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Dose finding in aspergillosis

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Invasive aspergillosis (IA) continues to represent a significant challenge for physicians in charge of immunocompromised patients. Voriconazole, caspofungin, itraconazole, and the different formulations of amphotericin B (AmB) are all approved for therapy of IA. To collect information on the effect of high dose of antifungals in the treatment of IA, data from the available medical literature were reviewed. For AmB there are no data demonstrating any better clinical activity of doses higher than standard. For liposomal-AmB preliminary data seem to show that high doses are not more efficacious than the standard dose, and it is probably more toxic. Anecdotal data of itraconazole suggest that high dosages might be feasible and it has been associated with good clinical results. Unpublished data about voriconazole suggest the absence of any better activity of high plasma concentrations. For caspofungin the efficacy of higher dosage did not seem to be better than that obtained with the traditional dosage. Prospective studies are required, because many confounding factors may obscure the effects of the higher dosages when data are retrieved retrospectively.

Keywords invasive, aspergillosis, dose, antifungal, high

Introduction

Invasive aspergillosis (IA) continues to represent a significant challenge for physicians in charge of immunocompromised patients, especially in the hematological field. The profile of subjects considered at risk for IA continues to expand, a finding explained by the use of more aggressive and intensive chemotherapeutic regimens for solid tumors and hematological malignancies, as well as steroids and other T cell suppressants for the treatment of Graft vs. Host Disease (GvHD) in hematopoietic stem cell transplant recipients (HSCT). In addition, other categories of patients appear to be at risk for IA, such as solid organ transplant recipients (especially lung, heart and liver tranplants) and patients with Chronic Obstructive Pulmonary Disease (COPD) undergoing long term steroid therapy [1,2]. In a recent review the overall case fatality rate was 58%, with the highest rates for bone marrow transplant recipients (87%) and for patients with cerebral or disseminated aspergillosis (88%), especially in the absence of rapid recovery of the predisposing immunological deficit [3]. The number of antifungal agents that are effective in IA is limited, and many questions remain regarding the optimal regimen. Voriconazole, caspofungin, itraconazole, and the conventional and lipid formulations of amphotericin B are all approved for first line or salvage therapy of IA, but more research is necessary to define the exact roles of each drug. *In vitro* data show that escalating drug levels might result in enhanced killing with certain antimicrobial drugs, but not with others. However, things are very complicated in the mycological field, since the behavior might vary according to the type of fungus involved and clinical results do not always reflect *in vitro* theoretical data. More importantly, other factors, such as toxic effects, might have a strong impact on clinical results, thus nullifying a theoretically better antifungal activity.

With the aim of collecting information on the effect of a dosage of antifungals higher than the approved one in the treatment of IA, data from the available medical literature were reviewed. Relevant studies published in the English-language literature were retrieved using 'aspergillosis' and 'high dose antifungal' as either a keyword or MeSH (medical subject heading)

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term in searches of the MEDLINE (US National Library of Medicine, Bethesda, MD) and EMBASE (Elsevier Science, New York, NY) bibliographic databases. In addition, abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), European Congress on Clinical Microbiology and Infectious Diseases (ECCMID) and American Society of Hematology (ASH) Annual meetings in the past three years were reviewed, as well as the registration dossiers of caspofungin and voriconazole. Information about the pharmacokinetic and pharmacodynamic characteristics of antifungal drugs will be very briefly summarized, since more details can be found in recent publications [4,5]. In this we have not included concepts about dosing that have arisen from the experimental animal model literature, as it is beyond the scope of this paper. Important observations on the efficacy or non-efficacy of dose escalation have been made in such experiments with various antifungal agents, and these observations may lead to clinical studies or corroborate conclusions from them. Some of these studies are cited and discussed elsewhere in this Supplement and in the previous Supplement from these meetings.

Deoxycholate amphotericin B

Until recently, deoxycholate amphotericin B (D-AmB) formed the mainstay of treatment of IA. The drug is usually administered as a slow intravenous (IV) infusion at a dose of 1–1.5 mg kg^{-1} d^{-1}. There is progressive accumulation in tissues with ongoing administration. Concentration in blood does not reflect tissue concentrations accurately, and these may well exceed the minimum inhibitory concentration (MIC). Nephrotoxicity is a common and serious dose-related side effect and it limits the chance to step up to 1.5 mg kg^{-1} d^{-1}, a dosage considered to be necessary in IA [6]. Amphotericin B has a fungicidal activity against both *Candida* and *Aspergillus*. The antifungal activity against *Aspergillus* appears to be concentration and dose-dependent in experimental models of invasive fungal infections, although whether or not the C_{max}/MIC is the main parameter of activity in aspergillosis is unknown [5]. The only available clinical data showing better efficacy of D-AmB at high dosage is in regard to the treatment of oral candidiasis in HIV-infected patients. In this study, D-AmB was prepared and infused in fat emulsion at different dosage up to 3 mg kg^{-1} d^{-1} showing a dose-dependent activity [7]. There are no data demonstrating any better clinical activity of doses higher that 1.5 mg kg^{-1} d^{-1} in IA. In disseminated and cerebral IA, D-AmB B is scarcely efficacious and mortality approaches 90% [8].

Lipid formulations of amphotericin B

Lipid formulations of amphotericin B were developed to obviate D-AmB nephrotoxicity, while allowing the administration of higher dosages. Indeed, there is no doubt that all the available lipid formulations cause fewer side effects and are less nephrotoxic than D-AmB and as a consequence can be administered at higher dosages (3–10 mg kg^{-1} d^{-1}). Most animal model studies have suggested that at the 1/1 ratio the lipid preparations are less effective than D-AmB and that therefore higher dosages are required to produce therapeutic effects equivalent to those obtainable with D-AmB. Therefore, the dosages used so far reflect the need to provide an activity equivalent to that of D-AmB. It is generally unclear how the dosages of lipid amphotericin B formulations were settled and some uncertainties remain about the optimal dosage. For example, an European Organization for Research and Treatment of Cancer (EORTC) study compared 1 vs. 4 mg kg^{-1} d^{-1} of L-AMB for the treatment of proven and probable IA in neutropenic patients. No difference was found in response rate or survival, although the higher dose was more effective in the small group of patients with proven infections [9], and the power of the study to discriminate differences was not great. In the light of the concentration-dependent activity of the polyenes, some investigators became interested in testing the clinical potential of higher dosages of the lipid formulation which is considered to be the one with the better tolerability, i.e. the only true liposomal preparation (L-AmB). In a maximum tolerated dosage study of 7.5, 10, 12.5 and 15 mg kg^{-1} d^{-1}, Walsh *et al.* [10] showed that the drug was well tolerated at each dosage with no dose-related differences observed for nephrotoxicity, infusion-related reactions, drug discontinuations because of adverse events, hepatotoxicity and anemia. However, severe hypokalaemia was observed at 12.5 and 15 mg kg^{-1-} d^{-1} dose levels (nine of 26 [35%] patients). The pharmacokinetics were nonlinear over a dose range of 7.5 to 15 mg kg^{-1} d^{-1} and the C_{max} and area under curve (AUC) reached maximal values at a dose of 10 mg kg^{-1} d^{-1}. Despite these data, whether high dose doses of liposomal amphotericin B (L-AMB) are more effective than lower doses remains unclear. However, this study provided the rationale for a randomized, prospective clinical trial in which two initial doses of L-AmB were compared (3 vs. 10 mg kg^{-1} d^{-1} for ten days) for the treatment of IA

From what we know from data presented at meetings, this study represents an instructive example of how the potentially better antimicrobial activity of a given treatment does not translate into any better efficacy, probably because of an excess of adverse events. Indeed, the overall rate of response for the two dosing regimens at end of treatment was associated with similar efficacy (50% in the standard dosing group vs. 46% in the high loading-dose group). Although no difference was statistically significant and the different dosage was not a factor associated with mortality in a multivariate analysis, survival at 12 weeks was 72% in the standard dose group and 59% in the high dose group. Patients who received the loading dose regimen experienced more adverse events in general and more nephrotoxity in particular. The $3\ mg\ kg^{-1}\ d^{-1}$ dose was better tolerated in this study. On the other hand, these results, if confirmed, show that in the setting of a controlled, well-designed and prospective clinical trial the performance of the standard dose regimen is similar to that obtained by other drugs approved for primary therapy of aspergillosis [11]. The summary of this study should be interpreted with caution however, because the study has not yet been published in a peer-reviewed journal, a process that can be pivotal for ensuring scientific validity in clinical research. As far as the purpose of our article is concerned, this study shows that escalating L-AmB dose should not be recommended. This does not mean, however, that alternative dosing regimens should not be explored [12].

Itraconazole

Itraconazole is usually administered at the dosage of 200–400 mg per day by oral route. The IV formulation is administered at 200 mg twice daily during the first two days of treatment and then at 200 mg per day [13]. Itraconazole has a species and strain-dependent fungicidal activity against filamentous fungi. Animal models have found a both concentration and time-dependent effect, suggesting that high dosages, if tolerated, might be more effective. Clinical data in patients receiving itraconazole prophylaxis have confirmed that a threshold blood concentration $<0.5\ \mu g/ml$ was associated with a higher risk of invasive fungal infections [14], while another study showed that this threshold was unfortunately associated with an excess of discontinuation events because of increased gastrointestinal complaints [15]. In terms of therapy, the optimal dose is not clear. There are some anecdotal indications that higher dosages might be effective in immunocompetent patients with cerebral and/or sinusal aspergillosis, but no definitive conclusion can be drawn [16–19].

Voriconazole

Voriconazole, a synthetic derivative of fluconazole, is generally considered to be fungicidal for *Aspergillus* spp. and represents a considerable step forward for antifungal therapy for aspergillosis. Data *in vitro* seem to show that voriconazole has a time-dependent antifungal activity, although in general the type of activity may vary according to species and strain [5]. Recent animal model studies with voriconazole have demonstrated the importance of the AUC/MIC parameter on drug activity [20]. Based on a prospective, randomized clinical trial in patients with proven and probable IA, voriconazole has been the first drug to be approved by the Food and Drug Administration (FDA) for the primary therapy of IA [21]. Like other azoles, voriconazole has a nonlinear pharmacokinetics, so that accumulation occurs and small changes in dose can lead to large changes in plasma concentrations. In addition, due to the variable genetic expression of the main cytocrome responsible for voriconazole metabolization (CYP19C), the drug exhibits considerable inter-individual variability in hepatic metabolization, with some patients exposed to very high drug concentrations [5]. The issue of the relationship between voriconazole concentration and clinical activity has been addressed during the development of voriconazole and information can be retrieved from the briefing document that was presented at the FDA during the registration process [22]. The issue has also been mentioned in a letter to *Clinical Infectious Disease* commenting on another letter about the safety of voriconazole [23,24]. According to Lutsar *et al.* [24], data on file at Pfizer based on 1134 samples from 208 patients with aspergillosis show the absence of any relationship between plasma concentrations and efficacy. Cumulative data from the phase II studies and from the randomized clinical trial showed that the proportion of therapeutic successes in patients with very low voriconazole plasma concentrations ($<0.5\ \mu g/ml$) was about 45% and 60% respectively, and did not differ in a statistically significant way with respect to patients experiencing medium/high concentrations (up to $6\ \mu g/ml$). The confidence intervals of the response rates overlapped significantly. Similar to what was observed in the high dose L-AmB study, there was a trend toward reduced efficacy in patients with the highest concentrations, probably due to the presence of comorbidity factors (related or unrelated to treatment) like hepatic insufficiency of severe clinical conditions, impacting the final outcome. These findings should again be taken with extreme caution and do not demonstrate unequivocally that high concentration of

voriconazole might achieve better clinical responses or higher rates of toxic effects able to impair any possible better activity. Indeed, we do not know many details about the blood sampling, including time with respect to dosing and time with respect to the clinical course, and whether the sampling was representative of the whole course of therapy for each patient. A very recent study [25] has suggested a relationship ($P < 0.025$) between disease progression and voriconazole serum concentration. Favorable responses were observed in 10/10 patients with concentrations >2.05 mcg/ml, whereas disease progressed in 44% of 18 patients with concentrations below that.

Caspofungin

Caspofungin is the first drug which became available for clinical use in a new class of antifungal agents known as the echinocandins. Caspofungin has linear pharmacokinetics and a relatively long half life (9–11 h). When given as salvage therapy for patients with IA, caspofungin obtained a complete or partial response in 45% of the cases [26]. Concentration-dependent pharmacodynamics *in vitro* and *in vivo* and the existence of prolonged post antibiotic effects (PAEs) support the current once-daily dosing regimen and, at the same time, provide a rationale for exploration of dose escalation for treatment of complicated invasive *Candida* infections. The pharmacodynamics of echinocandins against *Aspergillus* spp. are more complex and difficult to interpret, and perhaps suggest concentration-dependent dynamics beyond a certain threshold dosage [27]. Caspofungin has a peculiar mechanism of action against *Aspergillus,* which may have pharmokinetics (PK) and pharmodynamics (PD) implications [5]. With the intent of demonstrating the efficacy and safety of higher doses of caspofungin, Kartsonis *et al.* [28] studied 120 patients with IA. Dosages of caspofungin were 50 mg, 70 mg and 100 mg. No definitive conclusion could be drawn from the study, although the efficacy of caspofungin at 100 mg daily did not seem to be much better than that obtained with the traditional dosage. In detail, no efficacy differences were noted across the 50 mg and 70 mg groups (48% and 44%, respectively). Data at the highest dose (100 mg/d) were very limited (2/6, 33%).

In another similar study, a high dose (100 mg daily) was compared to a conventional dose (70 mg followed by 50 mg daily) of caspofungin in the treatment of invasive fungal infections in cancer patients. Logistic regression analysis at four-week assessment showed no difference in response between the two treatment groups, but the 12 week assessment showed a significant improved probability of favourable response in patients treated with high dose [29]. Safdar *et al.* [30] evaluated the efficacy of high dose caspofungin (100 mg daily) in 22 cancer patients with invasive fungal infections. The 12-week crude mortality was 41% and fungal-attributable deaths were 32%. Overall, caspofungin was well tolerated without serious adverse reactions. The drug was well tolerated at any dosage [28]. No information is retrievable about caspofungin maximum tolerated dosage.

Conclusions

In summary, although the definitive publication is not available yet, preliminary data seem to show that L-AmB at 10 mg kg^{-1} d^{-1} is not more efficacious than the standard dose, and it is probably more toxic. Anecdotic data with itraconazole suggest that the administration of high dosages might be feasible and has been associated with good clinical results. Scattered and partially unpublished data about voriconazole suggest no better activity in patients in which high plasma concentrations were achieved, because of the peculiar metabolism of the drug. Little information is available about the echinocandins, although at least one study suggested possibly a better activity of caspofungin at 100 mg/d. It seems logical to conclude that the polyenes and the triazoles probably have a relatively narrow therapeutic coefficient, not allowing dose escalation, while this could be possible with the echinocandins. Ad hoc prospective studies are definitively needed, because many confounding factors may obscure the effects of the higher dosages when data are retrieved retrospectively.

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