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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.

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 summarising 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 preemptive 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 co-morbidities, 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 sterilisation of blood cultures, more efficacy in critically ill patients or activity in device-related infections. All these aspects have to be further investigated. We summarise here the most important characteristics of the echinocandins and voriconazole – the newer drugs for the treatment of candidaemia.

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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 [MIC_{90}] 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 (MIC_{90} 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 colonised 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).

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 similar favourable response/mortality rates of 73.4%/34.2% vs. 67.7%/30.4% to patients treated with amphotericin B deoxycholate and less toxicity. 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 randomised 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. lusitaniae*). 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 μg/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