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Tolerability profile of the current antifungal armoury

Ahmad Mourad and John R. Perfect*

Division of Infectious Diseases, Department of Medicine, Duke University Medical Center, Durham, NC, USA

*Corresponding author. Hanes House, Room 163, Trent Drive, Duke University Medical Center, Durham, NC 27710, USA. Tel: +1-919-684-6854; Fax: +1-919-684-8902; E-mail: john.perfect@duke.edu

The tolerability of available antifungal agents is essential to the final outcome of the management of invasive mycoses. There are limited classes of antifungal agents for use, and they can have serious direct toxicities and/or drug–drug interactions. In this review, we examine the common toxicities noted for antifungal agents and attempt to both identify the issues around the adverse events and provide clinical context for their occurrence in these fragile patients.

Introduction

Invasive fungal infections continue to pose a serious threat to the growing populations of patients in immunocompromised states. It has clearly been shown and validated that early initiation of appropriate antifungal therapy is vital for improved survival in these patients with invasive mycoses.[1–3] However, in addition to selecting the most appropriate agent for systemic therapy in a timely manner, management of adverse events (Table 1) and drug–drug interactions associated with use of these powerful agents is crucial to a successful outcome. This task is not always easy with the relatively low number of approved antifungal drugs to treat these infections and with the relatively high number of patients who discontinue an antifungal agent owing to adverse events. For instance, clinical trials can accurately indicate the magnitude of adverse events and at times measure the actual impact on success of antifungal regimens. Two examples of drug toxicity in clinical trials include: (i) the Mora-Duarte *et al.*[4] study of candidiasis, in which failures due to drug toxicity occurred in 2.8% of patients on caspofungin treatment and 16.5% of patients on amphotericin B treatment; and (ii) the Kullberg *et al.*[5] study of candidiasis, which showed failure rates due to toxicity with voriconazole treatment of 15% versus 7% with amphotericin B/fluconazole treatment. Of course, clinical studies have strict criteria for adverse events and the impact on success within studies may not be relevant to general clinical practice. Nevertheless, the adverse event rates reflect measurable and, in some cases, significant toxicity at a frequency that warrants a thorough appreciation of the risks versus benefits and management approaches with the current antifungal armamentarium.

Understanding the tolerability and adverse event profile of antifungal agents is necessary to maintain optimal systemic antifungal therapy prescribing and thus to ensure improved outcomes. In this review, the tolerability and adverse event profiles of the main four classes of antifungal agents used for management of invasive fungal infections will be explored and their risks and benefits discussed.

Polyenes

Polyene antifungals exert their activity by binding to ergosterol in the fungal cell membrane, resulting in increased cell permeability and subsequent cell death. Amphotericin B is the polyene that has been the cornerstone of systemic therapy for decades, with the broadest spectrum of antifungal activity among all antifungals agents. Amphotericin B deoxycholate (AmBD) was the first formulation of amphotericin to be used, starting in the 1950s.[6] In the 1990s, lipid formulations of amphotericin B were developed to reduce the toxicity observed with AmBD: amphotericin B lipid complex (ABLC), liposomal amphotericin B (LAmB) and amphotericin B colloidal dispersion (ABCD). Overall, the estimated risk of patients developing adverse events necessitating discontinuation of therapy with all amphotericin B formulations is 13%.[7]

Amphotericin B is administered intravenously (iv), as well as locally in some circumstances. Nephrotoxicity is the most notorious adverse effect of iv amphotericin B preparations. By decreasing renal blood flow and causing distal tubular ischaemia, a transient decrease in glomerular filtration rate (GFR) and elevation in serum creatinine are encountered in up to 80% of patients on iv therapy.[8] AmBD can result in severe renal failure when administered with concomitant nephrotoxic or volume-depleting drugs, or in patients with underlying renal diseases. Importantly, patients who develop renal failure have been shown to have worse survival outcomes, longer hospital stays and greater costs of treatment.[9] It is clear that in modern medicine this nephrotoxicity cannot be tolerated and consequently, despite higher acquisition costs, much of the polyene use in resource-available health systems has converted to lipid formulations of amphotericin B.

With the development of the lipid formulations, nephrotoxicity has decreased. Several randomized clinical trials and meta-analyses showed that lipid formulations of amphotericin B had a significantly lower incidence of nephrotoxicity compared with AmBD.[10,11] There has been substantial discussion as to whether or not there is a difference between LAmB and ABLC in the incidence of nephrotoxicity. One study suggested LAmB was less nephrotoxic

Table 1. Overview of the main and unique toxicities associated with the various antifungal drugs

	Amphotericin B formulations					Azoles					Echinocandins		
Toxicity	AmBD	ABLC	LAmB	ABCD	5FC	FLC	ITC	VRC	POS	ISA	CAS	MCA	ANI
Gastrointestinal	✓	✓	✓	✓			✓	✓	✓	✓			
Hepatic	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Renal	✓	✓[a]	✓[a]	✓[a]									
Haematological	✓	✓	✓	✓	✓								
Neurological								✓					
Cardiac						✓	✓	✓	✓	✓			
Visual								✓					
Bone								✓[b]					
Skin						✓[b,c]		✓[b,d]					
Electrolyte disturbances							✓			✓			
Infusion-related	✓	✓	✓	✓[e]							✓	✓	✓

FLC, fluconazole; ITC, itraconazole; VRC, voriconazole; POS, posaconazole; ISA, isavuconazole; CAS caspofungin; MCA, micafungin; ANI, anidulafungin.
[a]Significantly less nephrotoxicity than with AmBD.
[b]Seen with long-term use.
[c]Includes chapped lips and alopecia.
[d]Includes chapped lips, alopecia, photosensitivity rash and skin cancers.
[e]Severe infusion reactions.

than ABLC, but a meta-analysis of multiple studies did not find a difference between these two formulations in nephrotoxicity.[12,13] It is likely that the risk of nephrotoxicity will not be a major factor in deciding between the use of these two lipid preparations. However, the incidence of nephrotoxicity is still high with the use of all polyenes. Therefore, it is recommended to adequately hydrate patients before and/or after a dose of any amphotericin B formulation as well as monitoring renal function daily for the first 2 weeks of therapy and then weekly.[14] A recent study assessing the use of *N*-acetylcysteine (NAC) during therapy to reduce nephrotoxicity of amphotericin B found that although NAC co-treatment was successful in reducing acute kidney injury, patients had a higher incidence of adverse reactions.[15,16]

Infusion reactions are commonly encountered in patients receiving iv AmBD and include nausea, vomiting, fever, chills, myalgias, bronchospasm and hypotension in severe cases. This reaction is thought to be due to the release of TNF-α and interleukin-1, and therefore premedication with acetaminophen, non-steroidal anti-inflammatory agents, low-dose steroids, meperidine or diphenhydramine may prevent or reduce the symptoms of these reactions.[17,18] ABCD has been reported to have severe infusion reactions and in fact this formulation is rarely used today owing to its toxicity.[19] LAmB has been associated with a lower incidence of infusion reactions compared with AmBD but it may result in particular adverse events such as flushing, urticaria, abdominal pain, chest pain, dyspnoea and hypoxia.[20] Importantly, patients who experience such reactions with one type of formulation do not necessarily have reactions to other formulations. For example, 85% of patients who previously had reactions to LAmB did not have infusion reactions to ABLC.[21] At times, less severe infusion reactions can be ameliorated by decreasing the infusion rate (and hence prolonging the infusion). Electrolyte disturbances, such as hypokalaemia and hypomagnesaemia, are common and can be frustrating when treating patients with prolonged polyene use. Biweekly monitoring throughout therapy is recommended. Reversible normocytic anaemia, thought to be due to suppression of erythropoietin, requires monitoring with weekly complete blood counts (CBCs).[22] However, profound anaemia with polyene therapies can occur in resource-limited countries in the acute management of cryptococcal meningitis in AIDS patients.[23,24] Measurement of liver function is only warranted if the patient experiences clinical evidence of liver toxicity, since hepatotoxicity due to polyene therapy is relatively rare.[25]

Flucytosine

Flucytosine (5FC) is a pyrimidine analogue that inhibits DNA and protein synthesis in fungal cells. It is no longer used as monotherapy owing to the rapid development of fungal drug resistance. Flucytosine, instead, is generally used in combination therapy with amphotericin B for the treatment of cryptococcal meningitis.[6]

Flucytosine is available intravenously (outside the USA) and as an oral capsule. Unfortunately, flucytosine has limited availability worldwide. The *in vivo* conversion of flucytosine to fluorouracil results in flucytosine's most significant toxicity, leukopenia and thrombocytopenia, by interfering with the synthesis of thymidine.[26] Interestingly, the toxicity has been more correlated with flucytosine levels than with fluorouracil levels.[27] Regular monitoring with CBCs is required during therapy and any significant decrease in neutrophil or platelet counts that cannot be attributed to another cause warrants dose reduction or discontinuation of flucytosine.

Hepatotoxicity is frequently encountered during flucytosine therapy, with patients developing elevations of serum aminotransferases and/or alkaline phosphatase, with some reports of hepatic necrosis.[26] Both haematological and hepatic toxicities have been

Table 2. Activity of the various triazoles on cytochrome (CYP) 450 enzymes[6,7,75–79]

CYP450 enzymes	Fluconazole	Itraconazole	Voriconazole	Posaconazole	Isavuconazole
Inhibition					
2C9	++	+	++		
2C19	+		+++		
3A4	++	+++	++	+++	++
Substrate					
2C9			+		
2C19			+++		
3A4		+++	+		*

+, Minimal activity; ++, moderate activity; +++, potent activity; *, sensitive but unclear.

associated with higher blood concentrations of flucytosine (>100 mg/L, 2 h after a dose). Thus, therapeutic drug monitoring is recommended 3–5 days after initiating therapy and after any changes in renal function, in order to keep the 2 h post-dose flucytosine levels between 30 and 80 mg/L.[28] Since flucytosine is excreted unchanged in urine, renal dysfunction results in higher blood concentrations and increases toxicity. Hence, dose modification for renal impairment is required.[26]

Azoles

The azoles inhibit synthesis of fungal ergosterol, increasing the cell membrane's permeability and resulting in fungal cell lysis and death. Imidazoles (e.g. ketoconazole) are not used for treatment of systemic mycoses at present because of their liver and hormonal toxicities. The triazoles are the newer generation of azoles and are represented by fluconazole, itraconazole, voriconazole, posaconazole and isavuconazole. These agents represent the backbone of systemic antifungal therapy today, with fluconazole being the mainstay of therapy for candidaemia in many parts of the world.[29] Contrary to their mechanism of action, the triazoles have demonstrated fungistatic activity against *Candida* species *in vivo*, with some having fungicidal activity against certain moulds, such as *Aspergillus* species.[30]

The most frequently encountered adverse events with all the triazoles are the generic symptoms of abdominal pain, nausea, vomiting and diarrhoea. These symptoms are more pronounced with oral itraconazole owing to the hydroxyl propyl-β-cyclodextrin vehicle used to increase its solubility.[31] Hepatotoxicity, ranging from elevation of serum aminotransferases to fatal hepatic failure, can also be encountered with all the triazoles.[32] Approximately 25% of patients receiving a triazole experienced some degree of hepatotoxicity.[33] However, unlike flucytosine, there is a less clear relationship with dose, duration of therapy or frequent administration of concomitant hepatotoxic drugs. To date, only voriconazole has been shown to have a blood drug concentration relationship with the potential development of hepatitis, such that trough levels >5.5–6 mg/L are associated with elevated serum aminotransferases.[34] Therefore, it is important to monitor serum aminotransferases in all patients after initiation of a triazole and, in the following weeks to months during prolonged therapy, to discuss with patients the symptoms of hepatitis and check chemistries periodically.

There are several general statements to be made about the triazoles. First, fluconazole, itraconazole, posaconazole, voriconazole and isavuconazole are cytochrome P450 (CYP450) inhibitors and/or substrates (Table 2), making drug–drug interactions common.[35] Dose modifications of the azoles and/or concomitant medications may be necessary with these interactions and careful consideration must also be given to readjusting dosing when discontinuing interacting drugs. The creation of new azoles (VT1161, VT1129 and VT1598; Viamet Pharmaceuticals, Inc.) using proprietary metalloenzyme chemistry has dramatically reduced CYP450 interactions and, thus, drug–drug interactions, but has retained potent antifungal activity, and these compounds have started clinical trials (NCT02267356, NCT02267382).[36] Second, all triazoles can prolong QT intervals so they must be evaluated in each individual patient with their other medications. Torsade de pointes physiology has also been linked to azoles. Isavuconazole seems to have some unique properties in that in almost half of patients the QT interval is actually shortened while receiving this triazole. Third, there have been reports with chronic azole use that peripheral neuropathies may occur[37] and this side effect is probably under-appreciated. Therefore, clinicians must be aware of extremity numbness, tingling or weakness in all patients on long-term azoles.

In addition to these general considerations, each of the triazoles has characteristic toxicities.

Fluconazole

Up to 20% of patients receiving long-term fluconazole for the treatment of endemic mycoses in one multicentre retrospective study experienced alopecia.[38] Chapped lips are another common and irritating side effect. These effects are not permanent and were reversible after dose reduction or discontinuation of fluconazole. In a meta-analysis of antifungal safety and tolerability by Wang *et al.*,[7] the rate of adverse events necessitating discontinuation of fluconazole was the lowest among the triazoles, at ∼2%, compared with ∼10% for voriconazole and ∼19% for itraconazole.[7] Fluconazole is a Category D drug for pregnancy and particularly its use during the first trimester and at high doses for prolonged periods may have implications for birth defects.[39,40]

Itraconazole

Hypertension, hypokalaemia, peripheral oedema and congestive heart failure, due to a negative inotropic effect and possibly an

aldosterone-like effect have been reported with the use of itraconazole. Some of these signs and symptoms are seen with higher doses such as 600 mg/day of itraconazole and therefore dosing higher than 400 mg/day is not generally recommended. It is also not recommended to use itraconazole in patients with heart failure or ventricular dysfunction.[41–43] In the aforementioned meta-analysis by Wang *et al.*,[7] the rate of adverse events requiring discontinuation of therapy with itraconazole was ∼19% and the highest among the triazoles.[7]

Voriconazole

A unique side effect of voriconazole is transient visual disturbances (photopsia), which have been known to occur a few minutes after receiving either oral or iv voriconazole. There is a suggestion that these effects are dose-related and occur more frequently with higher doses. The incidence of visual disturbances varies greatly among different studies and has been reported in the range of 6% to ∼45%, with higher rates being reported in the earlier trials.[44] These ocular side effects are generally reversible even when the drug is continued. Neurotoxicity has been associated with higher blood concentrations of voriconazole and may manifest as visual and/or auditory hallucinations, altered mental status, agitation and involuntary myotonic movements.[15] Up to ∼7% of patients experienced visual hallucinations in clinical trials.[44] It is important to distinguish between visual hallucinations and visual disturbances as the former is an indication of neurotoxicity and suggests higher than average voriconazole blood concentrations.

Voriconazole also has a series of other unique side effects. Rashes are common with voriconazole therapy and include a phototoxicity-like rash that is thought to be due to its metabolite voriconazole-*N*-oxide. Importantly, squamous cell carcinomas and melanomas have also been reported to develop on voriconazole therapy, mostly in immunocompromised patients receiving long-term voriconazole.[45–47] A thorough physical examination should be performed regularly in patients on long-term voriconazole to detect any suspicious skin lesions.

Alopecia involving the scalp, arms/legs, and eyebrows/lashes has been reported in ∼80% of patients on long-term voriconazole therapy, with some patients requiring a wig or hat to conceal the effects. Brittle, split or thinning nails occurred in 70% of patients.[48] These changes are mostly reversible and disappear within months of discontinuing or switching therapy.

Periostitis, inflammation of the periosteal layer of bone causing bone pain and elevated alkaline phosphatase, has been observed in patients receiving long-term voriconazole therapy. Periostitis is thought to be due to an excessive amount of fluoride, even resulting in fluorosis of the teeth at times. Voriconazole, which contains fluorine atoms in its structure, has been found to be associated with higher blood and tissue levels of fluoride during treatment.[49,50] Discontinuation of therapy reverses the periostitis.

QT prolongation and fatal arrhythmias have been reported in patients receiving voriconazole. However, these patients were severely ill and/or receiving concomitant interacting or QT-prolonging medications, and as noted in the general statements for the class, all azoles have generally had issues regarding QT prolongation.[51]

Intravenous voriconazole is limited to use in patients with a GFR >50 mL/min owing to the potential nephrotoxicity that can be caused by accumulation of sulphobutylether-β-cyclodextrin.[52] However, a small study did not find toxicity issues with the iv voriconazole formulation when used in patients with renal dysfunction for 7 days.[52] Owing to the dose–response relationship with voriconazole and its associated side effects, it is recommended, similar to flucytosine, that therapeutic blood concentrations should be monitored.[53]

Posaconazole

Intravenous posaconazole also contains a cyclodextrin solvent and thus has the potential for nephrotoxicity in patients with renal impairment.[54] It appears to have few other unique side effects but maintains the general issues of toxicity that surround the entire class.

With issues achieving stable therapeutic levels in patients receiving the oral suspension formulation, the development of the new extended-release tablet has made oral posaconazole a more attractive treatment option. In the Phase III clinical trial, the only adverse events encountered with the extended-release tablet were nausea (11%) and diarrhoea (8%).[55] Furthermore, the use of the oral tablet reduces the need for therapeutic drug monitoring. However, it may still be necessary to check blood concentrations in patients who do not respond to therapy or who require higher therapeutic levels.[55]

Isavuconazole

Isavuconazole is administered as its soluble prodrug, isavuconazonium sulphate. The iv formulation does not contain a cyclodextrin and hence carries no risk of accumulation or toxicity in patients with renal impairment. In addition to the common gastrointestinal symptoms and hepatotoxicity seen with the other triazoles, isavuconazole also causes hypokalaemia with shortening of the QT interval (unlike the QT prolongation seen with voriconazole and other azoles), and peripheral oedema.[56] It is contraindicated in patients with short QT syndrome. The incidence of infusion reactions is not clear but they are occasionally encountered with isavuconazole. In a large randomized trial in aspergillosis treatment, compared with voriconazole, isavuconazole was reported to have a lower incidence of drug-related adverse events and was generally well tolerated.[57]

Echinocandins

The latest addition to the antifungal armoury is the echinocandins. Introduced in the early 2000s, the echinocandins work by inhibiting synthesis of the fungal cell wall component 1,3-β-D-glucan. The resulting instability of the cell wall leads to cell lysis and death. This is the only class of antifungal agents at present that exerts activity on the fungal cell wall and not the cell membrane, resulting in no cross-reactivity with mammalian cell functions and thus reduced toxicity.[6] Unlike the azoles, echinocandins have significant fungicidal activity against *Candida* species and are currently recommended as first-line therapy for the treatment of candidaemia.[29,58–60]

The echinocandins are generally very well tolerated with few adverse events requiring discontinuation of the drug.[7] Compared with the triazoles, the echinocandins had less than half the

likelihood of discontinuation of therapy due to adverse events.[61] All the drugs in this class, caspofungin, micafungin and anidulafungin, have a similar tolerability profile. The most common adverse event is injection site pain or phlebitis, occurring in up to 25% of patients receiving caspofungin but in <1% with anidulafungin.[62]

Mild elevation of serum aminotransferases and alkaline phosphatase may necessitate monitoring but symptomatic abnormalities are rare. There have been animal studies that found tumours in animals receiving very large doses of micafungin.[63] However, this finding has not been replicated in humans and the echinocandins are generally not associated with significant liver toxicity. The incidences of serious hepatotoxicity in patients with no underlying liver disease were 0% and 6.5% for those receiving caspofungin and micafungin, respectively.[64] Our own experience with long-term use of both micafungin and caspofungin showed no differences in hepatic issues between these two echinocandins and no tumours.[65]

Infusion reactions (<5%) with echinocandins result from release of histamine, causing rash, hypotension, bronchospasm and angio-oedema, and are managed by slowing down the rate of infusion or premedicating with diphenhydramine or other antihistamines.[63]

Anaemia and cytopenias as well as cardiac toxicities have been reported but are extremely rare and do not warrant any monitoring during therapy.[66–69]

Rezafungin acetate (previously CD101; Cidara Therapeutics, Inc.) is a new echinocandin in development (Phase II study: NCT02734862). Preclinical data suggest that it has an improved safety profile compared with the other echinocandins due to its structural stability, minimal CYP450 enzyme interactions, and the lack of formation of reactive intermediates that is seen with other echinocandins.[70] This adverse event profile will need to be judged carefully since this echinocandin has a very prolonged half-life. So far, a Phase I clinical trial has shown rezafungin acetate to be very well tolerated at doses up to 400 mg administered once weekly for up to 3 weeks. There were no incidents of serious or severe adverse events and none requiring discontinuation of therapy, and the long half-life and linear pharmacokinetics of rezafungin suggest that less frequent dosing will be required for therapeutic success.[71]

With this favourable tolerability profile as a class, exploring the use of echinocandins for the treatment of invasive fungal infections as an alternative to amphotericin B and the triazoles has been critical to their use. In a large comparative trial, caspofungin was shown to have a response rate similar to that of a lipid formulation of amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia.[72] This is of great importance, as the patients on caspofungin had fewer adverse events that required discontinuation of the drug and therefore patients were able to remain on empirical therapy for a longer period of time. Similarly, in the candidaemia treatment study, caspofungin was equivalent to amphotericin B in efficacy but was much better tolerated.[4] Caspofungin and micafungin are currently recommended for empirical therapy and salvage therapy for invasive aspergillosis.[73] Echinocandins are recommended as first-line drugs for the treatment of candidaemia in both neutropenic and non-neutropenic patients.[29] Furthermore, although the acquisition costs of treatment with echinocandins were higher compared with fluconazole for the treatment of candidaemia and invasive candidiasis, their efficacy exceeded that of fluconazole by ∼15% and their side effect profile was minimal.[74]

Conclusions

The tolerability of antifungal agents has been a critical issue in their success for treatment of invasive fungal infections over the past 60 years. Fungi, like mammalian cells, are eukaryotes and so targets can be shared, making development of new drugs difficult. And yet new drugs are needed to treat systemic fungal infections. The original antifungal agent, amphotericin B deoxycholate, had such a narrow toxic–therapeutic ratio that it was given the well-earned nickname of 'amphoterrible' by clinicians. Clearly, such toxicity cannot be tolerated, especially in very sick and fragile patients who have life-threatening invasive fungal infections. The last two decades have seen substantial improvement in the development of antifungal drugs, and much of this improvement over amphotericin B deoxycholate has been in reduced toxicity. Amphotericin B is safer enwrapped in lipid formulations, triazoles are safer than the polyenes and the echinocandins are the safest of all antifungal classes. As clinicians, we are faced with balancing the tolerability of agents in the current antifungal armoury with the need for efficacious treatments. Advances in antifungal drug development that improve tolerability will serve to benefit our sick patients with invasive fungal infections.

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