

What is already known on this topic

Inhaled zanamivir is effective in reducing the symptoms and duration of influenza

Elderly people have difficulty in using inhalers

What this study adds

Elderly patients are unlikely to be able to use the dry powder inhaler that is used to deliver zanamivir

Improvements should be made to the inhaler

Particular attention should be paid to the loading and priming of the device

symptoms, shortening the course of the disease, and reducing complications. More studies of the effectiveness of zanamivir treatment of influenza are needed, but without an improved delivery system they will be difficult to interpret. Our study shows that zanamivir treatment for elderly people with influenza is unlikely to be effective. Better delivery systems for inhalers should be used or developed.

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Contributors: PD developed the scoring system and with VJ conceived the original idea for the study. PD, VJ, AH, and MM designed the study and the scoring of aspects of loading the Diskhaler and collected the data. CF contributed to the design of the study as well as the power calculations and performed the analysis. PD will act as guarantor for the paper.

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Comparison of effects of amphotericin B deoxycholate infused over 4 or 24 hours: randomised controlled trial

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Abstract

Objective To test the hypothesis that amphotericin B deoxycholate is less toxic when given by continuous infusion than by conventional rapid infusion.

Design Randomised, controlled, non-blinded, single centre study.

Setting University hospital providing tertiary clinical care.

Patients 80 mostly neutropenic patients with refractory fever and suspected or proved invasive fungal infections.

Intervention Patients were randomised to receive 0.97 mg/kg amphotericin B by continuous infusion over 24 hours or 0.95 mg/kg by rapid infusion over four hours.

Main outcome measures Patients were evaluated for side effects related to infusion, nephrotoxicity, and mortality up to three months after treatment. Analysis was on an intention to treat basis.

Results Patients in the continuous infusion group had fewer side effects and significantly reduced nephrotoxicity compared with those in the rapid infusion group. Overall mortality was higher during treatment and after three months' follow up in the rapid infusion than in the continuous infusion group.

Conclusion Continuous infusions of amphotericin B reduce nephrotoxicity and side effects related to infusion without increasing mortality.

Introduction

Amphotericin B deoxycholate has remained the mainstay of treatment for life threatening fungal infections in immunocompromised patients because of its broad fungicidal activity and cheapness. Treatment with amphotericin B, however, is associated with acute reactions related to infusion and dose dependent nephrotoxicity. It is recommended that amphotericin B is infused slowly over two to six hours, based on the assumption that the severity and frequency of toxic reactions increase during more rapid infusions.¹⁻⁴

Incorporation of amphotericin B into liposomal formulations reduces its toxicity, but the reasons for this are unclear.⁵⁻¹¹ As liposomes do not specifically target fungal cells it would seem that the reduction in toxicity, at least in part, depends on a slower delivery of amphotericin B to tissues. The question as to whether a slower delivery of amphotericin B from lipid formulations might be reproduced by a slow infusion rate therefore arises. The hypothesis that a continuous infusion of amphotericin B results in reduced toxicity

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Table 1 Dosages of amphotericin B deoxycholate and characteristics of patients receiving rapid (four hours) and continuous (24 hours) infusions of the drug. Values are numbers (percentages) of patients unless stated otherwise

	Infusion rate	
	Rapid (n=40)	Continuous (n=40)
Median age (range)	46 (20-75)	47 (17-74)
Median (range) No of days of treatment	12 (3-51)	16 (3-89)
Median (range) maximum daily dose (mg/kg)	0.95 (0.4-1.2)	0.96 (0.5-1.5)
Median (range) cumulative dose (mg/kg)	10.8 (2.1-42.7)	14.3 (1.8-89.0)
Male	22	27
Diagnosis:		
Acute myeloid leukaemia	29 (73)	25 (63)
Acute lymphatic leukaemia	4 (10)	5 (13)
Lymphoma	4 (10)	5 (13)
Solid tumour	2 (5)	2 (5)
HIV	0	2 (5)
Others	1 (3)	1 (3)
Neutropenia (<500/ μ l)	36 (90)	37 (93)
Concurrent treatment:		
Aminoglycosides	18 (45)	22 (55)
Vancomycin	10 (25)	11 (28)
Diuretics	18 (45)	16 (40)
Granulocyte colony stimulating factor	13 (33)	18 (45)

has not been addressed yet in a prospective study. We therefore conducted a randomised, controlled, and open trial to compare the toxicity of amphotericin B given as a continuous infusion with a conventional rapid regimen over four hours.

Patients and methods

Inclusion and exclusion criteria and treatment

All consecutive patients at our tertiary referral centre for adult internal medicine (Zurich University Hospital) were considered eligible for entry to the study, providing their doctors had decided to start treatment with amphotericin B. Exclusion criteria were a baseline serum creatinine concentration in excess of 300

μ mol/l or systemic treatment with amphotericin B within the past seven days.

Patients received either a continuous (24 hours) or a rapid (four hours) infusion of amphotericin B. The drug was given in 500 ml of 5% glucose without any additives through a separate intravenous line.

Drugs to prevent chills or fever were prohibited on day 1 of entry to the study.¹² To reduce nephrotoxicity from amphotericin B all patients received infusions of saline as standard care.¹³⁻¹⁵ The protocol gave no other restrictions on the use of any concomitant treatment.

Outcome measures

Chills, rigors, and vomiting were monitored prospectively. Each patient completed a standardised questionnaire daily until the end of the study and was interviewed regularly. Temperature was measured; fever was defined as a core temperature of at least 39.3°C.

Serum creatinine concentrations were measured daily during treatment and creatinine clearance based on lean body mass was calculated.^{16 17} Electrolytes were measured every other day. Further, we recorded overall mortality, mortality due to invasive fungal infections, and breakthrough fungaemia during treatment.

Statistics and study ethics

Analysis was on an intention to treat basis. We planned to randomise 40 patients to each arm to detect a difference in creatinine clearance of at least 20 ml/min between the treatments, with a power of 90% at a two sided α level of 5%.

We present continuous data as the median (range), which were compared using the Mann-Whitney U test. The effect of treatment was reported as the difference of medians between study groups.¹⁸ For the comparison of dichotomous data the Fisher's exact test was used. We reported the effect of amphotericin B treatment for dichotomous data as relative risk.¹⁹

Our study was approved by the institutional ethics committee of Zurich University Hospital. We obtained written consent from all patients at enrolment.

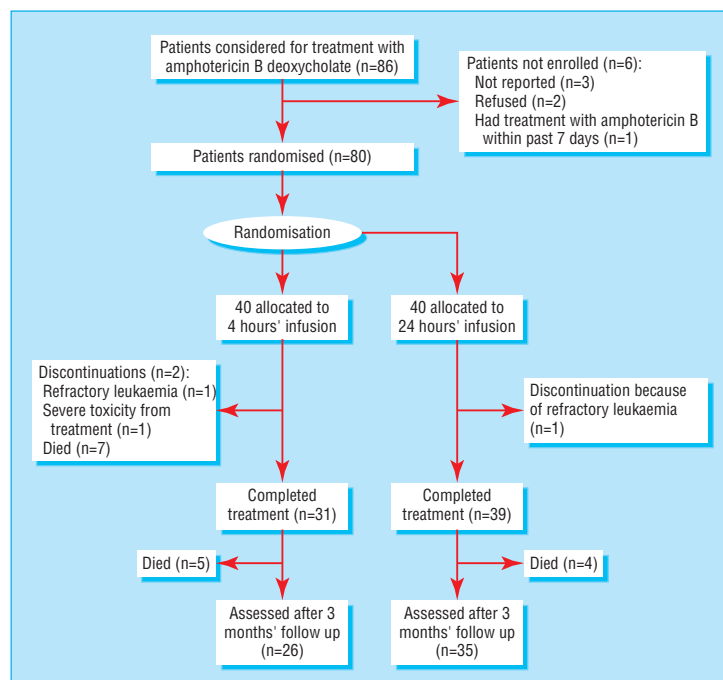
Assignment and follow up

The initial dosage for amphotericin B was chosen before randomisation by the doctors in charge, who were not members of the study team. Eligible patients were then randomised in blocks of 10 by sealed envelope. Treatment started immediately after randomisation. Patients were followed up three months after completion of treatment or when treatment was discontinued for any reason.

Results

Patients—Overall, 86 consecutive patients received amphotericin B during the study period (figure). Most of them were severely neutropenic, with haematological neoplasias. We enrolled 80 patients. The groups were comparable at baseline (table 1).

Dosage and dose reductions—Overall duration of treatment and cumulative and daily doses did not differ significantly between the groups. There was a non-significant trend towards longer duration of treatment and higher cumulative doses in the continuous infusion group. We observed significantly more dose



Trial profile

reductions or infusion interruptions due to side effects in the rapid infusion group (table 2).

Side effects—Side effects occurred mainly during the first three days of treatment. Patients receiving continuous infusions had fewer side effects. For those who had fever at the beginning of treatment there was also a significant difference in the mean time to defervescence (table 2). The concentrations of C reactive protein did not differ between the two groups at entry to the study, but there was a significant increase in the rapid infusion group 24 and 48 hours after the start of treatment (data given on bmj.com). Reflecting the reduced frequency of side effects in the continuous infusion group, these patients were less likely to receive drugs directed against febrile reactions or chills after the first treatment day (table 2).

Nephrotoxicity—Comparison of the calculated creatinine clearance ratios between both infusion groups illustrates a significantly less impaired creatinine clearance for patients with continuous infusions during and at the end of treatment (table 3). The occurrence of electrolyte disturbances did not differ between the two groups.

All seven deaths during treatment occurred in the rapid infusion group. Necropsy was carried out in six of these seven cases and severe pneumonia was found. Invasive fungi were proved in three cases; in one case *Pneumocystis carinii* was detected. In two patients no infection was found. Breakthrough fungaemia did not occur in any patient of either group.

Treatment was discontinued in two patients assigned to rapid infusion: one because of refractory leukaemia and the other because of severe nephrotoxicity from treatment. Treatment was discontinued in one patient in the continuous infusion group because of refractory leukaemia. After three months' follow up 12 patients in the rapid infusion group had died compared with four patients in the continuous infusion group.

Discussion

Continuous infusions of amphotericin B are significantly better tolerated than rapid infusions. Similar advantages of continuous infusions could be sought for other toxic drugs—for example, antineoplastic agents. Continuous applications are, however, not feasible if high peak values are necessary. The rapid infusion of amphotericin B over fewer hours has been adopted empirically in clinical practice. Despite a retrospective analysis suggesting fewer side effects from continuous infusions, no controlled trials have compared rapid and continuous infusions of amphotericin B.²

The reduction of side effects by continuous infusion of amphotericin B seems comparable to recent reports of liposomal amphotericin B.⁸ Amphotericin B triggers a proinflammatory response by activating different cytokines.^{20 21} Continuous infusions may be better tolerated because of delayed induction or release of such mediators, as reflected by differences in concentrations of C reactive protein and fever. We also observed a noticeable reduction of nephrotoxicity in the continuous infusion group. The mechanisms involved in amphotericin B nephrotoxicity are not yet fully understood.¹⁵ They can be broken

Table 2 Infusion related side effects and drugs to suppress febrile reactions in patients receiving rapid (four hours) or continuous (24 hours) infusions of amphotericin B deoxycholate. Values are numbers (percentages) of patients unless stated otherwise

	Infusion rate		P value	Relative risk (95% CI)
	Rapid (n=40)	Continuous (n=40)		
Reactions on day 1:				
Fever*	21 (53)	10 (25)	0.021	2.1 (1.1 to 3.9)
Chills or rigors	21 (53)	5 (13)	0.0003	4.2 (1.8 to 10)
Vomiting	14 (35)	4 (10)	0.009	3.5 (1.3 to 9.7)
Headache	4 (10)	0		
Others	1 (3)	0		
Overall reactions:				
Chills or rigors	25 (63)	8 (20)	0.0001	3.1 (1.6 to 6.1)
Vomiting	24 (60)	11 (28)	0.004	2.2 (1.2 to 3.8)
Headache	11 (28)	4 (10)		
Others	8 (20)	2 (5)		
Drugs after day 1:				
Meperidine	20 (50)	6 (15)	0.002	3.3 (1.5 to 7.4)
Steroids	18 (45)	3 (8)	0.0001	6 (1.9 to 19)
Acetaminophen	30 (75)	19 (48)	0.021	1.6 (1.1 to 2.3)
Dose reductions or infusion interruption	11 (28)	3 (8)	0.022	3.7 (1.1 to 12)
Median (range) defervescence† (days)	2 (1-10)	1 (1-4)	0.016	-1 (-2 to 0)‡

* $>39.3^{\circ}\text{C}$ core temperature (corresponding to an axillary temperature of 38.3°C).

†Fever within 24 hours before treatment was documented for 26 patients in the rapid infusion group and 22 patients in the continuous infusion group.

‡Median difference.

Table 3 Nephrotoxicity in patients receiving rapid (four hours) or continuous (24 hours) infusion of amphotericin B deoxycholate. Values are median (range) unless stated otherwise

	Infusion rate		P value	Median difference (95% CI)
	Rapid (n=40)	Continuous (n=40)		
Calculated creatinine clearance*:				
Minimal clearance:baseline	0.62 (0.29-1.05)	0.80 (0.39-1.10)	0.013	0.12 (0.03 to 0.22)
Clearance at end of study:baseline	0.65 (0.29-1.26)	0.86 (0.44-1.91)	0.001	0.19 (0.09 to 0.29)
Electrolyte abnormalities:				
No (%) with hypokalaemia (<2.5 mmol/l)	10 (25)	4 (10)	0.139	
No (%) with hypernatraemia (>155 mmol/l)	3 (8)	2 (5)	1.0	
No (%) with hypomagnesaemia (<0.5 mmol/l)	19 (48)	17 (43)	0.822	

*Creatinine clearance per 50 kg lean body mass calculated from serum creatinine concentrations.

What is already known on this topic

Amphotericin B is the cornerstone for treatment of invasive fungal infections, especially in neutropenic patients

Its use is limited by general toxic reactions and nephrotoxicity

What this study adds

By giving amphotericin B as a continuous infusion, nephrotoxicity and infusion related toxicity can both be lowered significantly without loss of efficacy

down into pretubular and tubular effects. It seems that, as with liposomal amphotericin B, a continuous infusion of amphotericin B primarily reduces pretubular toxicity.

Indications for amphotericin B in our study were proved fungal infections, probable fungal infections, possible fungal infections, and refractory fever during neutropenia. In clinical practice amphotericin B is often prescribed empirically. A definitive baseline diagnosis of invasive mycosis would require invasive diagnostic procedures that are seldom justified in neutropenic and thrombocytopenic patients. It is therefore scarcely ever possible to identify the true prevalence of invasive mycoses. As criteria for efficacy we therefore chose mortality, mortality due to invasive fungal infections, and breakthrough fungaemia. Although our study population was small we found a higher overall mortality during amphotericin B in the rapid infusion group. Mortality also remained significantly higher after three months' follow up. Consequently, our data support the notion that a continuous infusion of amphotericin B may be at least as effective as daily infusions over four hours. We therefore recommend continuous infusions of amphotericin B, where practical, as an effective and well tolerated alternative to the usual rapid infusions.

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Contributors: UE was responsible for preparing, coordinating, performing, and analysing the clinical trial and is the principal author of the paper. BS was responsible for statistical design and analysis. AS had the original idea for the study and participated in designing the protocol and analysing the study data and is coauthor of the paper. UE and AS will act as guarantors for the paper.

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One hundred years ago A hair as the nucleus of an appendicular calculus

The habit of biting one's moustache is one seemingly unattended with danger, but that it may lead to disastrous consequences the following experience of mine will show. I had occasion some few weeks ago to operate on J. T. H., a private patient, for recurrent attacks of appendicitis, the last one of which was of a severe type. At the operation the appendix was concealed behind the caecum by dense adhesions which matted together the caecum, ileum, appendix, and the peritoneum over the iliac vessels. On separating these adhesions I came across about a teaspoonful of soft chalky material, and then out popped a hard calcareous nodule, about the size of a large pea, which had ulcerated through a soft and ragged appendix. As much of the latter as was possible was removed, a gauze drain used for two days, and the patient made an uninterrupted recovery, being up and the wound soundly healed at the end of the third week.

The point of the case, however, lies in the calcareous nodule, which on being sliced, revealed at its centre a fine stiff rather auburn hair, about 1/12th of an inch in length. This exactly corresponded in colour and in texture with a hair taken from the patient's moustache, and under a lens the two were identical. The patient, a man of a quick nervous temperament, has the habit of pulling and biting his moustache, especially when worried about anything. No doubt a small end bitten off had managed to insinuate itself into the appendix and as the result of the irritation set up the calcareous nodule had formed. Preferring to be clean shaven myself, I had always looked upon the moustache and beard as insanitary, but their potentialities as factors in producing appendicitis had never occurred to me before.

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