

Double-Blind Randomized Study of the Effect of Infusion Rates on Toxicity of Amphotericin B

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Results of a double-blind randomized non-crossover study of rapid (45 min) versus slow (4 h) infusion of amphotericin B administered to 20 patients with proven or suspected fungal infection are reported. Toxicity was higher in the rapid infusion group than it was in the slow infusion group (mean total 7-day chill score, 173 ± 276 versus 20 ± 30 [$P < 0.01$]; mean total 7-day dosage of meperidine required to abate rigors, 180 ± 133 versus 58 ± 78 mg [$P < 0.05$]; and mean maximum total 7-day pulse rise, 225 ± 64 versus 135 ± 56 beats per min [$P < 0.02$], respectively). When analyzed on a daily basis, the mean chill score, meperidine dosage, and pulse rise were also higher; and in addition, nausea and vomiting (5 of 11 patients who received a rapid infusion versus 0 of 9 patients who received a slow infusion [$P < 0.01$]) appeared to be more common in those who received amphotericin B rapidly. The daily analysis approach proved that tolerance to these side effects developed with each subsequent infusion day, and by day 7 the incidence and severity were the same. This development of tolerance was significant for the mean chill score in the rapid infusion group ($P < 0.05$) and for the proportion of patients with chills ($P < 0.005$ for the slow infusion group; $P < 0.05$ for the rapid infusion group). A decrease in creatinine clearance to $>51\%$ of the baseline value was seen in two patients in each group. There were five deaths (four in the rapid infusion group, 1 in the slow infusion group) within 1 month, but none was clearly related to the amphotericin B infusion. The mean time to defervescence was similar for each group (10.8 ± 4.1 days in the slow infusion group versus 9.9 ± 5 days in the rapid infusion group). A rapid infusion regimen for amphotericin B cannot be recommended, at least during the first 5 to 7 days of treatment.

Amphotericin B is an antimycotic polyene antibiotic that is commonly used for the treatment of proven or suspected severe fungal infections. Its administration requires intravenous access and, conventionally, a 6-h-daily infusion for days, weeks, or months, depending on the nature of the fungal infection. The prolonged infusion time consumes excessive patient and nursing time, but it is said (9) to be necessary to minimize the formidable toxicity of amphotericin B, which includes rigors, hypotension, renal toxicity, and cardiac dysrhythmias. Occasional anecdotal reports (11) and studies (2, 5) have suggested no increase in toxic side effects if amphotericin B is administered over a much shorter period. The present study compares the toxicities of rapid versus slow amphotericin B infusion rates when it is given to patients with proven or suspected fungal infections.

MATERIALS AND METHODS

Twenty patients with suspected or proven severe fungal infections were randomly ascribed by a computer-generated code held by the Department of Pharmacy Services, King Faisal Specialist Hospital and Research Centre, to receive amphotericin B over either 45 min (rapid infusion) or 4 h (slow infusion). Patients were recruited sequentially, and their recruitment was dependent only on space availability in the monitoring unit. Patients with preexisting renal disease, as defined by a creatinine clearance of <40 ml/min, hypotension (blood pressure, $<100/60$ mm Hg), or significant myocardial dysfunction were excluded. In addition, patients who were judged to be too ill to comply with the study or

who were already toxic with hypotension, tachycardia, or impending respiratory failure (tachypnea, >25 breaths per min; reduced partial arterial O_2 on room air; pulmonary signs involving at least one localized segment), which would make interpretation of protocol parameters difficult, were excluded from the study. Full informed consent was obtained from the patients.

An initial test dose of 1 mg of amphotericin B (Fungizone; lot 9A 1670; E.R. Squibb & Sons, Inc.) was given over 30 min to exclude any acute severe reaction; then, preceded by premedication with hydrocortisone (0.7 mg/kg of body weight given intravenously) and diphenhydramine hydrochloride (Benadryl; 25 mg intravenously) given each day to each patient, amphotericin B (0.5 mg/kg) was administered daily for 7 days. In order to mask the infusion rates to both patients and observers, each patient received the contents of two infusion bags. Bag 1 contained amphotericin B to a final dilution of 0.25 mg/ml of 5% glucose. Bag 2 contained the same volume of 5% glucose, to which soluble vitamins were added to match the color of the bag with amphotericin B. Patients assigned to receive amphotericin B over 45 min received bag 1 over 45 min; this was followed immediately by bag 2 over 4 h. Patients assigned to receive amphotericin B over 4 h received bag 2 over 45 min; this was followed immediately by bag 1 given over 4 h. The concentration of amphotericin B (higher than the recommendation of the manufacturer) was selected to reduce the infusion volume, which may otherwise precipitate acute volume overload. Both groups received amphotericin B at the same concentration. Solutions were used within 24 h of preparation. Patients received concomitant medication with antimicrobial agents, blood products, etc., as appropriate; but these were

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TABLE 1. Characteristics of the two groups and mortality detail

Characteristic	Infusion speed		P
	Slow	Rapid	
No. of males/no. of female	3/6	7/4	NS ^a
Age (yr [range])	31.7 ± 9.7 (18–51)	22.2 ± 14.2 (13–64)	0.007
Neutropenia duration (days [range])	16.8 ± 2.7 (14–21)	11.8 ± 6.1 (4–21)	NS
No. with neutropenia	6/9	8/11	NS
No. febrile	6/9	9/11	NS
Duration of fever (days [range])	9.0 ± 4.2 (5–15)	10.2 ± 4.3 (4–15)	NS
No. with acute/no. with chronic fungus, infection (proven or suspected)	6/3	10/1	NS
No. who died/total no. of patients	1/9 ^b	4/11 ^c	NS

^a NS, not significant.

^b The patient died of pulmonary hemorrhage.

^c Patient deaths were caused by late renal failure, resistant myelofibrosis, nephrotoxic antibiotics ($n = 1$); *Acinetobacter* pneumonia ($n = 1$); fungal myocarditis ($n = 1$); and uncontrolled sepsis, renal failure, refractory hypotension, nephrotoxic antibiotics ($n = 1$).

withheld during the period of amphotericin B infusion in order not to confuse interpretation of any toxic parameters that were recorded.

A full blood count with differential and renal and liver profiles were made immediately prior to each daily infusion for the 7 days. Rectal temperature, supine pulse, cardiac rhythm, blood pressure, and arterial oxygen saturation (SaO₂) by pulse oximetry were recorded at time zero; 15, 30, 45, and 60 min; and then every half hour during the 6-h infusion. The times of onset and termination of chills were recorded; and their severities were classified and graded as follows: no chills, 0; minimal fasciculation confined to one or two muscle groups, 1; visible tremors with more than two muscle groups involved, 2; generalized shaking, 3.

Aliquots of 25 mg of meperidine were administered intravenously every 15 min as necessary to abate chills that lasted at least 3 min. The occurrence of headache, paraesthesia, cramps, flushing, phlebitis, nausea, and vomiting was noted. Patients were withdrawn from the study if severe toxic symptoms occurred; creatinine clearance fell by at least 51% from the value on day 1 within the 7-day study period; or the underlying condition of the patient worsened, necessitating intensive care and assisted ventilation in which recording of study data could not be monitored (institution of muscle paralysis, inotropes, or routine use of opiates and tranquilizers in this setting would make the protocol parameters impossible to interpret). Creatinine clearance was calculated by the following formula: creatinine clearance = [(140 - age) × weight × 0.85 (for females)]/(72 × creatinine) (1). On day 8, a decision was made to complete the amphotericin B course at the same blinded infusion rate, but apart from mortality, follow-up, renal function, and final outcome, no further detailed monitoring for study purposes was done.

Statistical methods. The aim of the data analysis was to ascertain whether (i) an overall difference in the measured variables existed between patients in the rapid and slow infusion groups during the study and (ii) tolerance was achieved or an acceptably high level of side effects occurred. For i, repeated measures analysis of variance (using MANOVA) would be the preferred test for continuous data. However, many of the data collected were not normally distributed and the design was unbalanced. In addition, patients were lost from the study, leaving fewer patients for longitudinal analysis. MANOVAs were performed for data obtained on all 7 days as well as for data obtained on the first 5 days only (to minimize case loss). If the 7-day results differed from the 5-day results, this is noted. If there were

indications of overall differences, individual differences were examined. MANOVA is fairly robust to minor deviations from normality, but a correction for lack of homogeneity of variance was used. To measure changes over time, a non-parametric frequency test was used for data that were nonparametric. For comparisons on a daily basis, the Mann-Whitney U test (6) instead of the *t* test was used for continuous data, since the *t* test is applicable only to normally distributed data. On dichotomous data, Fisher's exact probability (two-tailed) was calculated (6). The analysis was performed by using SPSS-X (8).

RESULTS

Eleven patients received amphotericin B over 45 min and 9 patients received it over 4 h. The characteristics of the patients are summarized in Table 1. Details of the underlying diagnosis and suspected or proven fungal infection on entry into the study and subsequently are recorded in Table 2. Apart from a slightly younger age of the rapid infusion group, the two groups were well matched for sex, proportion and duration of preexisting neutropenia, fever, underlying disease, and suspected or proven fungal infection.

Toxicity: rigors. In order to obtain the most realistic measure of rigor severity, the chill score was calculated by using the following formula: chill severity × duration (in minutes). The mean chill score for the total 7-day period was 173 ± 276 ($n = 11$) for patients who received the rapid infusion and 20 ± 30 ($n = 9$) for patients who received the slow infusion. This difference was significant ($P < 0.01$). The daily mean chill score (Fig. 2) was higher in the rapid infusion group ($P < 0.05$, day 1; $0.1 > P > 0.05$, days 2 to 4) and was seen to decrease with each subsequent infusion, but this decrease was significant for the rapid infusion group only ($P < 0.05$). Three of nine patients in the slow infusion group and 1 of 11 patients in the rapid infusions group experienced no rigors at any time. Over the 7-day period, the mean times that patients experienced any rigor were 3.1 ± 2.2 days in the rapid infusion group and 1.4 ± 2.1 days in the slow infusion group. This difference, unlike the total chill score, was not significant ($P = 0.1$). However, the proportion of patients who experienced rigors (Fig. 1) was consistently greater for the first 5 days in the rapid infusion group (significant at day 3 [$P < 0.05$]). For both groups, the change in this proportion with chills diminished significantly in time ($P < 0.05$ for the rapid infusion group; $P < 0.005$ for the slow infusion group). The mean time to chills (Table 3) was

TABLE 2. Underlying diagnosis and fungal infection at presentation and by 4 weeks by infusion rates

Diagnosis	No. of patients	
	Slow infusion group	Rapid infusion group
At presentation		
Acute neutropenia		
Fungus infection suspected		
Acute leukemia with ARNF ^a (recent chemotherapy induction)	5 (4)	7 (4)
Early bone marrow transplantation with ARNF	0	1
Acute fungus inspection diagnosed		
<i>Aspergillus</i> spp. on bronchoalveolar lavage	1 ^b	1
Normopenic		
Subacute fungal infection diagnosed		
Chronic bronchopulmonary <i>Aspergillus flavus</i>	0	1
<i>Aspergillus</i> spp., paranasal sinus	1	1
Intracranial aspergillosis	1	1
Mycetoma thigh, <i>Aureobasidium pullulans</i>	1	0
At >3/52^c after first study week		
<i>Aspergillus</i> septicemia and myocarditis	0	1
Suspected fungus cavity right upper lobe	0	1

^a ARNF, antibiotic resistant neutropenic fever.

^b The patient was also neutropenic.

^c 3/52, 3 weeks.

shorter in the rapid infusion group throughout the 7-day period of the study. However, since the number of patients with rigors fell substantially with each infusion day, there were insufficient data to calculate the statistical difference apart from days 1 and 2. At those times, the differences were significant.

Toxicity: meperidine dosage. The mean meperidine dosages required (total for the 7-day period) to abate rigors were 180 ± 133 mg (*n* = 11) and 58 ± 78 mg (*n* = 9) for the rapid

and slow infusion groups, respectively (Table 3). The difference was significant (*P* < 0.05). The dosage required was consistently higher in the rapid infusion group for each day and was significant on day 3 (*P* < 0.05) and approached significance on days 1 and 4 (*P* < 0.1) (Table 3). The meperidine requirement fell with each infusion day, and this change approached significance (0.01 > *P* > 0.05) over the 7 days of the study and was significant over the first 5 days (*P* < 0.01).

Toxicity: pulse rise. The means of the total maximum pulse rises (maximum pulse recorded during the 6-h observation period minus baseline pulse) over the 7 days of the study were 225 ± 64 (rapid infusion group) and 135 ± 56 (slow infusion group) beats per min, and the difference was significant (*P* < 0.02). On a daily analysis, the rise was higher over the first 5 days and was significant on days 1 and 3 (Fig. 3). The downward trend in pulse rise with subsequent infusion days was significant for the rapid infusion group (*P* < 0.01).

The following variables showed no significant overall differences over the 7-day period: maximum systolic and diastolic rises and falls, creatinine clearance, potassium dosage given, maximum temperature, and SaO₂. However, there were two isolated findings and differences on individual days, as follows. On day 1, for the maximum systolic blood pressure decrease, the rapid infusion group experienced a significantly greater decrease, namely, 18 ± 10 mm Hg (*n* = 11) versus 8 ± 8 mm Hg for the slow infusion group (*n* = 9) (*P* < 0.05); and on day 4, the rapid infusion group experienced a significantly greater systolic blood pressure increase, namely, 24 ± 8 mm Hg (*n* = 8) versus 13 ± 8 mm Hg for the slow infusion group (*n* = 8) (*P* < 0.05).

The proportion of patients with any other side effects (23 instances altogether), mainly headaches, nausea, vomiting, and cramps, was slightly higher in the rapid infusion group for the first 2 days, but the difference was not significant and thereafter the incidences were virtually identical in the two groups (Fig. 4). Nausea and vomiting were the most common side effects. Of the 10 instances of nausea and vomiting, 9

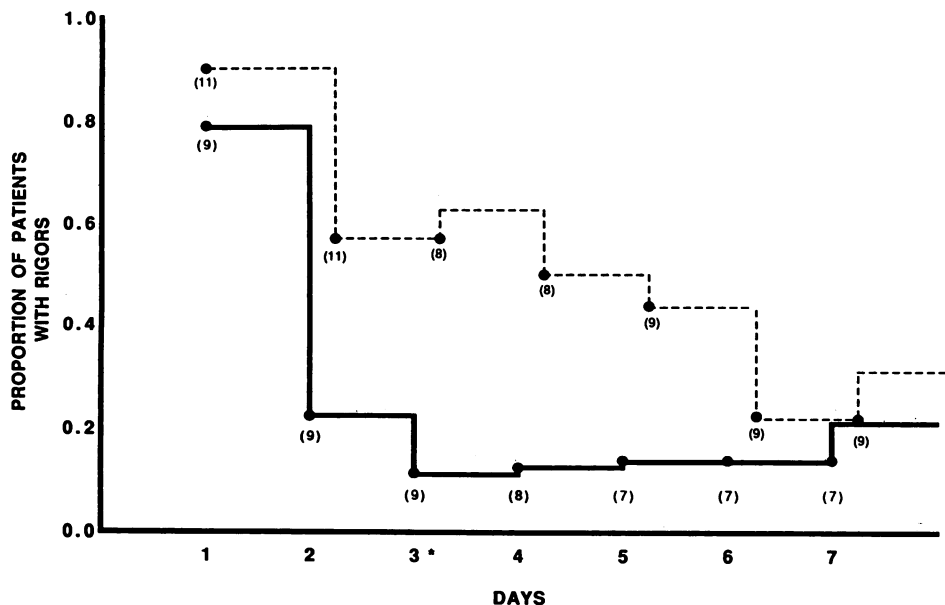


FIG. 1. Proportion of patients with rigors. Numbers in parentheses are number of patients for that observation. *, *P* = 0.0497. ---, rapid infusion; —, slow infusion.

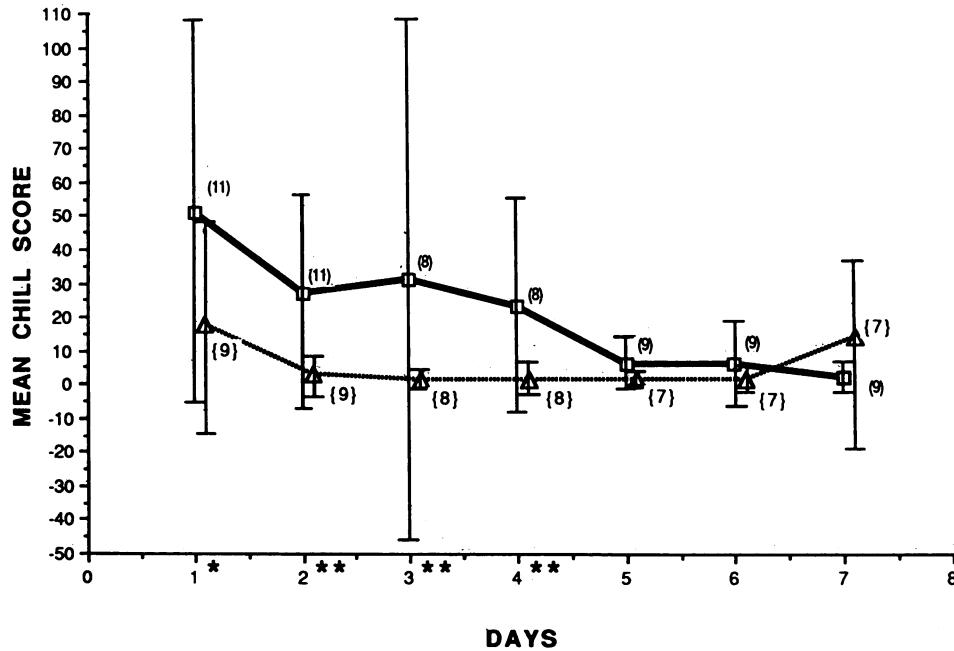


FIG. 2. Mean chill score. Numbers in parentheses are number of patients for that observation. *, $P < 0.05$; **, $0.1 > P > 0.05$. □, rapid infusion; △, slow infusion.

occurred in the rapid infusion group. On day 1, this was observed in 5 of 11 patients in the rapid infusion group but was observed in 0 of 9 patients in the slow infusion group ($P < 0.05$). Thereafter, it occurred exclusively in the rapid infusion group, apart from one instance in the slow infusion group.

For those patients who had fever at the beginning of the infusion, the mean time to defervescence was similar for each infusion group, namely, 10.8 ± 4.1 days for the slow infusion group and 9.9 ± 5 days for the rapid infusion group.

The mean creatinine clearance was marginally higher for the slow infusion group throughout the study, but the difference was not significant. It fell progressively with time for both groups (Table 3). Six of 11 patients in the rapid infusion group had a decrease in creatinine clearance of between 21 and 50%, whereas 2 of 9 patients in the slow infusion group had such a decrease in creatinine clearance, and 2 patients in each group had a decrease that exceeded 51%. Of these four patients with severe renal toxicity at day 7, one had a chronic fungal infection but was not receiving other antimicrobial antibiotics and received the slow infusion regimen. The other patient on the slow infusion regimen had acute myeloid leukemia complicated by streptococcal septicemia and was on concomitant therapy with vancomycin, ceftazidime, gentamicin, and, later, imipenem and acyclovir. The creatinine clearance in this patient fell by 62%. Two patients with severe renal toxicity were on the rapid infusion regimen, one of whom had acute myeloid leukemia, was receiving poly antimicrobial agents, and developed *Acinetobacter* pneumonia. The creatinine clearance in this patient fell by 83%. The other patient was receiving toxic quantities of vancomycin and amikacin and, in addition, had tumor lysis and disseminated fungal infection. In this patient, the creatinine clearance fell by 72%.

Six of the 9 patients on the slow infusion regimen and 9 of the 11 patients on the rapid infusion regimen had normal or mildly deranged liver function tests throughout (the alanine

aminotransferase level increased by up to twice the baseline level), but in no case was this clearly ascribed to amphotericin B and in no case did frank hepatic failure occur.

Exclusion or withdrawal of patients from the study. One patient was excluded from trial entry because he had preexisting renal disease. Four patients were unable to complete their 7 study days: one patient (rapid infusion regimen) developed acute renal failure secondary to toxic levels of vancomycin and amikacin and tumor lysis on day 3, one patient (rapid infusion regimen) died on day 3 from sudden overwhelming *Acinetobacter* septicemia, one patient (slow infusion regimen) had grand mal seizures related to intrathecal chemotherapy on day 3, and one patient (slow infusion regimen) developed acute renal failure and a leukoagglutinin reaction on day 5. Three of the four patients had no chills for the previous 2 days, and one patient had moderate chills of 3 to 16 min only. Two additional patients (both in the rapid infusion group) had their amphotericin B infusion withheld for 1 day each only because of an accelerated rising creatinine on days 3 and 4. Both of these patients resumed the study 24 h later. Neither patient had had any chills for at least the previous day, and neither patient had chills subsequently. The composition of each group on all days therefore remained matched, with no obvious excess of more ill patients in either infusion group.

Death, which occurred within 1 month of the start of amphotericin B infusion, was recorded in one patient who received the slow infusion and in four patients who received the fast infusion, but this difference was not significant. The causes of death are summarized in Table 1. On day 3, one patient died from sudden overwhelming *Acinetobacter* septicemia, and the other patients died from primary disease or secondary infective complications more than 3 to 4 weeks after the study period, but none of the patients appeared to die as a result of amphotericin B toxicity. The secondary infective complications were not apparent on entry into the study. The mean chill score in the four patients on rapid

TABLE 3. Toxicity parameters by day of infusion and infusion rate^a

Day of infusion and infusion rate	Creatinine clearance (ml/min)	Potassium (mmol/liter)	Maximum pulse rise (beats/min)	Meperidine dose (mg)	Maximum temp rise (°C)	No. of patients with chills	Time (min) to chills	Potassium dose (meq)
1								
Slow	142 ± 75 (9)	3.8 ± 0.4 (9)	18 ± 17 (9) ^b	25 ± 28 (9) ^c	0.7 ± 0.8 (9)	7 (9)	193 ± 85 (9) ^d	44 ± 72 (9)
Rapid	136 ± 72 (11)	4.0 ± 0.5 (11)	56 ± 26 (11) ^b	46 ± 25 (11) ^c	1.4 ± 1.2 (11)	10 (11)	71 ± 26 (11) ^d	36 ± 30 (11)
2								
Slow	134 ± 72 (7)	4.0 ± 1.4 (7)	24 ± 16 (9)	8 ± 18 (9)	0.3 ± 0.7 (9)	2 (9)	175 ± 42 (9) ^d	55 ± 71 (7)
Rapid	122 ± 70 (11)	3.6 ± 0.5 (11)	34 ± 22 (11)	23 ± 24 (11)	0.7 ± 0.7 (11)	6 (11)	84 ± 9 (11) ^d	54 ± 51
3								
Slow	120 ± 73 (9)	3.5 ± 0.8 (9)	12 ± 6 (8) ^d	3 ± 9 (8) ^d	0.5 ± 0.9 (8)	1 (9)	209 (9)	90 ± 61 (8)
Rapid	103 ± 69 (11)	3.6 ± 0.6 (11)	31 ± 20 (8) ^d	34 ± 36 (8) ^d	1.0 ± 0.7 (8)	5 (8)	91 ± 12 (8)	69 ± 52 (8)
4								
Slow	113 ± 74 (9)	4.0 ± 1.2 (8)	15 ± 10 (8)	3 ± 9 (8) ^c	0.7 ± 0.7 (8)	1 (8)	237 (8)	90 ± 61 (8)
Rapid	95 ± 55 (10)	3.6 ± 0.7 (10)	27 ± 18 (8)	25 ± 30 (8) ^c	0.8 ± 1.0 (8)	4 (8)	75 ± 13 (8)	70 ± 63 (8)
5								
Slow	104 ± 69 (8)	3.6 ± 0.7 (8)	21 ± 14 (8)	7 ± 19 (8)	1.1 ± 1.1 (8)	1 (7)	210 (7)	80 ± 63 (8)
Rapid	96 ± 51 (10)	3.6 ± 0.6 (10)	24 ± 14 (9)	17 ± 22 (7)	0.5 ± 0.5 (9)	4 (9)	89 ± 3 (9)	76 ± 62 (9)
6								
Slow	108 ± 65 (9)	3.4 ± 0.6 (9)	17 ± 12 (7)	7 ± 19 (7)	0.4 ± 0.5 (7)	1 (7)	360 (7)	80 ± 63 (6)
Rapid	97 ± 40 (9)	3.7 ± 0.8 (9)	15 ± 8 (9)	19 ± 35 (9)	0.1 ± 0.3 (9)	2 (9)	73 ± 18 (9)	92 ± 66 (9)
7								
Slow	101 ± 53 (9)	3.4 ± 0.7 (9)	21 ± 14 (7)	14 ± 25 (7)	0.4 ± 0.4 (7)	2 (7)	93 ± 39 (7)	97 ± 70 (6)
Rapid	89 ± 46 (10)	3.8 ± 0.9 (10)	13 ± 12 (9)	17 ± 35 (9)	0.4 ± 0.4 (9)	3 (9)	123 ± 50 (9)	81 ± 56 (9)

^a Except for number of patients with chills, values are means ± 1 standard deviation. Values in parentheses are number of patients available for that observation.

^b Difference between the infusion groups for the parameter is significant ($P < 0.005$).

^c Difference between the infusion groups for the parameter approaches significance ($0.1 > P > 0.05$).

^d Difference between the infusion groups for the parameter is significant ($P < 0.05$).

infusion who died was 8 ± 10 (range, 0–24) versus 59 ± 56 (range 14 to 180) for the patients who survived. Two of the four patients who died had experienced no chills; none of the survivors had no chills.

No patient developed an overt or uncontrolled fungal infection during the 7-day study period. Two patients in the rapid infusion group but none of the patients in the slow infusion group developed a serious fungal infection at 3 to 4 weeks following the completion of the study week.

Following the 7-day study period, 8 of 9 patients on the slow infusion regimen and 7 of 11 patients on the rapid infusion regimen completed their antifungal course on the same regimen and had a satisfactory outcome. Three patients on the rapid infusion regimen could not complete the course because of unacceptable renal toxicity. This included two patients who died.

The mean duration of amphotericin B treatment for those who completed their antifungal course was 11.1 ± 5.7 days (range, 3 to 21 days) for eight patients on the slow infusion regimen and 26.9 ± 20.4 days (range, 7 to 70 days) for seven patients on the rapid infusion regimen. Renal function was last assessed at a mean follow-up time of 20 ± 19 days for patients who received the slow infusion and 44 ± 27 days for those who received the rapid infusion. Creatinine clearances and electrolyte levels were within normal limits in all patients.

DISCUSSION

Amphotericin B has a formidable toxic spectrum which is unpleasant for the patient and which includes renal failure,

liver failure, and cardiovascular abnormalities which may prove fatal. A 6-h infusion has been recommended (9). An early case report (11) suggested that a 1-h infusion is safe. However, caution was noted following the observation of ventricular fibrillation in one patient during rapid infusion (3). Nevertheless, one report suggested that rapid infusion is safe (2). Although this study was not blinded to the observer, the different infusion rates may not have been dissimilar (45 min versus 2 h), and the design was of the within-patient crossover type, so that an uncorrected variable, tolerance, was introduced. A large retrospective noncomparative study of a 1.5- to 2-h infusion rate, which was defined as fast, appeared to support a safe and effective role for amphotericin B (7). A recent report (5) published after the completion of this study concluded that a rapid infusion rate is no more toxic than a slow one.

Our results indicate that systemic toxicity appears to be greater in patients who receive a rapid infusion of amphotericin B. Thus, we showed that patients who receive rapid infusions have statistically higher total 7-day mean chill scores, meperidine requirements, and pulse rises. Analysis of variables on a daily basis confirmed this, and we believe that this latter approach is more sound statistically, since tolerance to toxicity appeared to develop with each subsequent infusion day (see below). The proportion of patients with rigors and other side effects (including nausea and vomiting, which were particularly troublesome) was also greater in the rapid infusion group.

There were no significant differences in temperature increases during the infusion, but this may have reflected the

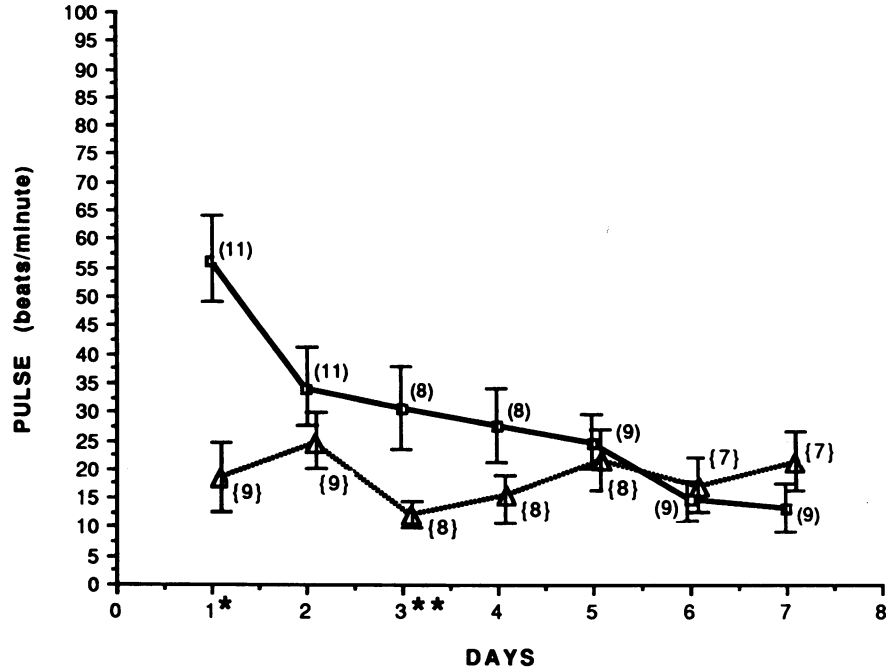


FIG. 3. Mean maximum pulse rise. Numbers in parentheses are number of patients for that observation. *, $P < 0.005$; **, $P < 0.05$. □, rapid infusion; △, slow infusion.

routine use of hydrocortisone. There were no dramatic differences in blood pressure decreases. The incidence of liver toxicity, a recognized toxic complication of amphotericin B therapy (9), appeared to be similar in each group, but it was not serious. Hematological toxicity was difficult to assess, particularly among the hematology patients who had preexisting bone marrow problems, but no clear hematological effect of the amphotericin B could be detected in any patient.

The number of patients in this study was small, and it may therefore have been easy to introduce bias in some way. For example, those who received the rapid infusion could have been more ill. However, the numbers of patients with neutropenia, fever, types of underlying hematological malignancies, and acute or chronic fungal infections were not dissimilar for each group. Furthermore, the conditions for entry into the study ensured that patients who were seriously ill were excluded. By using death as a final arbiter of illness

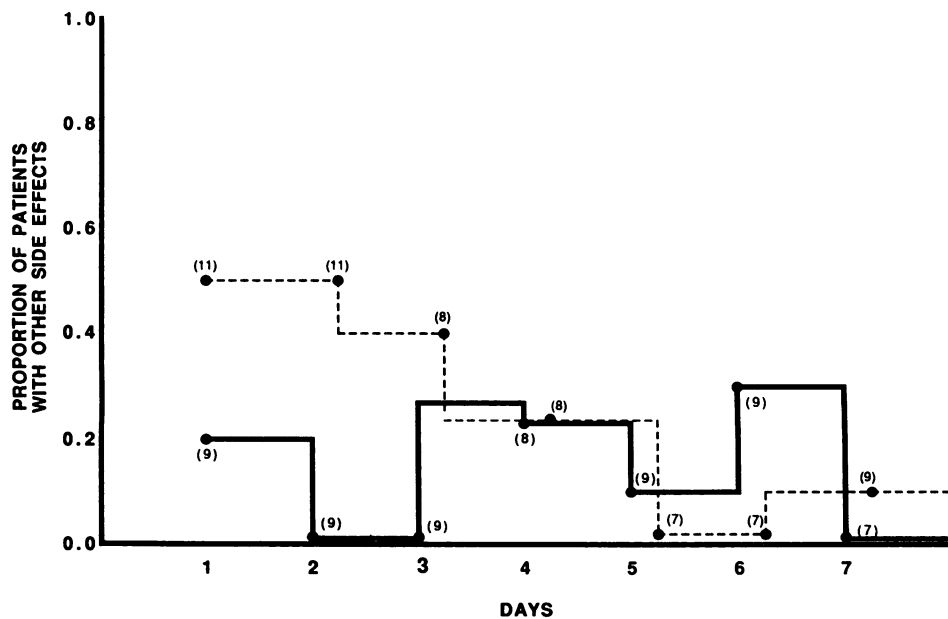


FIG. 4. Proportion of patients with other side effects. Numbers in parentheses are number of patients for that observation. - - -, rapid infusion; —, slow infusion.

severity and chills as a marker of severity, there was no relationship between illness severity and toxicity. Also, the systemic toxic effect of chills was closely related in time to the infusion of amphotericin B, so that the chills and chill scores recorded reflected amphotericin B toxicity and not sepsis or a worsening general condition of the patient. Moreover, there is not a priori reason why more ill patients should have been more susceptible to amphotericin B toxicity, even if there was a distribution bias. Age was the only significant difference between the two groups (although the actual mean age was not grossly dissimilar); patients who received the rapid infusion were younger. However, there is no information to suggest that age differences predispose a patient to the toxic effects of amphotericin B, although one might expect that because older patients are more susceptible to the toxic side effects of antimicrobial agents in general, they would therefore be more prone to those of amphotericin B. The premedication procedure with hydrocortisone and diphenhydramine hydrochloride could have had some effect on the severity of amphotericin B toxicity, but we had hoped to reduce bias by administering it daily to both groups of patients. Furthermore, this is standard practice in our hospital, according to the instructions of the manufacturer, and in many centers, and it was used by Cleary et al. (2) and Oldfield et al. (5). The concentration of amphotericin B used (0.25 mg/ml) rather than 0.1 mg/ml was selected to minimize the risk of an acute fluid overload during the rapid infusion. Past experience in our hospital has shown no increase in the number of side effects when amphotericin B is used at a concentration 0.25 mg/ml and infused over 4 to 6 h. Reports indicate that amphotericin B up to a concentration of 1.4 mg/ml is stable at 25°C for 36 h (4). The only clinical problem with higher concentrations of amphotericin B is the tendency for peripheral venous thrombosis if concentrations in excess of 0.1 mg/ml are used (10). We encountered no solubility problems with this concentration of amphotericin B, and all infusions were administered via a central vein, producing a considerable dilution effect after intravenous access. Finally, the same concentration was used for each group, and any bias was therefore eliminated.

Our results are therefore at variance with those recently reported by Oldfield et al. (5). However, that study examined patients who were on maintenance amphotericin B for the first time. Furthermore, their study (5) and another study (2) have incorporated a within-patient crossover design element which could confuse data interpretation, since tolerance to side effects may well develop. In addition, this approach fails to address the basic question of whether a rapid infusion is more convenient for the patient, since in clinical practice in this setting, patients consistently receive either a rapid or a slow infusion daily. Moreover, it is clear from our results that the incidence of systemic toxicity did indeed diminish over the 7-day study period, particularly for the rapid infusion group, and by day 7 it was virtually identical for each group. It is not clear whether a minor element of observer bias may have been introduced in a previous study (5), since if the concentration of amphotericin B was the same for each infusion bag, then volume differences between the two bags used might have become apparent, at least to the observer.

Creatinine clearance fell, as expected, with the daily amphotericin B infusions, and although these decreases were identical for both infusion groups on day 1, a greater but statistically insignificant decrease was seen for the rapid infusion group. The potassium level in serum remained within the normal range throughout the study period, and the

daily dose of potassium required to maintain this level was similar for both groups. A serious decrease in creatinine clearance occurred in four patients over the 7-day study period (two patients in each infusion group). The concomitant risk factors, including multiple nephrotoxic antibiotics and severe sepsis for renal toxicity in three of these patients, made the role of amphotericin B in the decrease in creatinine clearance impossible to assess. In the fourth patient, who received the slow infusion regimen, no other associated renal risk factor apart from amphotericin B existed, illustrating that in any particular patient amphotericin B-induced renal failure can occur irrespective of the infusion speed. It is important to assess renal toxicity after the 7-day period. Although the mean follow-up time in our study was short, renal function could be assessed in all patients at mean times of 20 and 44 days following discontinuation of amphotericin B in the slow and rapid infusion groups, respectively, and the results were normal.

In none of the five patients who died within 1 month from the start of amphotericin B therapy could the cause of death be directly attributed to amphotericin B, although four of the five patients received the rapid infusion regimen.

With such a small population, it is impossible to compare efficacy in terms of final outcome. However, the initial response measured by time to defervescence was similar in both groups.

In summary, therefore, our results indicate a tendency for increased toxicity in patients who receive amphotericin B for the first time over 45 min. Tolerance to toxicity appeared to develop, so that by 5 to 7 days the incidence of toxicity was the same in each group. The complicated pathology of many of the patients made it difficult to define the precise role that amphotericin B had in the genesis of these side effects. A much larger study with a more homogeneous population group would be required in order to clarify the issue further.

On the basis of our results, we cannot concur with previous suggestions that the rapid administration of amphotericin B is just as safe and acceptable as a slow infusion, at least during the first 5 to 7 days of treatment.

ACKNOWLEDGMENTS

We thank the nursing staff of the East Wing Special Care Unit and Bone Marrow Transplantation Unit at King Faisal Specialist Hospital and Research Centre for dedicated participation in this study and Bernadette Martinez and Sarah Lee Andrada for invaluable secretarial help in the preparation of the manuscript.

No external financial support was obtained for this study.

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