Randomized, Double-Blind Trial of 1- versus 4-Hour Amphotericin B Infusion Durations

EDWARD C. OLDFIELD III,^{1*} PAUL D. GARST,¹ CHARLES HOSTETTLER,²
MARTIN WHITE,³ AND DWAYNE SAMUELSON²

Departments of Internal Medicine (Infectious Disease Division)¹ and Pharmacy,² Naval Hospital, and Occupational Medicine Department, Naval Health Research Center,³ San Diego, California 92134-5000

Received 11 October 1989/Accepted 18 April 1990

We conducted a randomized, double-blind trial of 1- versus 4-h infusions of amphotericin B to determine whether there was any difference in infusion-related toxicity. A total of 128 maintenance infusions in 12 patients were studied; 62 were randomized to 1-h infusions (group A) and 66 were randomized to 4-h infusions (group B). We found no significant differences between patients in groups A and B in mean temperature, pulse, or systolic or diastolic blood pressure measured during the infusions. At a significance level of 0.05, the power to detect a mean difference in temperature of 2°C, a pulse difference of 20 beats per min, a decrease in diastolic blood pressure of 10 mm Hg, or a decrease in systolic blood pressure of 20 mm Hg was 0.95. Rigors and chills were noted in 15 of 62 (24.1%) infusions in group A patients and 12 of 66 (18.1%) infusions in group B patients ($P = 0.40$). Meperidine was required because of severe persistent rigors in 6 of 62 (9.6%) infusions in group A patients and 6 of 66 (8.9%) infusions in group B patients ($P = 0.91$). An increase in temperature was noted in five (8%) of the group A infusions and seven (10.6%) of the group B infusions ($P = 0.63$). The mean time to onset of rigors, an increase in temperature, and an increase in pulse occurred significantly earlier in group A than in group B patients ($P = 0.02$ for all comparisons). We conclude that there is no difference in the incidence or severity of the infusion-related toxicity of amphotericin B with a 1-h infusion rate compared with a 4-h infusion rate. However, the onset of infusion-related toxicity occurs significantly earlier with a 1-h infusion.

Amphotericin B (AMB), which was introduced in 1956, remains the standard agent for the treatment of many of the systemic mycoses. It has maintained this position despite its formidable and essentially unavoidable toxicity.

Infusion-related toxicity has been noted in up to 79% of infusions and has included fever, chills, headache, nausea, vomiting, flushing, and rarely, cardiac arrhythmias (15). In an attempt to avoid these infusion-related side effects, most authoritative sources have recommended prolonged infusion durations of 2 to 8 h (10-12, 14, 15). The *Physician's Desk Reference* (2) and the package insert recommend slow infusion over 6 h. However, others have anecdotally noted the safety and convenience of rapid infusions of 30 to 60 min (3, 4, 13; P. D. Hoepflich, *Infect. Dis. Newsl.* 3:62-63, 1984). One study even suggested that infusion-related toxicity could be decreased with 1-h infusions (3).

There has been a recent increase in the use of AMB as empirical therapy in the treatment of neutropenic patients and in the treatment of disseminated fungal infections in patients with the acquired immunodeficiency syndrome (AIDS). A 1-h infusion time of AMB would make outpatient therapy much more convenient with less interference in daily activities. It would also be beneficial for immunocompromised patients, who often require many other intravenous medications through a limited number of infusion sites.

We compared the infusion-related toxicities of 1- versus 4-h infusions of AMB in a randomized double-blind trial.

MATERIALS AND METHODS

All patients over the age of 18 who were started on AMB were evaluated for entry into the study. All study patients voluntarily signed an informed consent, as required by

SECNAVINST 3900.39B. Neither the investigators nor the patients knew which infusion (group A or B) was being administered, and the code was not broken until after data entry was completed. The first study infusion occurred at the point at which the patient's planned maintenance dose began, with the exception of one patient, who was enrolled in the study after having received multiple maintenance infusions. Test doses and early incremental doses were not included in the study. Each infusion for each patient was randomly assigned to either group A (1-h infusion) or group B (4-h infusion). For group A, all of the AMB (Fungizone; E. R. Squibb & Sons, Princeton, N.J.) for that dose was placed in the first bag and infused over 1 h. Sodium heparin (1,000 U) and hydrocortisone sodium succinate (25 mg) were also added in the first bag. In addition, a second bag that appeared to be identical to the first bag but contained only 5% glucose and water with multivitamins (MVI-12; Armour Pharmaceutical Co., Blue Bell, Pa.), to impart a yellow color to the solution, was infused over a 3-h period. The total infusion time for the two bags was 4 h. For group B, 25% of the AMB dose was placed in the first bag, which was infused over 1 h, and 75% of the dose was placed in the second bag, which was infused over 3 h. Thus, the total duration of the AMB infusion for group B was 4 h. Each bag containing AMB also contained hydrocortisone sodium succinate and sodium heparin at 25 mg and 1,000 U, respectively, with 25% of the dose placed in the first bag and 75% placed in the second bag. For each infusion, AMB was diluted in at least 10 ml of 5% glucose in water for each 1 mg of AMB.

All patients were premedicated with diphenhydramine, 50 mg orally, and acetaminophen, 650 mg orally, 30 min prior to the infusion. If the patient developed chills or rigors of greater than 5-min duration, meperidine hydrochloride, 0.6 mg/kg, was administered intravenously while the AMB

* Corresponding author.

infusion was continued. The infusion was discontinued if rigors continued for more than 10 min after the meperidine hydrochloride was infused or if hypotension, confusion, or a temperature in excess of 40.6°C developed. Temperature, pulse, and blood pressure rates were recorded prior to infusion, every 15 min during the first hour of the infusion, hourly for the remaining 3 h of the infusion, and at 1 h postinfusion. Each patient was also questioned at the same intervals about infusion-related symptoms of nausea, warmth, chills, rigors, weakness, and dyspnea.

Patients were excluded from the study if their creatinine clearance, as calculated by the Cockcroft-Gault method (5a), was less than 25 ml/min, if they had an altered mental status, or if they were hypotensive. Participation in the study was terminated when the patient finished the course of AMB or if the creatinine clearance decreased to below 25 ml/min.

An increase in pulse was defined as an increase of greater than 20 beats per min over the base line within 1 h of the end of the AMB infusion. A decrease in blood pressure was defined as a decrease in systolic pressure of more than 20 mm Hg or a decrease in diastolic pressure of more than 10 mm Hg from the base line. An increase in temperature was defined as an increase from the base line of 2°C if the patient was already febrile or an increase of 1°C from less than 38°C to more than 38°C within 1 h of the end of the infusion.

Statistical methods. A number of statistical procedures were used to determine whether there were any differences in infusion-related toxicity between the 1- versus 4-h infusion times. We were unable to do a paired comparison test because the randomization into either group A or B resulted in unequal pairing. However, the 128 infusions could be treated as independent samples since chi-square and correlation analyses showed no association between cumulative dosage and the values of any of the measured parameters. Discriminant analysis was used to determine whether any of the variables being measured could discriminate between the two treatment groups. In addition, analysis of variance, Student's *t* test, and chi-square tests were used to compare differences between the two treatment groups.

RESULTS

From January through September 1987, 12 patients were enrolled in the study. These patients received a total of 128 maintenance infusions of AMB; 62 were randomized to 1-h infusions (group A) and 66 were randomized to 4-h infusions (group B).

A total of 23 patients were evaluated for the study, but 11 were excluded. Six patients were excluded because their altered mental status precluded giving of informed consent, four refused to enter the study because of personal concerns, and one was not entered into the study because of concerns over tenuous fluid balance.

TABLE 1. Diagnoses of patients receiving AMB

Diagnosis	No. of patients
Hematologic malignancy with neutropenia and persistent fever	5
AIDS	2
Systemic fungal infection	
Cryptococcosis	1
Candidiasis	1
<i>Torulopsis</i> infection	1
Coccidioidomycosis	2

TABLE 2. Vital signs recorded during 128 infusions^a

Group (n)	Temp (°C)	Pulse (beats/min)	Blood pressure (mm Hg)	
			Systolic	Diastolic
A (62)	98.05	86	112	66
B (66)	98.40	91	110	64
<i>P</i> value	0.09	0.17	0.47	0.22

^a Values are group means.

The patients' mean age was 45.3 years, with a range of 25 to 80 years. There were 10 males and 2 females in the study. The calculated mean creatinine clearance was 84.5 ml/min, with a range of 35 to 140 ml/min. The indications for AMB are listed in Table 1. Four of the patients were ambulatory with minimal or no symptoms from their underlying disease. Six of the patients were moderately ill from their underlying disease but in a stable condition. Two of the patients were severely ill and were on ventilators in the intensive care unit. The daily dose of AMB ranged from 16 to 50 mg, with a mean of 28.6 mg. The dose of AMB ranged from 0.29 to 0.50 mg/kg, with a mean total dose of AMB of 149 mg for group A and 160 mg for group B. The total AMB doses were 1,790 and 1,922 mg, respectively, for groups A and B. The patients received from 1 to 32 AMB infusions, with a mean of 10.5 infusions.

Prophylactic meperidine was administered because of the persistent severity of the rigors for 17 infusions administered to one patient (7 were 1-h infusions and 10 were 4-h infusions). All statistical comparisons were made with and without these 17 infusions. There were no statistically significant differences between any of the variables when these 17 infusions were excluded. Therefore, all results and statistical analyses are presented with these 17 infusions included.

There was no significant difference between patients in groups A and B in the mean temperature, pulse, or systolic or diastolic blood pressure measured during the infusions (Table 2). The power to detect a mean difference in temperature of 2°C, a pulse difference of 20 beats per min, a decrease in systolic blood pressure of 20 mm Hg, or a decrease in diastolic blood pressure of 10 mm Hg between patients in groups A and B was 0.95 at a significance level of 0.05.

Rigors or chills were noted in 15 of 62 (24.1%) infusions in group A patients and 12 of 66 (18.1%) infusions in group B patients (*P* = 0.40) (Table 3). There was no difference in the severity of the rigors between the two groups. Meperidine was required because of severe persistent rigors in 6 of 62 (9.6%) group A infusions and 6 of 66 (8.95%) group B infusions (*P* = 0.91). Only one infusion (a 4-h infusion) was stopped because of the severity of the rigors and the lack of response to meperidine.

TABLE 3. Number of doses with infusion-related side effects

Group (n)	No. of doses				
	Increase in pulse rate	Decrease in blood pressure	Temp elevation	Rigors or chills	Meperidine required
A (62)	9	1	5	15	6
B (66)	12	10	7	12	6
<i>P</i> value	0.57	0.006	0.63	0.40	0.91

FIG. 1. Mean systolic and diastolic blood pressure, temperature, and pulse for each patient for all recordings during the infusions. One patient was excluded because there was only one infusion. Group A, 1-h infusion; group B, 4-h infusion.

An increase in temperature was noted in five (8%) of the group A infusions and seven (10.6%) of the group B infusions ($P = 0.63$). An increase in pulse of greater than 20 beats per min from the base line within 1 h of the end of the infusion was noted in 9 (14.5%) of group A and 12 (18%) of group B infusions ($P = 0.57$).

A decrease in systolic blood pressure of more than 20 mm Hg or a decrease in diastolic pressure of greater than 10 mm Hg from the base line was noted in 1 patient in group A and 10 patients in group B ($P = 0.006$). No patient became symptomatic from the drop in blood pressure, and the lowest recorded systolic pressure was 96 mm Hg. No infusions were slowed or discontinued because of a decrease in blood pressure. In 6 of 10 infusions in group B in which patients had a decrease in blood pressure, there was a difference of less than 5 mm Hg between the lowest recorded blood pressure and the postinfusion recording at 5 h. A drop in blood pressure in one infusion was temporally related to intravenous morphine sulfate that was administered to the patient for agitation.

When individual patient means were considered for systolic and diastolic blood pressure, pulse, and temperature, there was considerable variability among patients but no significant difference related to the duration of the infusion (Fig. 1).

When analyzed for time for the beginning of the infusion and protocol, analysis of variance revealed no significant difference in the mean body temperature, pulse, or systolic

or diastolic blood pressure between groups A and B (Fig. 2). However, the mean time to onset of rigors, increase in pulse, and increase in temperature was significantly shorter in patients given the 1-h infusion than in patients given the 4-h infusion (Table 4).

DISCUSSION

Despite its formidable toxicity, AMB remains the drug of choice for most of the systemic mycoses. At Duke University Hospital (Durham, N.C.), the use of AMB increased almost 10-fold from 1978 to 1984 (9). This increased usage was noted primarily in the empirical therapy of persistently febrile neutropenic patients and on the surgical service for patients with suspected disseminated candidiasis. There has also been an increasing need for prolonged outpatient therapy in patients with AIDS who have disseminated fungal infections.

Because of the commonly encountered infusion-related toxicity, AMB is usually infused over 4 to 6 h. These prolonged infusion times are inconvenient for both outpatients and immunocompromised patients who receive many other parenteral medications. There has been concern over shortening the infusion time because of fear that there may be an increase in infusion-related toxicity. However, a study in rabbits noted a decrease in pyrogenicity with a bolus infusion compared with a slow infusion (1), and there have been anecdotal reports of a decrease in infusion-related

FIG. 2. Mean systolic and diastolic blood pressure, temperature, and pulse plotted against time for groups A (1-h infusion) and B (4-h infusion).

toxicity with shorter infusion times (3, 15). One study of 16 infusions in three patients noted no difference in toxicity between 45-min and 5-h AMB infusions (8). Cleary et al. (5) noted no significant difference in the frequency of fever and chills between 45-min and 2-h infusions given to 17 bone marrow transplant recipients.

In this randomized, double-blind study of infusion-related toxicity, we found no difference between the mean temperature, pulse, or systolic or diastolic blood pressure during 1-h compared with during 4-h AMB infusions (Table 2). At a significance level of 0.05, the study had a power of 0.95 to detect what we considered to be clinically important differences in mean pulse (increase of ≥ 20 beats per min), temperature (rise of $>2^{\circ}\text{C}$), systolic blood pressure (decrease of >20 mm Hg), or diastolic blood pressure (decrease of >10 mm Hg), if they existed.

We could detect no significant difference in the number of infusions with rigors, the number requiring meperidine, or the number terminated from the study because of toxicity (Table 3).

There was a significant difference in the number of patients who were noted to have a drop in blood pressure: one

patient who received a 1-h infusion compared with 10 patients who received a 4-h infusion ($P = 0.006$). In reviewing the infusions during which there was a drop in blood pressure, it was noted that there was often an elevation of the base-line blood pressure, which may have been due to an anticipatory anxiety. Thus, for 6 of the 10 infusions in which there was a drop in blood pressure during a 4-h infusion, the lowest recorded blood pressure was within 5 mm Hg of the postinfusion recording at 5 h. No patients became symptomatic in association with a drop in blood pressure, and no systolic blood pressure fell below 105 mm Hg, with the exception of one patient who received morphine sulfate for anxiety. In addition, six patients with 1-h infusions were noted to have a decrease in diastolic blood pressure of greater than 10 mm Hg between 1 and 3 h after completion of the infusion.

When means were compared for each patient (Fig. 1), we noted that although there was variation between patients for each parameter measured, there was no significant difference related to the infusion rate. This lack of effect of the infusion rate on the vital signs was also noted when the means were plotted against time (Fig. 2). The onset of toxicity occurred significantly sooner in the 1-h infusion group than it did in the 4-h infusion group (Table 4).

Results of this study cannot answer the question of the overall safety of 1-h infusions of AMB, because the number of patients and infusions were too small to detect infrequent events such as the rarely reported asystole and ventricular fibrillation (6, 7), which have occurred in patients with hyperkalemia and renal failure. We specifically excluded all patients with a creatinine clearance below 25 ml/min. A large study with electrocardiographic monitoring is needed to

TABLE 4. Time to onset of infusion-related toxicity

Group	Time (min) to onset of:		Rigors
	Increase in temp	Increase in pulse rate	
A	120	76	66
B	180	145	107
P value	0.018	0.024	0.023

answer the question of the safety of 1-h infusions. We also limited our study to maintenance infusions and, thus, cannot address whether there was toxicity from the initial doses. However, one study found no significant difference in toxicity between 45-min and 2-h AMB infusions for the first two infusions after the test dose (5).

In summary, we conclude that there is no difference in the incidence or severity of the common infusion-related toxicities of AMB when a 1-h infusion rate is compared with a 4-h infusion rate. However, the onset of rigors, increase in pulse, and temperature elevations occur significantly earlier with 1-h infusions than with 4-h infusions.

ACKNOWLEDGMENT

This study was performed under protocol no. 87-16-2249-00 of the Navy Clinical Investigation Program.

LITERATURE CITED

1. Arroyo, J. C. 1984. Amphotericin B fever in rabbits. *Life Sci.* **34**:1249-1252.
2. Barnhart, E. R. 1988. Physician's desk reference. **42**:2052.
3. Barreuther, A. D., R. R. Dodge, and A. M. Blondeaux. 1977. Administration of amphotericin B. *Drug Intell. Clin. Pharm.* **11**:368-369.
4. Campbell, G. D. 1982. Using amphotericin B. *Intern. Med. Specialist* **3**:95-102.
5. Cleary, J. D., D. Weisdorf, and C. V. Fletcher. 1988. Effect of infusion rate on amphotericin B-associated febrile reactions. *Drug Intell. Clin. Pharm.* **22**:769-772.
- 5a. Cockcroft, D. W., and M. H. Gault. 1976. Prediction of creatinine clearance from serum creatinine. *Nephron* **16**:31-41.
6. Craven, P. C., and D. H. Gremillion. 1985. Risk factors of ventricular fibrillation during rapid amphotericin B infusion. *Antimicrob. Agents Chemother.* **27**:868-871.
7. DeMonaco, J. H., and B. McGovern. 1983. Transient asystole associated with amphotericin B infusion. *Drug Intell. Clin. Pharm.* **17**:547-548.
8. Fields, B. T., J. H. Bates, and R. S. Abernathy. 1971. Effect of rapid intravenous infusion on serum concentrations of amphotericin B. *Appl. Microbiol.* **22**:615-617.
9. Gross, M. H., W. W. Pickard, and J. R. Perfect. 1987. Retrospective review of amphotericin B use in a tertiary care medical center. *Am. J. Hosp. Pharm.* **44**:1353-1357.
10. Kucers, A., M. N. Bennett, and R. J. Kemp. 1987. The use of antibiotics, 4th ed., p. 1447. J. B. Lippincott Co., Philadelphia.
11. Mandell, G. L., R. G. Douglas, and J. E. Bennett. 1985. Principles and practice of infectious diseases, p. 365. John Wiley & Sons, Inc., New York.
12. Medical Letter. 1988. Drugs for treatment of deep fungal infections. *Med. Lett.* **30**:30-32.
13. Tarala, R. A., and J. D. Smith. 1980. Cryptococcosis treated by rapid infusion of amphotericin B. *Br. Med. J.* **2**:28-29.
14. Terrell, C. L., and P. E. Hermans. 1987. Antifungal agents used for deep-seated mycotic infections. *Mayo Clin. Proc.* **62**:1116-1128.
15. Utz, J. P., J. E. Bennett, M. W. Brandriss, W. T. Butler, and G. J. Hill. 1964. Amphotericin B toxicity. *Ann. Intern. Med.* **61**:334-54.