Is 24 hours infusion of amphotericin B deoxycholate as good as liposomal amphotericin B?

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Infections are frequent complications in the postoperative period after organ transplantation. Bacteria and cytomegalovirus account for the majority of pulmonary infections in lung transplant recipients. However, fungal infections are increasing in the immunocompromised host and often pose a diagnostic and therapeutic challenge. *Candida* species are the most frequent isolates followed by *Aspergillus spp*. after lung transplantation. Infectious complications due to *Candida* include candidemia, empyema, mediastinitis and bronchial anastomic site infection [1, 2]. The treatment of choice of *Candida albicans* infections is fluconazole. Genuinely azole-resistant yeasts such as *C. krusei* or yeasts with variable sensitivity to fluconazole such as *C. glabrata* and *C. parapsilosis* pose a challenge for successful treatment. Amphotericin B is the mainstay of antifungal therapy and still the gold standard for life-threatening fungal infections. Amphotericin B is a polyene macrolide produced from a strain of *Streptomyces nodosus*. Amphotericin B binds to ergosterol in the fungal cell membrane, leading to the formation of pores and loss of protons and cations from the cell, resulting in cell death. The main problems with amphotericin B are the infusion-related symptoms and the renal toxicity. Severe toxicity has been a limitation to the clinical application of amphotericin B deoxycholate prompting research for the development of new lipid formulations. There are three lipid formulations on the market, liposomal amphotericin B (Ambisome®), amphotericin B lipid complex (Abelcet®) and amphotericin B colloidal dispersion (ABCD; Amphocil®, not available in Switzerland).

According to the manufacturer's recommendation, amphotericin B deoxycholate is slowly infused over a 2–6 hour interval. Amphotericin B pharmacokinetics and metabolisms are complex and not completely understood. After intravenous administration amphotericin B is bound to serum proteins (90–95%), especially β-lipoprotein [3]. Most of the drug leaves the circulation promptly, perhaps bound to cholesterol-containing cytoplasmic membranes. Thus, measured blood levels do not correlate with efficacy. Amphotericin B is stored in the liver and other organs and reenters the circulation slowly. The blood levels, however, are not influenced by hepatic or renal failure. The initial half-life is about 24 hours. Serum concentrations can be detected for at least 7 weeks after the end of therapy, reflecting the release from cell membranes.

In this issue, Speich et al. studied an infusion rate of amphotericin B over 24 hours in order to decrease infusion related symptoms and renal toxicity [4]. Given the facts that the pharmakokinetics and pharmakodynamics of amphotericin B are poorly understood, that the blood levels do not correlate with efficacy and that severity of toxic reaction increases with rapid infusion, such an investigation is valuable. Another study conducted at the University Hospital of Zürich previously showed that in neutropenic patients side effects such as fever, chills, rigors and renal insufficiency can be decreased by a 24 h infusion compared to a 4 h infusion rate [5]. According to these results Speich et al. performed a study to investigate the tolerability, safety and efficacy of the 24 h infusion of amphotericin B in lung transplant recipients. The study reports of 6 patients who were treated with a 24 h continuous infusion of amphotericin B for azole-resistant candidal infections. No patient showed the characteristic side effects such as fever, chills, headache or vomiting. Since all patients were also treated with cyclosporine A, a potentially nephrotoxic substance, the change of the creatinine level during amphotericin B deoxycholate adminstration is of particular interest. In all patients, the serum creatinine levels increased, however only in one patient did it double. This patient needed haemofiltration for a period of 7 days. After discontinuation of the amphotericin B treatment, the creatinine levels rapidly decreased in all patients to levels similar to those observed prior to antifungal therapy.

This study offers an interesting therapeutic option in lung transplant patients with fungal infection and concomitant potentially nephrotoxic substances. It confirms the previous study by Erikson et al. [5], demonstrating that a continuous infusion of Amphotericin B is less toxic, especially

less nephrotoxic. The incidence of amphotericin B nephrotoxicity is very high, and acute renal failure is common. In the study by Wingard et al. [6] serum creatinine doubled in 53% of the patients and 29% had a serum creatinine >250 µmol/L, representing a decrease in renal function of 70%. Fifteen percent of all patients in this study required dialysis. The pathophysiology of nephrotoxicity involves vasoconstriction with decreased renal blood flow and glomerular filtration. Furthermore, amphotericin B forms pores in membranes that cause tubular dysfunction. These two mechanisms induce acute renal dysfunction. In the study by Erikson et al. [5], it is suggested that the continuous infusion of amphotericin B over 24 h may prevent a decrease in the renal blood flow, thus limiting the renal insufficiency. However, the standard therapy of patients with renal insufficiency and fungal infection nowadays is a lipid formulation of amphotericin B. In two studies the liposomal amphotericin B (Ambisome®) seemed to be the least nephrotoxic agent with a reported doubling of creatinine levels of less than 20% [6, 7]. So, why do we not use liposomal amphotericin B more often? The answer is: costs! A daily dose of 5 mg/kg of liposomal amphotericin B for a patient of 70 kg body weight is 22 times more expensive than a daily dose of 1mg/kg of amphotericin B (CHF 2353.– for Ambisome® versus CHF 104.– for Fungizone®. Prices according to the "Arzneimittelkompendium der Schweiz 2002"). Therefore, alternative therapies for severe fungal infection are under investigation. The pilot study by Speich et al. indicates that a continuous infusion of amphotericin B over 24 h offers a possibility to reduce side effects at no additional costs. However, a randomised study comparing liposomal amphotericin B with continuous administration is lacking, as well as studies including more patients. Furthermore, there are new antifungal drugs available such as caspofungin (Cancidas®) and voriconazole (Vfend®). Both drugs are not nephrotoxic, but are expensive. Further studies will show which drug or which combination of drugs will have the most effectiveness and the least toxicity.

The study by Speich et al. [4] has some important limitations, especially regarding outcome. First, the number of patients investigated is small (n = 6) and no conclusion about efficacy or outcome can be drawn. Second, only patients with candidal infections were included. Although candidal infections play an important role in lung transplant recipients, they are in general less difficult to treat than *Aspergillus* infections. Thus, even if the outcome of these 6 patients was favorable, no conclusion about efficacy should be stated.

In summary, the continuous administration of amphotericin B is promising in reducing side effects such as fever, chills and nephrotoxicity. However, so far the studies published [4, 5] included a too small number of patients in order to evaluate effectiveness. Further studies will show whether the continuous application of amphotericin B, or a new drug (caspofungin, voriconazole) or even the expensive liposomal amphotericin B is the most cost-effective overall treatment considering not only antifungal treatment but also treatment of side effects including possible haemodialysis and lengths of hospitalisation.

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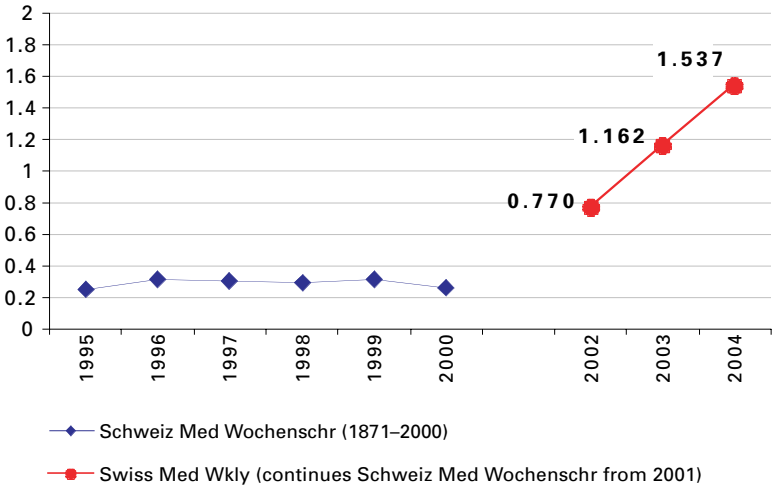

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