydii* have been numbered among the uncommon, but significant pathogens associated with relative or absolute amphotericin B resistance [38-41]. Rare isolates of other fungi have also developed amphotericin B resistance.

Administration of amphotericin B

The commercial form of amphotericin B is a deoxycholate micellar suspension. It is administered intravenously generally as 50 mg in 500 ml of 5% glucose. Admixture with saline causes precipitation, and if exposed to light for long hours, the drug degrades. The dosage varies, and has currently been suggested as 0.7 mg/kg for cryptococcosis, 0.5-1 mg/kg for candidemia, and 1 to 1.5 mg/kg for more difficult pathogens such as *Aspergillus* and zygomycetes [1,7]. Total dose may range from less than one gram to more than 3 grams, depending on the infection, the tolerance, and the clinical status of the patient.

Minimizing toxicities

There has been some argument about duration of time for infusion, and one to 4 hours (or longer in patients with renal failure) have been suggested. The advantage of one hour is s shorter time of fevers and chills, but it is argued that there may be arrhythmias, hypotension, or other problems with more rapid infusions [31,42]. Administration of acetominophen, meperidine [25-50 mg), or diphenhydramine is often used to block these inflammatory reactions, which are characteristically most intense in the first few days of therapy. Also, in order to counter the glomerulotubular ischemia, a 500 to 1000 ml of saline may be infused just before the dose [32]. For treatment of coccidioidal meningitis, amphotericin B must be given intrathecally [43,44]. This is extremely irritating, requires the concomitant administration of corticosteroids to minimize arachnoiditis, and has largely been replaced with high dose fluconazole [45].

Recent developments

Amphotericin B has been at once the most rapidly acting, the most potent, and the most toxic of the systemic antifungal drugs. As we have increasingly appreciated the high failure rate of this our "most potent" drug in invasive aspergillosis and zygomycosis, there has been a search for ways to administer this drug or other polyenes in larger doses with reduced toxicity. This has led to the development of the lipid formulation for amphotericin B and nystatin [46-51]. Basically, the incorporation of the amphophilic amphotericin B or nystatin molecule into

lipid vehicles has enabled them to bypass the kidney. Lipid amphotericin B formulations are thought to deliver the drug to tissues such as the spleen and liver, and to sites of infection, where there are accumulations of phagocytic cells. The pharmacodynamics of these preparations can be altered by changing the charge and lipid content of the vehicle, but the clinical consequences of this remains unclear.

There is now extensive experience with three preparations, Abelcet (amphotericin B lipid complex), Amphotec (amphotericin B colloidal dispersion), and AmBisome (Liposomal amphotericin B). Their characteristics are summarized in Table 1. All of these drugs can be administered at doses up to 5 mg/kg/day, and they have been administered to patients for periods as long as a year. AmBisome can be doses up to 15 mg/kg/day, at least for short periods of time [52]. For efficacy, these drugs are likely to show the same range as Fungizone for candidemia, as shown in large multi-center study (unfortunately still not published) comparing ABLC with Fungizone [50]. Similarly, for cryptococcal meningitis in patients with AIDS, AmBisome has been found of similar efficacy as Fungizone. Two week culture conversions in cerebrospinal fluid were 54% of 94 patients receiving 6 mg/kg/dose of AmBisome versus 54% of 87 patients receiving Fungizone [53].

Table 1.- Characteristic of lipid formulations of amphotericin B.

	ABLC*	ABCD**	Liposome***
Brand name	Abelcet	Amphotec Amphocil	AmBisome
Company	Liposome	Sequus	Nexstar-Gilead Fujisawa
Morphology	Ribbons	Disks	Spheres with aqueous core
Approximate per cent amphotericin B	35	50	10
Frequency Adverse Reactions****			
Infusion	+++	++++	+
Renal			
Glomerular	+	+	+
Distal Tubular (manifested by hypokalemia)	++	++	++

*Amphotericin B lipid complex
**Amphotericin B colloidal dispersion
***Amphotericin B in true liposomes
**** all preparations have been associated occasionally with dyspnea and hepatotoxicity, though uncommonly.

The place of greatest hope and least certainty is aspergillosis. The best evidence for superiority of a lipid formulation is the large study by Walsh et al, comparing AmBisome with Fungizone for empiric therapy of febrile neutropenic patients [54]. AmBisome was significantly superior to Fungizone, but the end points were resolution of fever and absence of mycosis, not resolution of documented mycoses. There were fewer mycoses in he AmBisome arm, but not enough to prove better efficacy against *Aspergillus* per se. Another study, by White et al, shows amphotericin B colloidal dispersion to be at least as effective as Fungizone [49]. Nevertheless, a number of investigators, including myself, have the impression that these drugs offer perhaps more potency in aspergillosis than Fungizone. Another mycosis which has responded well is *Fusarium*. In an open study Walsh et al found that ABLC had 9/11 patients responding, a much better record than that traditionally recorded [55]. Thus, for efficacy, the lipid amphotericins are being studied and used in the environment where aspergillosis is a particular risk, the bone marrow allogeneic transplant recipient, and also in heart/lung transplantation, where aspergillosis is also a large risk.

The other major use for these formulations is in the patient with nephrotoxicity. All three of these drugs cause much less glomerular toxicity, and likely cause less intense hypokalemia as well. Nyotran also has reduced nephrotoxicity [46]. Most of the comparative studies are done only in the acute phase of drug administration, so long term sequellae are less clear. There is a concern that in avoiding the kidney as a target site for toxicity these preparations might also avoid the kidney as a site of infection. Augustin et al have recently reported three patients who failed treatment with ABLC for *Candida* urinary tract infection. Both of two tested isolates were susceptible to amphotericin B *in vitro* [56].

So with probably similar efficacy among the three licensed formulations, and with arguable but perhaps similar lower grade nephrotoxicity, is there anything which clearly distinguishes these drugs? Two characteristics, infusion reactions and cost, define the major differences. As of the present time, ABCD is much less used than the other preparations, largely because infusion reactions are as severe if not worse than Fungizone. ABLC has somewhat less intense infusion reactions than Fungizone, but they are still significant. AmBisome has the fewest of all in terms of acute infusion reactions. Unfortunately, AmBisome is also much more expensive than ABLC, which in turn is much more expensive than Fungizone. In one European study AmBisome was compared at 1 and 4 mg/kg/day for "invasive aspergillosis" [57]. The outcomes were similar. If the authors conclusions are correct, that aspergillosis responds equally well to both doses, this would allow much lower doses of AmBisome to be used, and make AmBisome commercial far more attractive. However, the study was critically flawed in that the definitions used for more than 2/3 of their patients for "probable" aspergillosis were very loose and did not require microbiologic confirmation of the organism. If the majority of patients did not have aspergillosis at all, of course the response to antifungal therapy would be similar, whatever the dose of AmBisome, or water, for that matter.

The other two formulations of polyenes are Nyotran and a home mixture [46,47]. Nyotran is still in investigational stages, and while data show efficacy in animal models of some mycoses, the clinical experience is small, and without Phase III comparisons [59,60]. It appears that Nyotran has less nephrotoxicity than Fungizone, but its role has yet to be determined clinically. The home mixture if Intralipid and Fungizone has gone through multiple births, deaths, and reincarnations [58,61, 62]. It was initially developed as a cheap way to mix prepared Intralipid with Fungizone, and give people the advantages of the commercial formulations but without the costs. Studies in France showed some efficacy and this formulation became transiently popular. More recent studies suggested that the nephrotoxicity is really not less than Fungizone, that the drug may not stay tightly associated with the lipid, and that the advantages of this were ephemeral at best. However, Nucci *et al.* have revived the argument, showing that homemade lipid amphotericin B was effective and well tolerated in their patients [58]. While very attractive from the viewpoint of costs, the efficacy and toxicity data have not yet convinced me that this formulation should replace the commercial forms.

Finally, a variety of analogues of amphotericin B have been synthesized. None are in extensive clinical trials at present, and the future of this line of work is unclear.

Flucytosine

Mechanism

Flucytosine is a water soluble nucleoside analogue which is readily absorbed orally, well distributed into tissues, and functions by conversion to 5-fluoruracil within fungal cells [63]. Because of ready emergence of resistance, flucytosine has been only used in conjunction with other antifungals. The drug is excreted primarily as parent drug through the urinary tract route. One problem is that fungi can become resistant at multiple sites, including cytosine permease, cytosine deaminase, and other sites.

Toxicity

Flucytosine may be converted by intestinal bacteria in part to 5-fluorouracil in the gut [64]. This is absorbed and causes toxic marrow depression or gastrointestinal side effects. Flucytosine is also the cause of \occasional hepatotoxicity.

Minimizing toxicity

Because of renal excretion of unchanged drug, the dose must be altered for renal function abnormality. Recent studies with flucytosine in cryptococcal meningitis indicated that this drug is effective and well tolerated when used at a reduced dose of 25 mg/kg.6 hours [7].

Major uses

Flucytosine has long been in search of a home, and has never quite achieved real name recognition. It is still unavailable in many countries. Flucytosine is now used in initial therapy of cryptococcal meningitis, usually 100 mg/kg/day combined with amphotericin B as Fungizone, at 0.7 mg/kg. It can be effective used alone, but this is not usually done. In a recent conference on management of candidemia, some of a series of experts recommended the addition of flucytosine for the severely ill patient [65]. Flucytosine has also seen used in chromoblastomycosis and in aspergillosis, though data are scattered [63].

Azole antifungals

Mechanism

All of the antifungal azoles share a common mechanism of action [66,67]. They bind to lanosterol demethylase, a cytochrome P450 enzyme responsible for an early step in the pathway of synthesis of fungal cell membrane ergosterol. By blocking enzyme activity, they inhibit synthesis of ergosterol, and a variety of intermediate sterols are produced. Membrane integrity is reduced, and ion exchange is uncontrolled. These sterols do not support fungal viability, in part because the activity of oxidative enzymes is altered by the substituted sterols. The action of azole antifungals is quite slow compared with polyenes, as several generations of fungal cells are required to incorporate sufficient azole to reduce the membrane ergosterol.

Today we have available a wide variety of topical and systemically administered azole antifungals. The systemically administered azoles are differentiated by a) the specificity of binding to mammalian versus fungal cytochrome enzymes b) water solubility c) oral absorption vs solubility for parenteral administration d) hepatic versus renal clearance e) fungal spectrum and f) auto-induction of hepatic cytochrome enzymes which degrade the azole drugs.

Initial drugs

The first systemically administered azole was clotrimazole [68]. It was short-lived because of auto-induction of hepatic degrading enzymes, making it a “suicide” drug. Clotrimazole now enjoys widespread topical use. Ketoconazole was the first azole antifungal which could be administered orally. Absorption was erratic, and optimized by ingesting it with an acid beverage; clearance was via hepatic degradation, and toxicities, though less than amphotericin B, were multiple. These included nausea, vomiting, hepatitis (sometimes lethal) and polyhypoendocrinopathies [66,69-72]. Dose dependent inhibition of androgen and cortisol synthesis were found due to nonspecific binding to and inhibition of cytochrome enzymes involved in steroid hormone synthesis. Disruption of female menstrual cycling, loss of hair color, impotence, and impaired vitamin D metabolism were all linked to ketoconazole. Hyperlipidemias also were a consequence of altered fat metabolism by ketoconazole. Multiple drug interactions were appreciated [3,66]. Rifampin accelerated hepatic degradation of ketoconazole to the point where it was useless. Other drugs competed with ketoconazole for excretion by liver enzymes [73,74]. Either ketoconazole or the other drug or both drugs would have serum and tissue levels raised [75]. Despite these problems, ketoconazole was the first broad spectrum antifungal triazole, and showed potency in multiple endemic mycoses, *Candida* infections, phaeohyphomycosis, and sporotrichosis [65,76]. Ketoconazole enjoyed relatively widespread if brief predominance as a systemic antifungal. As it was replaced by fluconazole and itraconazole ketoconazole has evolved into topical form used, among other areas, in antifungal shampoos for dandruff. Ketoconazole is still used extensively in the third world, in part because it is off patent and relatively inexpensive. The importance of ketoconazole cannot be overstated, because this drug showed the pharmaceutical companies that a broad spectrum orally administered antifungal azole could be effective in life-threatening systemic mycoses like histoplasmosis.

The second important lesson from ketoconazole was that antifungal azoles needed to be more specific for fungal enzymes, that a spectrum against Aspergillus was desired, and that simple kinetics of excretion could reduce many of the adverse reactions.

From ketoconazole there evolved two classes of triazole antifungals, based on their pharmacokinetics. Both classes are far more specific for fungal than mammalian target enzyme [66]. Hepatitis and hypoendocrinopathy are quite rare for both. Fluconazole is the sole representative of the first class [77]. Fluconazole is water soluble, easily administered orally or intravenously, is not tightly protein bound, and penetrates readily into most body tissues. Drug interactions caused by fluconazole are few and generally only moderate. Fluconazole is cleared by largely renal mechanisms, and is well tolerated to doses as high as 2 grams per day. For kinetics, fluconazole is far superior to any of its competitors.

The second class is represented by one licensed drug, itraconazole, and two drugs that will be licensed shortly, voriconazole and posaconazole (SCH56592) [77-80]. Per pharmacokinetics, itraconazole and the other drugs are very poorly water soluble. Absorption after oral administration has been irregular, and special vehicles are required to solubilize them for parenteral administration. For itraconazole, this is b hydroxy-cyclodextrin. For voriconazole another cyclodextrin is used. For posaconazole a water soluble but inactive prodrug is converted *in vivo* to

an active intermediate, which in turn is converted to posaconazole [81-83]. Clearance is hepatic, via cytochcrome enzyme degradation, and is nonlinear, increasing over time, reflecting saturable kinetics. Both itraconazole and posaconazole have metabolically active antifungal intermediates. As with ketoconazole, rifampin, phenytoin, rifabutin, carbamazepeme, nevirapine, effavirenz, and barbiturates accelerate hepatic degradation. Conversely, drugs such as cyclosporine A, tacrolimus, digoxin, benzodiazepines, the "statins", oral hypoglycemics, astemizole, terfenidine, and antiretroviral protease inhibitors all compete for this route of excretion (cyp3A4) and both their concentrations and the triazole drug may be raised substantially. There is much more known about itraconazole than the other two drugs, as per relative potency of these drug interactions. In addition, voriconazole has a transient "flashing lights" phenomenon which occurs in early therapy, and then clears despite continuing therapy. Posaconazole in dogs has shown a problem with demyelinating neurologic lesions, which only occurs after long treatment, and the consequences of which are unclear at this time.

One might ask why, with all of these kinetic problems, are these drugs widely used? The twofold answers are vastly great potency and much broader spectrum and in the case of posaconazole, the potential for actually killing fungi in host tissue. Fluconazole has excellent kinetics and good activity against some *Candida* species, *Cryptococcus neoformans*, and to lesser degree the endemic mycoses. Fluconazole resistance among *Candida* isolates has become a significant problem. Itraconazole, on the other hand, is active against all fluconazole susceptible *Candida*, up to half of fluconazole resistant *Candida*, *Aspergillus* species, and is more potent against endemic mycoses, *Sporothrix schenckii*, and phaeohyphomycetes than fluconazole [23,84-91]. Both voriconazole and posaconazole share the spectrum of itraconazole, but are somewhat more potent, and also show some activity against *Fusarium*, and even zygomycetes (posaconazole) [79]. These are important additional niches.

Itraconazole in the capsule form is well tolerated, but irregularly absorbed. Taking it with an acidic beverage and lipid containing food increases absorption [96]. A new formulation, in cyclodextrins, increased oral absorption and eliminates the need for an acid beverage or food. However, the cyclodextrins are not well tolerated per taste or gastric disturbance. An intravenous form in cyclodextrins has just been released, but experience is very small [97-99]. Orally administered cyclodextrins are broken down in the alimentary tract, but intravenously administered cyclodextrins are cleared renally. It is unclear what effect renal failure will have on intravenously administered cyclodextrin/itraconazole. A practical maximum dose for oral itraconazole is 600-800 mg per day. At these and higher doses there is a more frequent occurrence of a syndrome of edema, hypertension and hypokalemia, the etiology of which remains unclear [100].

Itraconazole today is widely used for endemic mycoses and sporotrichosis and phaeohyphomycosis, where it is generally more potent than fluconazole. Itraconazole may also be useful in treatment of patients with allergic bronchopulmonary aspergillosis and the less fulminating forms of invasive aspergillosis, and for some fluconazole resistant *Candida* infections [23,101]. It is not recommended for urinary tract infections because the active drug does not appear in the urine.

At present it is unclear whether voriconazole and posaconazole will replace itraconazole or compete with it.

Echinocandin/Pneumocandins

Mechanism

These are cyclic polypeptides, with the initial drug developed for clinical use being cilofungin (Lilly). Cilofungin was unsuccessful because its vehicle was toxic. It also had problems with a narrow spectrum and rapid clearance. However, this drug gave rise to a later far more successful series of drugs. All of the pneumocandins (named for activity against *Pneumocystis carinii* and *Candida*) act by irreversibly binding to and inhibiting activity of the enzyme beta 1-3 glucan synthase [102]. This is a critical enzyme in synthesis of the glucan cell wall of fungi. Without the glucans, fungi are less stable to osmotic and other stresses, and poorly form mycelial buds. These drugs act within moments, and are rapidly fungicidal to yeasts *in vitro*. They are also highly active against *Aspergillus* species and some other mycelial fungi. Although they cause considerable damage, they are less clearly fungicidal to these organisms. Animals infected with yeasts are rapidly cured, with great reductions in tissue counts. Animals infected with Aspergillus respond very well (mice) but some (rabbits) survive longer, and with persistent lesions. There is also activity *in vivo* against *Histoplasma capsulatum*, *Coccidioides immitis*, and *Blastomyces dermatitidis*.

Drugs

There are three drugs in clinical development. These are Ver-02 (Versicor 02, previously Lilly LY703366), Fujisawa FK463, and Cancidas (formerly caspofungin, Merck 0991, and LY 743872). On the positive side, these drugs all have similar *in vitro* activity [103-106]. They are water soluble (a great advantage over cilofungin), cleared relatively slowly (once daily dosing is feasible) and are cleared by non-cytochrome p450 hepatic mechanism. This is also a great advantage in reducing drug interactions. They are not nephrotoxic. They may have additive activity with other antifungals, though this is not yet clear *in vivo* [107]. A clinical study comparing fluconazole with and without FK463 for prophylaxis of mycoses in bone marrow transplant or stem cell recipients did not show and advantage of the combination. However, the primary purpose was safety and kinetics, and the study was not powered for therapeutic response determination. FK463 is well tolerated up to 200 mg per day with no renal toxicity [108] On the negative side, these drugs are not absorbed after oral ingestion, and have limited activity against some troublesome pathogens such as Fusarium and zygomycetes, and are not absorbed after oral administration. Also, there may be liver toxicity with concurrently administered cyclosporine A (but not tacrolimus). In clinical trials, Cancidas has proven extremely effective, with responses equal or superior to amphotericin B in thrush and esophagitis, responses in fluconazole resistant mucosal candidiasis, and some responses in salvage therapy of aspergillosis [109] FK463 is also effective in esophageal candidiasis [110]

At present it is unclear exactly what role these drugs will play in the future. If they have no major toxicities discovered, they are likely to see a primary role in very sick intensive care unit patients, where candidemia carries a 30-40% attributable mortality rate [12] It is likely that they will replace amphotericin B in this setting. Their value in aspergillosis and infection caused by endemic mycoses, as well as their use in antifungal prophylaxis and empiric therapy, remains undefined.

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