

Tolerability, safety and efficacy of conventional amphotericin B administered by 24-hour infusion to lung transplant recipients

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Summary

Background: Fungal infections cause serious morbidity and mortality in lung transplant recipients. Expensive lipid formulations of amphotericin B (AmB) are generally used because of fear of adverse effects due to concomitant cyclosporine A and other nephrotoxic drugs. However, a 24-hour dosing regimen of AmB may be well tolerated even in these patients.

Methods: In an open pilot study 6 out of 94 lung transplant recipients with invasive or semi-invasive bronchopulmonary azole-resistant candidal infections (3 *parapsilosis*, 2 *glabrata*, 1 *krusei*) were treated for 40 (17–73) days by 24-hour continuous infusions of AmB 1 mg/kg. Additionally, patients received at least 1000 ml of 0.9% saline intravenously per day. Beside cyclosporine A at serum trough levels of 240 (195–273) µg/l, five patients additionally received aminoglycosides for at least 2 weeks, and 4 were treated with ganciclovir.

Results: Calculated creatinine clearance de-

creased from 57 (43–73) ml/min to a nadir of 35 (28–39) and recovered to 52 (33–60) after cessation of therapy. One patient needed temporary haemofiltration for 7 days after 30 days of AmB, most probably because of the use of contrast media in conjunction with furosemide and hypovolaemia. Besides three episodes of mild hypokalaemia no other side effects attributable to AmB were recorded. While in one case an asymptomatic candidal colonisation persisted for 10 months, the other 5 were cured from their infection.

Conclusion: These preliminary data show that conventional AmB administered by 24-hour infusion is well tolerated, safe, and efficacious in lung transplant recipients receiving cyclosporine A and other nephrotoxic substances.

Key words: amphotericin B; lung transplant recipients; fungal infections

Introduction

With the advent of effective prevention against cytomegalovirus, fungal infections have become the most serious threat to the recipients of lung or heart-lung transplants [1, 2]. In up to 84% of the patients positive respiratory cultures for fungi may be found some time after transplantation. Two thirds of the isolates are *Candida* sp. and one third *Aspergillus* sp. Since colonisation with *Aspergillus* sp. is a significant risk factor for the development of invasive aspergillosis, most lung transplant centres successfully use preventive or pre-emptive treatment with either oral itraconazole or inhaled amphotericin B in patients colonised with *Aspergillus* sp. [2].

Infections with *Candida* sp. often present as a necrotising bronchial anastomotic infection [3, 4]. Whereas semi-invasive infections with *C. albicans*

may be successfully treated with oral or intravenous azoles, the genuinely azole-resistant yeasts such as *C. glabrata*, *C. parapsilosis* or *C. krusei* pose a significant therapeutic challenge. Up to one third of the patients infected with these strains may die of the serious complications [5]. Since treatment with conventional intravenous amphotericin B administered over a period of 4 hours is often restricted by serious toxicity, most centres use the expensive liposomal amphotericin B formulations [1, 6]. Recently, however, Eriksson et al. could demonstrate in a randomised controlled trial that continuous infusions of conventional amphotericin B impressively reduced nephrotoxicity and other side effects without increasing mortality in 80 neutropenic patients with refractory fever and suspected or proven invasive fungal infections [7].

Thus, the present open pilot study was performed to examine efficacy, safety and tolerability of this regimen in lung transplant recipients generally be-

lieved not to tolerate conventional amphotericin B due to concomitant cyclosporine A treatment.

Patients and methods

Between November 1992 and April 2000 94 patients, 52 females and 42 males with a median age of 39 (12 to 66) years, received 69 bilateral, 17 single right and 5 single left lung transplants. The indications for lung transplantation and details of surgery and postoperative management are described elsewhere [8]. Maintenance immunosuppressive drugs were cyclosporine A, azathioprine and prednisone. Since April 1999 mycophenolate mofetil has been routinely used instead of azathioprine. Perioperative antibiotic prophylaxis consisted of ceftriaxone or an anti-pseudomonas combination therapy tailored to the pre-transplant bacteriology in cystic fibrosis patients. Postoperative antibiotic treatment was adapted according to the detected bacterial strains. Monthly surveillance bronchoalveolar lavage and transbronchial lung biopsy procedures were routinely performed in clinically and physiologically stable recipients during the first six postoperative months, and in each patient with new symptoms, signs, roentgenographic infiltrates, or declining lung function.

In the presence of positive cultures of *Aspergillus* sp. or azole-sensitive *Candida* sp. treatment with oral itraconazole 200 mg bid. and inhaled amphotericin B 5 to 10 mg tid. was begun. *Candida* species considered to be genuinely azole-resistant included *C. glabrata*, *C. parapsilosis* and *C. krusei*. In vitro sensitivity testing was not routinely performed. Invasive or semi-invasive disease due to these organisms was considered to be an indication for intravenous amphotericin B. Invasive fungal lung disease was defined as otherwise unexplained radiographic infiltrates and repeated heavy growth of fungi from bronchoscopic secretions or bronchoalveolar lavage fluid, or pos-

itive cultures from sterile sites such as pleura or pericardium. Semi-invasive tracheobronchitis was diagnosed in the presence of endobronchial, mostly anastomotic lesions with necrotic pseudomembranes and positive bronchoscopic cultures [4]. One patient was heavily colonised preoperatively and deemed to be at high risk for anastomotic infection. Patients received a continuous (24 hours) infusion of amphotericin B 1 mg/kg body weight in 500 ml of 5% glucose as described previously [7]. Additionally, at least 1000 ml of 0.9% saline was administered intravenously per day. The dosage of cyclosporine A was not reduced during amphotericin B treatment.

Three patients died of invasive aspergillosis within a few days despite treatment with intravenous amphotericin B and were not included in the present case series. Another patient was successfully treated with the conventional short 4-hour infusion of amphotericin B in 1993. She developed anuric renal failure and required haemofiltration for nine weeks.

The typical side effects of conventional 4-hour amphotericin B treatment such as fever, chills, headache or vomiting were prospectively recorded as being present or absent on the daily ward-rounds. A standardised questionnaire was not used. Creatinine and electrolytes were measured on a daily basis. Creatinine clearance was calculated by the Cockcroft-Gault formula [9]. Data are expressed as median values and ranges. Paired data were analysed by the Wilcoxon matched pairs test and between-group comparisons were done with the Mann-Whitney-U test. Significance was defined as $p < 0.05$.

Results

Six out of 94 lung transplant recipients (6%) were treated with continuous infusions of amphotericin B over 24 hours for azole-resistant candidal infections. The patients' characteristics and type of fungal infections are shown in the table. Treatment was started after a median of 22 (range 1–1469) days postoperatively and continued for a median of 40 (17–73) days. All patients were concomitantly treated with cyclosporine A at a median trough level of 240 (195–273) $\mu\text{g/l}$. In addition, five patients received aminoglycoside antibiotics, four intravenous ganciclovir and one teicoplanin.

During the whole treatment period no patient complained about the characteristic amphotericin-associated side effects such as fever, chills, headache or vomiting. There were three episodes of mild hypokalaemia. The median calculated creatinine clearance before treatment was 57 (43–73) ml/min and decreased significantly by 37% to a nadir of median 35 (28–39) ml/min during treatment ($p = 0.028$). Serum creatinine levels

increased from 118 (88–138) $\mu\text{mol/l}$ to 183 (115–252) $\mu\text{mol/l}$ ($p = 0.0022$). Only one patient doubled her serum creatinine level. She needed temporary haemofiltration for a period of 7 days, but her oliguric renal failure was probably due to inappropriate hydration and administration of furosemide before the infusion of 150 ml contrast media for a computed tomography examination. After discontinuation of the amphotericin B treatment the creatinine clearance of the six patients almost completely recovered to a median of 52 (33–60) ml/min, and their serum creatinine levels decreased to 123 (86–173) $\mu\text{mol/l}$. These values were neither significantly different from the pre-treatment levels ($p = 0.14$) nor from the values of the lung transplant recipients who had never received amphotericin B (creatinine clearance 62 ml/min, range 24–101; $p = 0.18$).

The eradication of the fungal infection was successful in 5 of 6 patients. One patient had recurrent colonisation with *C. glabrata* subsequently to the early discontinuation of the intra-

Table 1

Patient characteristics (n = 6), treatment, clinical course, and renal function.

Patient age/sex	Disease	Candida species	Lung involvement	Start of therapy (pod)	Duration of therapy (d)	CCr before therapy (ml/min)	CCr nadir (ml/min)	CCr after therapy (ml/min)	Mean cyclosporin through level (mg/l)	Other nephrotoxic drugs	Complications or side effects
60, m	COPD	glabrata	Lung	1469	69	43	28	33	221	AG, GCV	None
18, f	CF	krusei	Lung Pleuropericardial	33	73	60	38	60	273	RCM, GCV Teicoplanin Furosemide	Need for haemofiltration (7d)
13, f	CF	glabrata	Tracheobronchial	4	34	45	35	47	219	AG, GCV	None
25, m	CF	parapsilosis	Heavy colonisation	1	46	73	35	60	250	AG	None
59, m	IPF	parapsilosis	Tracheobronchial	11	26	53	39	49	272	AG, GCV	None
23, m	CF	glabrata	Tracheobronchial	43	16	60	33	54	195	AG	None

COPD = chronic obstructive pulmonary disease; CF = cystic fibrosis; IPF = idiopathic pulmonary fibrosis; pod = postoperative day; CCr = creatinine clearance; AG = aminoglycosides; GCV = ganciclovir; RCM = radiographic contrast media.

venous amphotericin B treatment after 16 days. Aerosolised amphotericin B 10 mg five times daily was administered thereafter, and fungal

colonisation was eventually eradicated 10 months later.

Discussion

The present study demonstrates the tolerability, safety and efficacy of conventional amphotericin B infused continuously over 24 hours in lung transplant recipients. Patients suffered from invasive or semi-invasive azole-resistant candidal infections and concomitantly received potentially nephrotoxic drugs such as cyclosporine A, and at least one antimicrobial agent such as aminoglycosides, ganciclovir and/or teicoplanin.

Although there was a significant decrease in the calculated creatinine clearance during treatment with amphotericin B, the dosage was reduced to 0.5 mg/kg in only two patients after 13 and 16 days, respectively, because of clinical improvement and increasing serum creatinine levels. The characteristic major side-effects such as chills, fever, headache and vomiting generally observed in patients receiving amphotericin B over the period of 4 hours did not occur in any of our patients.

Due to the generally perceived disadvantage of conventional amphotericin B in solid organ transplant patients receiving cyclosporine A and other nephrotoxic drugs, liposomal formulations of amphotericin B are recommended by and used in most centres [1, 6, 10, 11]. In a series of 187 transplant recipients (89 bone marrow and 98 solid organs) liposomal amphotericin B had to be discontinued due to side effects in only 3% of the cases [11]. The overall mean increase in serum creatinine level was 20%. However, it has to be emphasised that the median duration of treatment was only 11 days with a maximum daily dose of 1.5 mg/kg, which is much less than the recommended 3 mg/kg/d. In a study using a daily liposomal amphotericin B dose of 3 mg/kg in neutropenic cancer patients, a doubling of the serum creatinine

levels occurred in 19% [12], comparable to the 16% (1 out of 6 patients) in the present study. Thus, albeit small, our study demonstrates that conventional amphotericin B infused continuously over 24 hours is comparable with respect to tolerability, safety and efficacy to the experience reported in studies using the liposomal formulations of amphotericin B in neutropenic cancer patients [12] and transplant recipients [10, 11]. As has been shown for neutropenic patients [7], continuous infusion of conventional amphotericin B has fewer side effects and is significantly less nephrotoxic than infusions over 4 hours and may even be more effective. In addition to the extension of the infusion time sufficient hydration with at least 1000 ml of 0.9% intravenous saline per day and the avoidance of other nephrotoxic substances are crucial, especially radiological contrast-media, whose use should be minimised and accompanied by adequate preventive measures. Last but not least, using continuous infusions of conventional amphotericin B is much less costly than lipid formulations with a calculated net daily savings of up to 1000 US\$ per patient per day.

Eradication of the fungal infection was successful in 5 of 6 patients. In one patient, recurrent asymptomatic colonisation after early discontinuation of intravenous amphotericin B was eventually eradicated 10 months later.

In conclusion, continuous infusion of conventional amphotericin B is tolerable, safe, and effective even in lung transplant recipients receiving cyclosporine A and other nephrotoxic substances. This regimen may also be applicable to other solid-organ or haematopoietic stem cell transplant recipients suffering from fungal infections.

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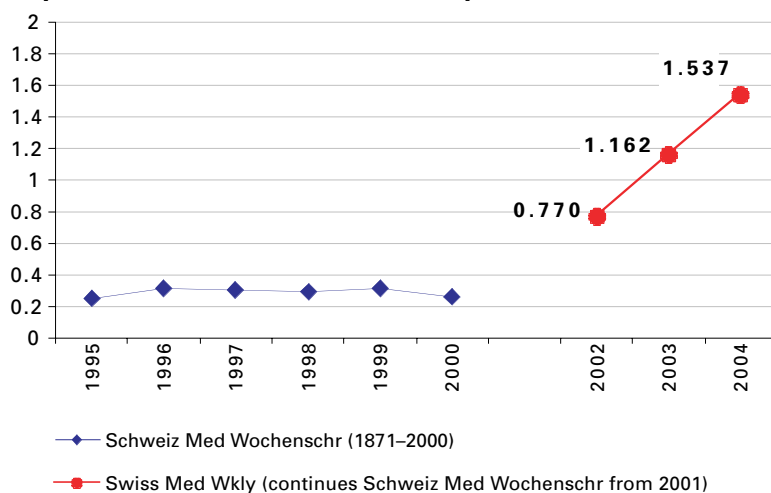
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