Controlled pilot study of rapid amphotericin B infusions

H Dele Davies, Susan M King, John Doyle, Anne Matlow, Gideon Koren, Robert Hamilton, Carol Portwine

Abstract

This pilot study compared the toxicity of a one hour with a four hour amphotericin B infusion in children. There were more severe chills in the former group on the first day of infusion, and more hypotension in the latter group over the study duration.

(*Arch Dis Child* 1997;76:165-166)

Keywords: amphotericin B; toxicity.

Cumulative evidence in adults suggests that short duration infusions of amphotericin B have similar side effects to longer duration infusions,¹⁻⁵ but there are no studies in children. We report a randomised, placebo controlled, double blinded pilot study of infusion related toxicity of one compared with four hour infusions of amphotericin B in children.

Methods

The study was conducted at the Hospital for Sick Children, Toronto, Canada from 1 November 1992 to 30 October 1993. Children aged between 1 month and 19 years prescribed amphotericin B treatment were enrolled. Exclusion criteria included: creatinine clearance <50% of age normal, as estimated using serum creatinine concentrations,⁶ uncontrolled congestive heart failure or life threatening arrhythmias, amphotericin B infusion within one week of study, and failure to obtain informed consent. The study was approved by the hospital ethics review committee.

Eligible children were randomised by pharmacy in blocks of four into two groups: group 1, children who received daily one hour infusions and group 2, those who received daily four hour amphotericin B infusions for four days. Demographic and clinical data and a 14 lead electrocardiogram were obtained at baseline as were daily measurements of serum sodium, potassium, chloride, calcium, magnesium, blood urea nitrogen, creatinine, aspartate aminotransferase, alkaline phosphatase, and complete blood counts. A continuous cardiac monitor with alarm was attached and a study nurse/investigator was always at the bedside during infusions.

The initial dose of amphotericin B was 0.5 mg/kg body weight, diluted in 10 ml of 5% dextrose solution per 1 mg of drug and was increased to 1 mg/kg/day as needed or tolerated. For group 1, all of the amphotericin B dose was infused in one bag over one hour, followed by a second identical appearing bag

containing 5% dextrose, water, and multivitamins, infused over three hours. For group 2 infusions, 25% of the amphotericin B dose was infused in one bag over one hour, while the remaining 75% of the dose was infused in a second bag over three hours. All patients were premedicated with 1 mg/kg of diphenhydramine and 10 mg/kg of acetaminophen. Meperidine hydrochloride (0.6 mg/kg) was given for chills lasting more than five minutes and hydrocortisone (1 mg/kg) was infused for chills lasting more than 10 minutes. Chills were graded between 0 and 3 using a previously described ordinal chill scale.⁵ A tympanic thermometer was used for measurement of temperature. Hypotension was defined as a decrease in systolic or diastolic blood pressure of more than 20% from the baseline, or a fall to less than 2 SDs for age normal.

Group proportions were compared using χ^2 or Fisher's exact test, with $p < 0.05$ considered statistically significant. Repeated measures analysis of variance (ANOVA), with temperature and pulse as repeated measures, was used to compare groups over each of the four different infusion times.

Results

Twelve patients were randomised into each group (table 1). Six patients in group 1 and 11 in group 2 completed all four days of infusion. The mean chill scores of those who developed chills are shown in fig 1. In group 1, three patients with chill scores of 3 were withdrawn after day 1 by their parents and three others had their treatment stopped after day three because the attending physician felt it was no longer clinically indicated. One patient in group 2 was withdrawn after day 2 because of symptomatic bradycardia.

Mean (SD) temperature during infusions was 37.7(1.5)°C for group 1 compared with 37.3(1.0)°C for group 2 patients. There was no difference in the changes in temperature from baseline between the two groups ($p = 0.80$, repeated measures repeated measures ANOVA). Four patients in group 1 (33.3%) and two patients in group 2 (16.7%) developed hypothermia (temperature <35.9°C).

There was no difference in the mean pulse rate between groups over the infusion period ($p = 0.14$, repeated measures ANOVA). Two group 1 and no group 2 patients developed systolic hypotension, while three patients in group 1 and seven in group 2 developed diastolic hypotension.

Hospital for Sick Children, Toronto, University of Toronto, Canada, Department of Paediatrics: Division of Infectious Diseases
H Dele Davies
S M King

Division of Haematology
J Doyle
C Portwine

Division of Pharmacology
G Koren

Division of Cardiology
R Hamilton

Department of Microbiology
A Matlow

Correspondence and reprint requests to: Dr H Dele Davies, Child Health Research Unit, Alberta Children's Hospital, 1820 Richmond Road SW, Calgary, Alberta T2T 5C7, Canada.

Accepted 4 September 1996

Table 1 Characteristics of patients in the two infusion groups before amphotericin B infusions

Characteristic	Duration of infusion	
	One hour (group 1, n=12)	Four hours (group 2, n=12)
Males/females*	10/2	5/7
Age range (years)	0.4-16.1	0.1-18.4
Mean (SD) age (years)	5.7 (5.4)	6.6 (6.5)
No with neutropenia	9	8
No with fever	11	9
No with confirmed fungal infections	2	4
Underlying diagnosis		
Acute lymphocytic leukaemia	2	4
Acute monocytic leukaemia	3	4
Non-Hodgkin's lymphoma	0	1
Rhabdomyosarcoma	1	0
Neuroblastoma	1	0
Wilms' tumour	0	1
Severe combined immunodeficiency	0	1
Immunodeficiency	1	0
Bone marrow transplant	1	0
Aplastic anaemia	1	0
Short gut syndrome	0	1
Chronic candidal mastoiditis	1	0
Histiocytosis X	1	0

* p Value = 0.04.

Figure 1 Mean chill score for each group for those with chills by day of infusion.

Hypokalaemia occurred in no group 1 and one group 2 patient. Two patients in each group had creatinine clearance rates that dropped to <50% of normal. No patients in either group had abnormalities in liver function, calcium, or magnesium during or up to one week after the study. No patients died during or within one week after their infusion was discontinued.

Discussion

In the present pilot study, we found similar toxicity associated with one and four hour amphotericin B infusions in children. However, the withdrawal of three children in the rapid infusion group on day 1 suggests greater severity of chills. For patients who remained in the study, the similarities in mean chill score in the two groups after day 1 suggests that one approach to minimising the chill effect is to give the first dose as a standard (four hour) infusion, with subsequent infusions given over one hour.

Although no patients had arrhythmias, the most serious infusion related toxicity of amphotericin B, it is notable that the only patient to develop symptomatic bradycardia was in the standard infusion arm, and more patients with diastolic hypotension were also in this group. Since one hour infusions for children have the potential benefit of ease in scheduling other medications, total parental nutrition, and outpatient treatment, a larger trial is warranted.

The authors gratefully acknowledge the editorial assistance of Helen Kominic, nurses Helena Makkonen and Jennifer Craven, and the statistical assistance of Derek Stevens.

The study was supported by a grant from the Physician Services Incorporated Foundation of Ontario. H Dele Davies was supported by the Eli Lilly Canadian Infectious Diseases Fellowship Award and the Ontario Ministry of Health Research Personnel Development Award.

This work was presented in part at the 34th InterScience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Florida, October 1994.

- 1 Oldfield EC III, Garst PD, Hostettler C, White M, Samuelson D. Randomized, double-blind trials of 1- versus 4-hour amphotericin B infusion durations. *Antimicrob Agents Chemother* 1990;34:1402-6.
- 2 Spitzer TR, Creger RJ, Fox RM, Lazarus HM. Rapid infusion of amphotericin B: effective and well-tolerated therapy for neutropenic fever. *Pharmatherapeutica* 1989;5:305-11.
- 3 Cruz JM, Peacock JE Jr, Loomer L, et al. Rapid intravenous infusion of amphotericin B: a pilot study. *Am J Med* 1992; 93:123-30.
- 4 Arning M, Dresen B, Aul C, Schneider W. Influence of infusion time on the acute toxicity of amphotericin B: results of a randomized, double-blind study. *Recent Results Cancer Res* 1991;121:347-52.
- 5 Ellis ME, al-Hokail AA, Clink HM, et al. Double-blind randomized study of the effect of infusion rates on toxicity of amphotericin B. *Antimicrob Agents Chemother* 1992;36:172-9.
- 6 Schwartz G, Brion L, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am* 1987;34:571-90.