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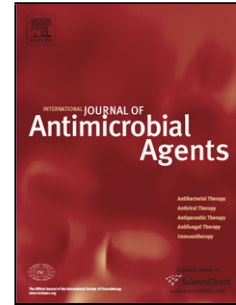
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New antifungal agents for the treatment of candidaemia

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Abstract

Suspected or proven invasive candidiasis is an important indication for antifungal drugs and a leading cause of death. Prompt initiation of effective therapy has a marked effect on survival, but the indiscriminate application of different risk factor-based prediction models is massively increasing the number of patients treated unnecessarily. Fluconazole resistance levels are <5% in most European centres and the use of low doses is still common. Candins are fungicidal, have efficacy against device-related infections, have few interactions and are well tolerated. Accordingly, the use of newer, more expensive drugs must be carefully balanced in each case. Campaigns directed towards stewardship in antifungal drug use must take into consideration the choice of the drug, the dose and route of administration, and the length of therapy. Early microbiological information and medical education may contribute to better use of these important drugs. We review the characteristics of the new antifungals used for the treatment of candidaemia.

Keywords:

Candidaemia

Echinocandins

Voriconazole

Anidulafungin

Micafungin

Caspofungin

1. Introduction

Candida spp. are the most common cause of nosocomial invasive mycosis. Although the fourth most frequently isolated microorganism from blood cultures, it is the leading cause of related mortality, which remains near 40% in most series.

Different studies demonstrate that the rate of candidaemia is increasing. Figures from our institution demonstrate that the incidence of candidaemia per 100 000 inhabitants has increased from 1.7 episodes in 1985 to 12.5 in 2006 ($P < 0.0001$) [1]. This trend has been confirmed by other authors. A large series summarizing 10 319 418 cases of sepsis from a sample of non-federal acute care hospitals in the USA showed that cases of fungaemia increased by 207% from 1979 through 2000 [2].

It is estimated that 33–55% of candidaemia episodes occur in intensive care units, but many hospital departments are affected by the problem. In a recent European study the proportions of surgical and critical patients affected were 44.7% and 40.2%, respectively [3].

The cost of a candidaemia episode has been estimated at US\$44 000 for adults and US\$28 000 for neonates [4,5]. However, the exponential increase in hospital expenditure on antifungal drugs (fourfold increase since 2001) is not justified by the increase in the number of proven infections. The reasons are multiple, but a change in the way drugs are prescribed and the use of newer antifungal drugs, sometimes in combination, are part of the problem. The cost of treating a candidaemic episode with fluconazole is around €240, and with an echinocandin is over €6000. The change in the way drugs are prescribed relates to the observation that at least 70% of drugs prescribed are part of a pre-emptive strategy [6]. Drugs are frequently started after using one of the available predictive scores (Ostrosky 1 or 2, Candida score, etc.) [6–

9], without taking into account that, although their negative predictive value is high, their positive predictive value is <15%.

Candidaemia can be treated with several classes of drug (azoles, candins or polyenes), the choice of which depends on the local epidemiology, the percentage of strains resistant to fluconazole, the origin of the infection, and the patient's comorbidities, among others [10]. Although non-albicans strains have clearly increased, in most European centres the rate of resistance to fluconazole is <5% [3,11,12].

Rapid detection of resistance directly from blood samples may help in this decision [13]. Newer antifungal drugs may, however, confer advantages, such as more rapid sterilization of blood cultures, more efficacy in critically ill patients or activity in device-related infections. All these aspects have to be further investigated. We summarize here the most important characteristics of the echinocandins and voriconazole – the newer drugs for the treatment of candidaemia.

2. In vitro antifungal activity of echinocandins and voriconazole

During the past decade, the antifungal armamentarium against *Candida* spp. invasive infections has been extended by the introduction of a new family of very effective antifungal agents, the echinocandins. The new triazoles – voriconazole and posaconazole – also have high in vitro activity against *Candida* spp. isolates, although they are less commonly used for the initial treatment of invasive candidiasis [14].

The echinocandins target the fungal cell wall and act by inhibiting 1,3- and 1,6- β -D-glucan synthesis, showing fungicidal activity against *Candida* spp. [15]. Pfaller et al. demonstrated the potent in vitro activity of the echinocandins against invasive *Candida* isolates (minimum inhibitory concentration [MIC₉₀] for *Candida* spp.:

0.25 µg/ml for caspofungin, 1 µg/ml for micafungin and 2 µg/ml for anidulafungin) [16].

Despite this practically uniform susceptibility there are some slight differences in the antifungal susceptibility of different species to these agents. Most isolates of *C. albicans*, *C. glabrata*, *C. tropicalis* and *C. krusei* have a modal MIC ≤ 0.06 µg/ml. By contrast, *C. parapsilosis* and *C. guilliermondii* yield systematically lower susceptibility (MIC₉₀ 1–2 µg/ml). Fluconazole-resistant strains are susceptible to echinocandins [17].

Although observed infrequently to date, some *Candida* isolates are resistant to echinocandins. The mechanisms are not completely established. The echinocandins are rarely affected by the efflux pumps, however, mutations in the *FKS1* gene encoding the target enzyme (FKS1) may lead to decreased susceptibility to these agents [18–24]. Resistance to one of the echinocandins confers resistance to the others. The Etest seems to be more efficient than the microdilution procedure for detecting these mutants.

3. Clinical efficacy, pharmacokinetics and toxicity of the echinocandins and voriconazole

The new guidelines published by the Infectious Diseases Society of America in 2009 [25] recommend the use of one of the three candins as initial therapy for the treatment of candidaemia in non-neutropenic adult patients (A-I) if the patient has been recently exposed to azoles, is colonized by a resistant strain or is haemodynamically unstable (shock). In Europe, micafungin and caspofungin are also indicated for candidaemia in neutropenic (A-III) patients and in children and neonates.

We will briefly review the most important clinical trials that led to these indications and mention some key characteristics of each drug.

3.1. Caspofungin

3.1.1. Clinical data

Caspofungin showed comparable clinical efficacy but less toxicity than amphotericin B deoxycholate for the treatment of invasive candidiasis in a non-inferiority trial including adult patients (Table 1) [26]. The study recruited patients aged >18 years with *Candida* isolated from blood cultures or other sterile sites, and with clinical evidence of infection. Patients were stratified according to APACHE score (Acute Physiology and Chronic Health Evaluation) and the presence or absence of neutropenia. They were assigned to receive caspofungin (70 mg loading dose followed by 50 mg per day) or amphotericin B (0.6–1.0 mg/kg per day).

[Table 1 here]

A total of 224 patients were analysed, most of whom had candidaemia. *C. albicans* and *C. parapsilosis* were the species most frequently isolated. Patients treated with caspofungin showed favourable response/mortality rates of 73.4%/34.2% vs. 67.7%/30.4% in patients treated with amphotericin B deoxycholate. The outcome was worse in patients with neutropenia or an APACHE score >20, but there was no difference according to the *Candida* species. Caspofungin showed higher efficacy than amphotericin B against *C. parapsilosis* (70% vs. 65%), but five of the nine patients with persistent candidaemia were infected by *C. parapsilosis*. More than half of the patients included in each group had a central venous catheter at the time of the diagnosis, and the management of the catheters did not differ significantly between groups.

Another study suggested that higher doses of caspofungin did not improve clinical efficacy [27]. A total of 197 adult patients with invasive candidiasis were randomized to receive caspofungin at 150 mg vs. 50 mg per day. The rates of response were 77.9% and 71.6%, respectively and treatment was well tolerated at both dosages. Although non-fungaemic invasive candidiasis is considered a poor prognostic factor, Cornely et al. reported overall success in 81% of patients with proven non-fungaemic invasive candidiasis receiving caspofungin; outcomes were similar across different *Candida* species [28].

In order to get a better understanding of the clinical efficacy of caspofungin for the treatment of candidaemia caused by non-albicans *Candida* species, Colombo et al. performed a retrospective analysis including 212 patients treated with caspofungin [29]. At the end of caspofungin therapy, the rate of success ranged from 70% (*C. krusei*) to 100% (*C. lusitanae*). Of interest, a favourable outcome was achieved in 74% of patients with candidaemia caused by *C. parapsilosis*.

Zaoutis et al. evaluated the safety, tolerability and efficacy of caspofungin in 38 children (aged from 3 months to 17 years) with invasive candidiasis (92% with candidaemia) in a prospective multicentre open-label study [30]. Most patients were receiving caspofungin as the primary treatment, were carrying an intravenous catheter (79%), were receiving broad-spectrum antibiotics (74%) or were immunosuppressed (55%). A favourable outcome was achieved in 81.1% [64.8–92%] of patients. Of interest, seven of the eight patients infected by *C. parapsilosis* had a favourable outcome. Adverse events were common (clinical 23.7%; laboratory 39.5%), however, none of them required treatment discontinuation [30,31].

3.1.2. Pharmacokinetics and adverse events

As with the other candins, caspofungin is not absorbed after oral administration and is only available for intravenous infusion. Caspofungin showed pharmacokinetic linearity, with clearance from plasma and $t_{1/2\beta}$ values independent from the dose [32]. Adjustment of doses in patients aged ≥ 65 years, or in those with renal insufficiency, is not required as renal clearance of caspofungin is very slow [32]. It is highly protein-bound (96%) and cannot be removed by haemodialysis. However, in patients with moderate liver disease (Child–Pugh 7–9) the recommended dose of caspofungin is 35 mg per day.

Serum levels $>1 \mu\text{g/ml}$, a concentration that exceeds the MIC at which 90% of clinically relevant isolates of *Candida* are inhibited, are achieved through therapy with daily doses of 50 mg plus a loading dose of 70 mg [32,33]. Caspofungin is spontaneously degraded and further metabolism implies hydrolysis and *N*-acetylation. Caspofungin is not an inhibitor of cytochrome P450 and not a substrate of the P protein; however, ciclosporin increases the caspofungin area under the curve by 35% and they should be used together with caution. By contrast, caspofungin decreases the plasma concentration of tacrolimus. Interference with rifampicin, efavirenz, phenytoin, dexamethasone and carbamazepine has also been described.

Adverse events related to the administration of caspofungin are common, occurring in around half of patients. However, they are usually mild (headache, chills, fever, local tolerability, nausea and vomiting) and require treatment discontinuation in a small proportion of patients (2.6%) [26,32]. Caspofungin showed a significantly lower rate of adverse events requiring discontinuation than amphotericin B [26].

3.2. Anidulafungin

3.2.1. Clinical data

Anidulafungin is a semi-synthetic lipopeptide derivate of *Aspergillus nidulans*. The clinical efficacy of anidulafungin vs. fluconazole for the treatment of invasive candidiasis was assessed in a randomized double-blind non-inferiority trial [34]. The study included 245 adult patients (only 12 solid transplant recipients). Clinical efficacy was assessed as the global, clinical and microbiological response at the end of the intravenous treatment given for a minimum of 10 days. *C. krusei* species were excluded from this study.

A global response was achieved in 75.6% of patients who received anidulafungin, compared with 60.2% in patients who received fluconazole. Of interest, 29 patients were infected by *C. parapsilosis*, and those receiving anidulafungin had significantly lower eradication rates (69%) than those treated with fluconazole (88%). Global mortality was also lower for patients receiving anidulafungin (23%) than for patients receiving fluconazole (31%), but the difference did not reach statistical significance.

As with other echinocandins, the clinical efficacy of high doses of anidulafungin has been assessed in a randomized double-blind study, which included 68 patients with candidaemia or invasive candidiasis treated with different doses of anidulafungin (50 mg, 75 mg and 100 mg per day). The success rates at follow-up were 72%, 85% and 83%, respectively, and at 2 weeks after the end of therapy were 84%, 90% and 89%, respectively. Although there was a trend to achieve higher success rates at doses >50 mg, the authors did not find statistically significant differences [35].

There are practically no data in special populations yet. One multicentre study included 12 neutropenic paediatric patients aged 2–17 years, in whom the safety of

anidulafungin was evaluated. Patients were treated with anidulafungin 0.75 or 1.5 mg/kg of body weight per day; two patients had drug-related adverse effects (fever and facial erythema) [36].

3.2.2. *Pharmacokinetics and adverse events*

Anidulafungin has good tissue penetration and a prolonged post-antibiotic effect. Its metabolism is markedly different from the other echinocandins, its clearance appearing to be primarily due to slow non-enzymatic chemical degradation by plasma peptidases in serum to an inactive metabolite, with no evidence of hepatically mediated metabolism. Anidulafungin has been shown to be eliminated in the faeces, predominantly as degradation products, and only a small fraction (10%) as unchanged drug. Faecal elimination likely occurs via biliary excretion [37]. As a consequence, anidulafungin has no interaction with other drugs metabolized in the liver and it can be safely used in patients with hepatic and/or renal insufficiency. A retrospective study evaluated anidulafungin in 35 patients with hepatic dysfunction (70%) and candidaemia or invasive candidiasis. Ten patients were solid or hematopoietic stem cell transplant recipients. A favourable outcome was assessed in 77% of 13 patients who were evaluated [38]. No dosage adjustment is necessary, even in patients undergoing haemodialysis.

Since it has no hepatic metabolism via cytochrome P450, it is ideal for transplant recipients receiving calcineurin inhibitors, although more data are needed. Dowell et al. conducted a study in healthy volunteers and observed that anidulafungin did not alter the metabolism of ciclosporin or voriconazole [39,40]. In another retrospective study there was no interaction with metronidazole [38].

The most common adverse events related to the use of anidulafungin were hypokalaemia, hypotension, nausea, vomiting, constipation and pyrexia (5–13%) [35]. Anidulafungin has fewer side effects than fluconazole [34,41].

3.3. *Micafungin*

3.3.1. *Clinical data*

Micafungin was approved by the US Food and Drug Administration in 2005 to treat oesophageal candidiasis and for prophylaxis of *Candida* infections in hematopoietic cell transplant recipients. In 2008 the indications were expanded to include the treatment of invasive candidiasis or candidaemia in adults, neutropenic patients and in children and neonates.

The clinical efficacy of micafungin as first-line treatment of invasive candidiasis or candidaemia was demonstrated in a double-blind randomized multinational non-inferiority study that compared micafungin (100 mg per day) with liposomal amphotericin B (3 mg/kg per day) [42]. A total of 115 centres and 531 adult patients were included, of which 57 were neutropenic and 90 were solid organ transplant recipients. The end point was clinical and mycological response (complete or partial) at the end of treatment. Overall treatment success rates in the modified intention-to-treat population receiving micafungin or liposomal amphotericin B were 74.1% and 69.6% (95% CI 4.5; -3.5 to 12.4), respectively. Neutropenic patients were included, 32 treated with micafungin and 25 with liposomal amphotericin B. The success rates in this population were 59.4% and 56% (95% CI 4.9; -3 to 12.8), respectively.

One study to date has compared two candins – micafungin and caspofungin. This study was a randomized double-blind multinational study in adult patients with candidaemia and invasive candidiasis, stratified by APACHE II score. Caspofungin

was given to 188 patients at 50 mg per day and micafungin to 191 patients at 100 mg per day and to 199 at 150 mg per day. The study included 16 solid organ transplant patients. The end point was clinical and microbiological success at the end of blinded intravenous treatment. Patients continued with intravenous treatment for a minimum of 10 days. Treatment success was similar in the three groups (76.4%, 71.4% and 72.3%, respectively). The higher dose of micafungin was not associated with a better outcome [43].

A study including paediatric patients compared micafungin (2 mg/kg per day) with liposomal amphotericin B (3 mg/kg per day) as first-line treatment of invasive candidiasis [44]. The study included 98 patients <16 years old (including neonates) with clinical signs of systemic *Candida* infection and with one or more positive *Candida* cultures from blood or another sterile site. The primary end point was clinical and mycological response at the end of therapy. Forty-eight patients received micafungin (response rate 72%) and 50 patients received liposomal amphotericin B, 76% reaching a clinical response. There were no differences in overall mortality at 3-month follow-up (25% vs. 24.1%) or in the related mortality rates (7.7% vs. 5.6%).

One study including four premature infants retrospectively analysed the efficacy and tolerability of micafungin for treating *Candida* infections. All patients responded to the treatment and no side effects were reported [45].

There is evidence that micafungin is effective for the treatment of invasive candidiasis in transplant recipients. An open-label non-comparative study was performed in 13 countries and included 126 patients. Micafungin was given as first-line therapy in 72 patients and as salvage therapy in 54 patients. Eighteen (14.3%) were bone marrow transplant recipients, 29 (23%) had neutropenia and 4 (3.2%)

patients had received a solid organ transplant. Global response at the end of therapy was 83.3% (95% CI 76–89); the response to micafungin as first-line therapy 87.5%; and the responses to salvage therapy 79.3% (combined with another antifungal drug) and 76% (alone) [46]. A study that included 18 transplant patients showed therapeutic efficacy in all of them with excellent tolerance (only one had an increase in sirolimus levels) [47].

Micafungin is fungicidal and has demonstrated in vitro and in vivo efficacy against yeast embedded in biofilms. The in vitro effectiveness of micafungin in the reduction or control of fungal biofilms associated with silicone medical devices has been demonstrated. Micafungin was able to induce a significant and persistent reduction in the yeast metabolic activity of intermediate and mature biofilms of *Candida albicans* when used in catheter lock solutions (5 mg/L) [48]. This effect may be essential, since not removing the intravenous catheter has been a consistently poor prognostic factor. This may not hold true if micafungin is used. Nucci et al, in a post hoc analysis of two prospective phase 3 micafungin trials [42,43] showed that prompt removal of a baseline central venous catheter by 24 or 48 h after treatment initiation with micafungin was not associated with overall treatment, 28-day survival, or 42-day survival [49]. This is clearly one of the most promising areas in the field, and good-quality prospective data are warranted.

3.3.2. Pharmacokinetics and adverse events

Micafungin is the only candin that does not need a loading dose. The recommended daily dose is 100 mg/day. Micafungin shows linear pharmacokinetics, with a long elimination $t_{1/2}$ for once-daily doses. It has hepatic metabolism mediated by the action of an arylsulfatase and catechol-O-methyltransferase; it is metabolized to a lesser

extent by the cytochrome P450 isoenzymes. It has a low clearance of 0.197 mL/min per kg, an elimination half life of 13.9 h and the urinary recovery is <1% [50].

Micafungin is a weak substrate of cytochrome P3A4 [51], and may increase levels of sirolimus (up to 21%), nifedipine (up to 18%) and itraconazole (up to 22%). By contrast, no changes were observed in plasma levels of other drugs such as tacrolimus, mycophenolate, ciclosporin, fluconazole, prednisone and voriconazole [52–55].

Undre et al. studied the pharmacokinetics of micafungin in eight subjects with severe hepatic dysfunction, and although the intrinsic clearance was higher than in the control group, the difference was not statistically significant and it was concluded that no dose adjustment was necessary [56]. In experimental animals, hepatic tumours were reported after 3 months of treatment with high doses of the drug. This effect has not been detected in humans.

It is a well-tolerated drug and the discontinuation of treatment was requested only in 3.0–4.9% of patients, compared with 9% of patients treated with liposomal amphotericin. The most common adverse effects are nausea, vomiting, diarrhoea, phlebitis, fever and hypokalaemia. The largest difference, compared with liposomal amphotericin B, is the lower renal toxicity associated with micafungin [42].

In paediatric patients, adverse effects were fever, vomiting, diarrhoea, anaemia, thrombocytopenia and hypokalaemia, and additionally in this population the proportion of treatment withdrawals was inferior to that of liposomal amphotericin B (3.8% vs. 16.7%, $P = 0.005$) [44]. No dosage adjustment is necessary in renal failure or haemodialysis [57,58]. During pregnancy it should be used with caution (category C).

3.4. Voriconazole

3.4.1. Clinical data

Voriconazole showed high in vitro antifungal activity against *Candida* isolates [59,60]. In 52 patients with invasive candidiasis intolerant of or refractory to other antifungal agents, voriconazole showed an overall rate of response of 56% (95% CI, 41–70) [61]. Voriconazole efficacy has been assessed in non-neutropenic patients with candidaemia. Patients were randomized to receive voriconazole ($N = 283$) or amphotericin B followed by fluconazole ($N = 139$). Voriconazole was not inferior to amphotericin B/fluconazole (success rates 65% and 71%, respectively) in the primary efficacy analysis [62].

3.4.2. Pharmacokinetics and adverse events

Voriconazole is available in both oral and parenteral formulations. The oral bioavailability of voriconazole is 190%; it is not affected by gastric pH but it decreases when the drug is administered with food. Oral voriconazole can be used as sequential therapy for completing therapy in patients with fluconazole-resistant strains [63].

Cerebrospinal fluid and vitreous penetration of voriconazole is excellent [64]. The corresponding maximum plasma concentration found in serum was 1.88 mg/L (200 mg), 4.84 mg/L (300 mg) and 5.27 mg/L (400 mg) when determined after 7 days of oral dosing. The plasma protein binding of voriconazole is moderate (58%).

Because of the potential for cyclodextrin accumulation among patients with significant renal dysfunction, intravenous voriconazole is not recommended for patients with a creatinine clearance <50 mL/min; however, oral voriconazole does not require dosage adjustment. Voriconazole is the only triazole requiring dosage

reduction for patients with mild-to-moderate hepatic impairment. It shows wide variability in serum levels, which must be monitored. Drug–drug interactions are very common [25]. Adverse events and laboratory abnormalities are relatively common, although not usually severe. One of the most distressing adverse effects is visual disturbance.

4. New antifungals in development

Isavuconazole (BAL4815) is an experimental triazole currently in phase 3 trials for the treatment of fungaemia. It has shown excellent in vitro antifungal activity against different species of *Aspergillus*, *Mucorales*, *Candida*, *Cryptococcus* and other rare yeast pathogens [65–67]. To date, three clinical trials evaluating isavuconazole for the treatment and prevention of invasive fungal infections are in progress or have been completed. Unfortunately, clinical efficacy results are not yet available.

Aminocandin is a water-soluble echinocandin that has shown potent in vitro and in vivo activity against *Candida* and *Aspergillus* spp. [68]. However, no data on clinical efficacy in humans are available.

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Table 1

Summary of trials in patients with invasive candidiasis (IC)

Accepted Manuscript

Antifungal	Clinical efficacy [reference]	Clinical indication	IDSA guidelines	Dosages and interactions	Adverse events	
Caspofungin	Caspofungin is not inferior to amphotericin B deoxycholate	[26]	Treatment of IC in adult patients	Initial therapy adult non-neutropenic (A-I) and neutropenic (A-III) patients with candidaemia, especially patients exposed to an azole or in severely ill patients	70 mg loading dose followed by 50 mg per day for 14 days	Adverse events common (approx. 50% of patients) but usually mild (headache, chills, fever, local tolerability, nausea, and vomiting) Treatment discontinuation in a small proportion of patients (2.6%)
	Caspofungin is effective for the treatment of IC in children	[30]	Treatment of IC in children (12 months to 17 years)	In neonates, caspofungin should be used with caution (B-III)	70 mg/m ² loading dose followed by 50 mg/m ² per day for 14 days	
Anidulafungin	Anidulafungin is not inferior to fluconazole in patients with IC.	[34]	Treatment of IC in adult patients	Initial therapy for treatment of adult non-neutropenic (A-I) and neutropenic (A-III) patients with candidaemia, especially patients exposed to an azole or in severely ill patients	200 mg loading dose followed by 100 mg per day No interaction with calcineurin inhibitors or azoles	Anidulafungin has fewer side effects than fluconazole (11 vs. 16 patients)
	Anidulafungin is safe and effective for treating IC	[35]	Treatment of IC in adult patients with different doses (50, 75 and 100 mg)			Hypokalaemia, hypotension, nausea, vomiting, constipation and pyrexia (5–13%).
	Micafungin is not inferior to liposomal amphotericin B	[42]	First-line treatment of IC or candidaemia in adult patients			2–3% nausea, vomiting, diarrhoea, phlebitis, fever and hypokalaemia 8% hepatic alteration
	Micafungin is not inferior to caspofungin	[43]	Treatment of IC and candidaemia in adult patients			3% discontinue therapy due to an adverse treatment effect