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Assessment of the Efficacy, Safety and Cost-Effectiveness of Micafungin Compared to Caspofungin and Low Dose Liposomal Amphotericin B for the Treatment of Candidaemia and Clinically Diagnosed Invasive Candidiasis: A Retrospective Audit

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Abstract

Despite several studies having highlighted that candidaemia and invasive fungal disease (IFD) are associated with high mortality and increased costs, there are currently few published studies which provide an insight into real-life practice of invasive candidal diseases. In a medium-sized district general hospital in the UK we sought to compare the efficacy, safety and treatment cost of micafungin versus caspofungin and low dose of liposomal amphotericin B (L-AmB) 1mg/kg/day for the treatment of confirmed candidaemia or clinically diagnosed invasive fungal disease (CDIFD). In the present retrospective audit, a total of 126 patients with candidaemia or CDIFD were reviewed from hospital records and 94 were included in our audit. Twenty-eight had candidaemia and 66 had CDIFD. At baseline, the three treatment arms were comparable in relation to demographics and severity of disease. Presence of *Candida non-alibicans* species were high both in candidaemia and CDIFD among which *C. glabrata* or *C. koseri* confirming the need to adapt the empirical treatment based on the local epidemiology. The clinical and microbiological successes were comparable between groups but, significant differences were observed in terms of safety and treatment cost. Micafungin was the drug the most frequently associated with hepatotoxicity (28%) compared to caspofungin (3%, $P<0.05$) and L-AmB group ($P<0.005$). L-AmB appears to be the cheapest drug (total treatment cost) with a mean cost of £2782 compared to £3986 for micafungin ($P<0.005$) and £4616 for caspofungin ($P<0.0001$). The present audit suggests that using low dose of L-AmB (1mg/kg/day), a favourable benefit/risk balance is obtained when compared to micafungin and a favourable cost-benefit is reached when compared to caspofungin and micafungin. Further prospective studies may be useful to study more in depth the clinical advantage of low dose L-AmB compared to other antifungal therapies.

Keywords: Liposomal amphotericin B; Caspofungin; Micafungin; Candidaemia; Invasive fungal disease

List of Abbreviations: CDIFD: Clinically diagnosed Invasive Fungal disease; LFTs: Liver function tests; SPC: Summary of Product Characteristics; PBR: Payment by Results; NS: Not significant; L-AmB: liposomal amphotericin B; CASP: Caspofungin; MICA: Micafungin; IA: Invasive Aspergillosis; IDSA: Infectious Diseases Society of America; MIC: Minimum Inhibitory Concentration; EORTC-MSG: European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group; ICU: Intensive Care Unit

Introduction

Echinocandins (such as micafungin and caspofungin) and polyenes such as liposomal amphotericin B, have broad-spectrum activity against *Candida* species. The prevalence of *candida* species has been demonstrated to vary in different patient populations and geographical regions. Candidaemia and invasive fungal disease (IFD) are associated with high mortality and increased costs [1,2]. For many years *Candida albicans* was established as the most common cause of candidaemia. However in recent years there has been an increase in the isolation of *Candida non-albicans* species driving a re-analysis of protocols [3-12].

The choice of an antifungal agent for suspected IFD is quite complex and is dependent on many factors [13,14]. These include but are not exhaustive to: history of recent azole exposure, prevalence of different *Candida* species (i.e., knowledge of one's local epidemiology), current antifungal susceptibility data in the clinical unit/medical centre, severity of illness, relevant comorbidities that increase the risk of fluconazole-resistant *Candida* species (e.g., neutropenia), penetration of the chosen antifungal agent to the site of infection, antifungal spectrum of activity and history of intolerance to an antifungal agent. This is confirmed in the literature by the latest published International Antifungal guidelines where the IDSA specifically state that: "*the choice will still be voluntary for the clinician due to individual variation among patients', variation in specialities for each centre and depending on patients' individual parameters*" [13].

In our hospital, fluconazole was recommended (subject to previous triazole exposure and potential drug interactions) as first line therapy for empirical and confirmed non-neutropenic *Candida albicans* candidaemia or invasive fungal disease. Liposomal amphotericin B (L-AmB) 3mg/kg/day or voriconazole were recommended for invasive aspergillosis, an echinocandin or L-AmB 1mg/kg/day for empirical or confirmed non-neutropenic *Candida non-albicans*. Interestingly, there is a paucity of clinical experience with the 1mg/kg/day dose despite it being a licenced dose specifically listed for systemic mycoses.

Supported by the Drugs and Therapeutic Committee, a formulary decision was taken in August 2012 at our large provider of acute hospital services in Surrey (serving a population of 380,000 people) to replace the echinocandin of choice (caspofungin) with micafungin due to the fact that micafungin was cheaper and, on the opposite of caspofungin, licenced in neonates. However, there were concerns expressed by clinicians in regards to the hepatotoxicity associated with micafungin.

Consequently, an audit was settled to evaluate the efficacy, safety and treatment cost of micafungin in comparison to the existing standard of care within the hospital trust (caspofungin and low-dose liposomal amphotericin B).

Materials and Methods

The current audit was conducted for internal hospital guidance as a service evaluation, and was initiated at the request of the Antibiotic Group in Ashford & St. Peter's Hospitals (ASPH) NHS Foundation Trust. Neither consent, nor ethical approval was needed as the data collection was retrospective and for local guidance. It was not deemed to be a formal research project.

Medical notes of patients with candidaemia or CDIFD who had received micafungin (100 mg, once a day), caspofungin (first day at 70 mg once a day and from day 2, 35 mg once a day (if hepatic impairment with Child-Pugh score of B) or 50 mg once a day (if <80kg) or 70 mg once a day (if ≥80kg) or L-AmB (1mg/kg after initial test dose of 1mg over 10 mins) between January 2008 and June 2014 were retrieved and reviewed retrospectively. The diagnosis of Candidaemia was confirmed if there was found to be *Candida* species present in the blood and also compatible clinical signs. CDIFD was defined as a persistent mycological positive culture and compatible clinical signs [15]. Patients were included in the audit, if they were adults (>18 years old), they received one of the three drugs for at least 3 days and, had a temperature ≥38 °C or ≤36 °C. Patients were excluded if they received another systemic antifungal agent (except fluconazole) or, if they suffered from an Invasive Aspergillosis. Patients who had fluconazole were not included in this audit as fluconazole doesn't have the same spectrum of cover as caspofungin or micafungin or Liposomal amphotericin B therefore won't be comparable.

Age and microbiological data were recovered and patients were classified using the Candida score based on the following criteria: multifocal candida colonization (1 point), surgery (1 point), receipt of Total Parenteral Nutrition (1point) and clinical signs of severe sepsis (2 points) [16]. This allows predicting invasive candidiasis in non-immunocompromised patients, especially in those who are critically ill. Patients are at high risk if they have a score of ≥3 while a score ≤2 is considered low risk for invasive candidiasis

Three end points were evaluated: the clinical efficacy, the safety and the cost-effectiveness.

(i) The clinical outcome was classified as: success, failure, indeterminate or relapse. Success was defined as the improvement of clinical symptoms combined with a negative culture. Failure was defined as the continuing or worsening of clinical symptoms and the presence of positive culture despite at least 3 days of treatment. Indeterminate was categorised by the inability of the treating physician to make a clinical judgement on the outcome due to their inability to repeat or obtain a further culture (or where culture was inconclusive). In addition, the classification may have been defined as indeterminate if other risk factors and co-morbidities may have resulted in mortality where no post-mortem was conducted to determine the true cause of death and fungal diagnostics were not performed before death. Relapse was categorised as repeated positive culture within 2 months of initial treatment. Relapse was deemed to have occurred if it could be confirmed by positive culture >14 days after patients had been classified as having been clinically cured with confirmation by persistently negative blood cultures. The local guidelines follow the latest published International Antifungal guidelines for Candidaemia and Invasive Candidiasis by the Infectious Diseases Society of America (IDSA) [13]. These guidelines recommend repeating a positive culture after 3-5 days and continuation of treatment for 14 days following the last negative culture to prevent relapse.

(ii) The safety was based for the hepatotoxicity on increases in Liver Function Tests (LFTs), specifically transaminases and worsening of Child-Pugh score and for the nephrotoxicity, on an increase in baseline serum creatinine of ≥50% if it could be confirmed that it was specifically not due to sepsis or chronic renal failure. Systemic reactions were also extracted.

(iii) The treatment cost analysis was possible by retrieving data of patients receiving thanks to the micafungin, caspofungin or

L-AmB from the NHS England PBR (Payment by Results) monthly database. Currently the National Health Service (NHS) commissioning in England reimburses high cost antifungals such as micafungin, caspofungin and L-AmB. The procedure involves the hospital submitting their PBR data to the NHS commissioning team directly. They in return will review expenditure and query anything viewed or deemed inappropriate before crediting the money back. Those data were retrieved for patients treated with micafungin for the period of August 2012 to June 2014 and for those treated with caspofungin and low dose L-AmB from January 2008 to December 2012. The approximate prices of the antifungal agents which were available to the hospital at the time of the audit were: micafungin (Mycamine®) 100mg vial: £289, caspofungin (Cancidas®) 70mg vial:£373, caspofungin (Cancidas®) 50mg vial: £293 and L-AmB(AmBisome®) 50mg vial:£96.

Statistical analysis was performed using Fisher's exact test for discrete variables and ANOVA test for continuous variables. Post-hoc analysis of continuous variable was performed using Tukey HSD. All tests were performed with JMP 13.2.1 (SAS Institute inc.).

Results

One hundred and twenty-six patients who received micafungin, caspofungin or L-AmB were recovered from the medical notes. Among which 94 fulfilled our inclusion and exclusion criteria. Twenty eight had candidaemia and 66 had CDIFD. In total 79/94 (84%) of patients had proven IFD; as 28/94 patients had positive blood cultures and 51/94 had deep-sterile cultures. 16% (15/94) were superficial cultures and could therefore be classified as probable/possible IFD.

Twenty nine patients were treated with micafungin (9 in the candidaemia group and 20 in the CDIFD). Thirty patients were treated with caspofungin (9 in the candidaemia group and 21 in the CDIFD). Thirty five patients were treated with L-AmB 1mg/kg once daily (10 in the candidaemia group and 25 in the CDIFD). As shown in Table 1, the three groups were comparable in age and severity of disease. The average candida score was: 4.4 and 3.3 for the candidaemia and CDIFD respectively. The exposure to prior broad-spectrum antibiotics or prior fluconazole was also similar between groups.

	Candidaemia				CDIFD			
	Micafungin (n=9)	**Caspofungin (n=9)**	**L-AmB (n=10)**	**P Value**	**Micafungin (n=20)**	**Caspofungin (n=21)**	**L-AmB (n=25)**	**P value**
Age (years)	71.7	74.4	69.7	NS	68.5	67.7	64.2	NS
Average Candida score	4.2	4.6	4.4	NS	3.4	3.1	3.4	NS
Duration of treatment (days)	13.6	12.7	13.9	NS	13.9	13.4	13.5	NS
Development of ARDS (%)	33	44	30	NS	15	14	12	NS
Prior use of broad-spectrum antibiotics (%)	100	100	100	NS	85	90.5	88	NS
Prior exposure to fluconazole (%)	11	22	20	NS	15	14	20	NS
Clinical outcome (%)								
Success	56	67	60	NS	70	81	76	NS
Failure	22	22	20	NS	15	0	12	NS
Relapse	0	0	10	NS	0	0	4	NS
Indeterminate	22	11	10	NS	15	19	8	NS
Mortality (%)	44	33	40	NS	30	19	24	NS
Adverse events (%)								
Hepatotoxicity	22	0	0	NS	30	5	0	<0.5[a]
Systemic reactions	0	0	0	NS	0	0	0	NS
Average cost/patient (£)	3918	4439	3149	NS	4017	4692	2635	<0.0001[b]

NS: Not significant; **ARDS:** Acute respiratory distress syndrome

[a]Post hoc analysis showed a statistically significant difference between micafungin and caspofungin groups ($P<0.05$) and between micafungin et L-AmB ($P<0.005$)

[b]Post hoc analysis showed a statistically significant difference between micafungin and L-AmB ($P<0.001$) and between caspofungin and L-AmB ($P<0.0001$)

Table 1: Comparison between micafungin, caspofungin and L-AmB for the treatment of candidaemia and CDIFD in terms of demography, clinical outcome, safety and treatment cost

Identification of a fungal pathogen was reported in 100% of cases. The most common *Candida* species grown in the candidaemia group was reported as *C. non-albicans*, identified in 55% patient samples compared to *C. albicans* grown in 45% of the samples. *C. glabrata* was the most prominent isolate in the *non-albicans* group 12/18 (67%) and the other *Candida* includes *C. tropicalis*, *C. dubliniensis* and *C. krusei*. In patients developing candidaemia who were receiving CASP, 4 patients grew *C. glabrata*, 4 grew *C. albicans* and 1 grew *C.tropicalis* + *C.albicans* (i.e., dual infection). In the MICA group, 4 patients grew *C. albicans*, 2 grew *C. glabrata*, 1 grew *C. glabrata* + *C. albicans*, 1 grew *C. glabrata* + *C. tropicalis* and 1 grew *C. dubliniensis*. In the L-AmB group, 3 patients grew *C. albicans*, 3 grew *C. glabrata*, 1 grew *C. Krusei*, 1 grew *C. tropicalis*, 1 grew *C. albicans* + *C. glabrata* and 1 grew *C. dubliniensis* + *C. albicans*.

In the CDIFD group there were more isolates of *C. albicans* (56%) compared to *C. non-albicans* (44%). The *C. non-albicans* isolates included *C. glabrata*, *C. tropicalis* and *C. krusei*.

Overall, 56% of patients (53/94) were hospitalised in an intensive care unit (14 in the micafungin, 21 in the caspofungin group and 18 in the L-AmB group, NS). Average APACHE II score for the 53 intensive care unit hospitalised patients was high, 20 for the micafungin arm (n=20), 23 for the caspofungin arm (n=21) and 22 for L-AmB arm (n=21) but, it did not differ between groups. Approximately 36% (19/53) of the patients developed Acute Respiratory Distress Syndrome (ARDS).

The clinical efficacy is shown in Table 1, no difference was observed between the three groups. The success rate for treating the most prominent species (*C. glabrata*) for the 3 drugs was 25%, 50% and 50% for micafungin, caspofungin and L-AmB, respectively (NS). The overall mortality rate at day 28 for the candidemia and CDIFD groups was 39% and 24% respectively. In the candidaemia group it was 44% (4/9) for MICA, 33% (3/9) for CASP and 40% (4/10) for L-AmB (NS). In the CDIFD group the mortality was: 30% (6/20) for micafungin, 19% (4/21) for caspofungin and 24% (6/25) for L-AmB (NS).

As shown in Table 1, differences were observed between groups in terms of safety and treatment cost. In term of safety, micafungin was the drug the most frequently associated with hepatotoxicity with 8 cases of adverse events (28%) compared to 1 in the caspofungin group (3%) and none in the L-AmB group (0%). The observed difference was statistically significant for both caspofungin (P=0.0448) and L-AmB (P=0.0048) when compared to micafungin. Interestingly, no renal nor systemic adverse reaction was reported for MICA and CAPS. Two patients developed nephrotoxicity in the L-AmB group (1 with candidaemia, 1 with IFD) although this was not statistically different to the other groups.

In terms of treatment cost; overall L-AmB was the cheapest drug with a mean cost of £2782 compared to £3986 for micafungin (P<0.005) and £4616 for caspofungin (P<0.0001). The difference was particularly true for patients treated for CDIFD.

One of our limitations in the results as that we did not have the epidemiology to compare the results with previous ones.

Discussion

The present audit shows that micafungin is as effective as caspofungin and L-AmB for the treatment of candidaemia and CDIFD. Yet, micafungin is associated with frequent hepatotoxicity and therefore the benefit/risk balance is not favourable when compared to caspofungin or L-AmB. The two later drugs have similar efficacy and safety profile but caspofungin generates higher cost. L-AmB could therefore be seen as the preferred drug. Yet, this could only be achieved because of the use of a low dose of L-AmB (1 mg/kg/day).

The rationale for using L-AmB at a dose of 1mg/kg/day is multi-factorial and includes the following: licenced starting dose for mycoses, well-tolerated in relation to renal toxicity, well-tolerated for patients in receipt of haemofiltration and well tolerated in patients with liver failure [14-17]. Furthermore, 1 mg/kg/day are sufficient to achieve adequate concentrations for the pathogens to still be susceptible [18,19]. There are also published data supporting the use of a 1mg/kg dose [20-22].

Treating confirmed or suspected IFD in critically ill patients is very challenging as the mortality is particularly high. Consequently, many ICU clinicians are reluctant to wait until full confirmation of diagnosis before antifungal therapy is commenced. Furthermore, because many fungal infections have the ability to rapidly progress, ensuring you are using the most appropriate treatment from the beginning is vital. Average APACHE II scores for the ICU hospitalised patients was high compared to the national average score seen within general intensive care populations [23,24]. As shown in the present audit, the mortality rate for the candidaemia and CDIFD groups was high with 39% and 24% respectively. Many centres throughout the U.K. are still using fluconazole as their first line empiric antifungal of choice in the ICU setting as its deemed cost-effective. Yet, fluconazole is less active against *C. non-albicans* such as *C. glabrata* or *C. koseri* and, as reported in the present study, *C. non-albicans* is frequently identified in both candidaemia and CDIFD and therefore should be covered by the empirical treatment prescribed to the patients. Micafungin has a broader spectrum of cover compared to fluconazole but few licenced indications for treatment compared with either caspofungin and/or L-AmB [14,15]. Caspofungin does have a good range of licensed indications and a broad spectrum of activity against *Candida* species but not against moulds [25]. Importantly, caspofungin is fungicidal against *Candida* species but fungistatic against *Aspergillus* where its activity focuses on the growing apical tips of the fungus. L-AmB also has a broad spectrum of activity and is fungicidal for both yeasts and mould pathogens [26,27]. This is particularly important to take into account for centre such as ours who send their samples to a reference laboratory and need to wait up to 7 days to get the identification and sensitivities back.

This can clearly compromise clinical outcome especially if fluconazole had been used empirically in region where *C. glabrata* or *C. koseri* are frequent; therefore starting with a broad-spectrum antifungal might be more appropriate whilst awaiting diagnostic results.

The data collected in this audit was recovered retrospectively. It is widely acknowledged that retrospective studies are exposed to bias, and that caution should be exercised in interpreting their findings. There were admittedly some limitations to our data, such as the fact that it is a single centre study with low number of fungal infections and that no specific criteria was used to evaluate the clinical efficacy, only the opinion of the auditors. Nevertheless, these real-live data show how those drugs are handled in practice. Audits are necessary to validate formulary changes and sharing these data may encourage other centres to conduct and report real-life antifungal audits, for which there is currently a paucity of data.

Audits are also critical to share local epidemiology and provide help with the selection of the most appropriate, well tolerated and cost-effective antifungal agents.

Conclusion

The present audit suggests that there is no difference in efficacy between micafungin, caspofungin and low daily doses of L-AmB. However, using L-AmB (1mg/kg/day) was shown to be more cost-effective and well tolerated. The epidemiological data confirmed that fluconazole should not be used empirically due to a higher percentage of *C. non albicans* species. Further prospective studies may be useful to study more in depth the potential advantage of low dose L-AmB compared to other antifungal therapies.

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