Risk of Ventricular Dysrhythmias during 1-Hour Infusions of Amphotericin B in Patients with Preserved Renal Function

WILLIAM A. BOWLER,†* PETER J. WEISS, HAL E. HILL, KAREN A. HOFFMEISTER, R. PETER FLECK, ALBERT R. BLACKY, AND EDWARD C. OLDFIELD III

Departments of Internal Medicine (Infectious Disease Division and Cardiology Division) and Clinical Investigation, Naval Hospital, San Diego, California 92134-5000

Received 6 February 1992/Accepted 7 September 1992

In order to assess the safety of 1-h infusions of amphotericin B (AMB), we prospectively monitored 213 1-h infusions of AMB (dose range, 0.27 to 0.89 mg/kg of body weight) in 27 patients with creatinine clearances of >25 ml/min. Holter monitor tracings during 1-h infusions were compared with those during a 4-h baseline period of monitoring. There were no ventricular dysrhythmias during 1-h infusions of AMB that were not present during baseline monitoring. Nausea and/or rigors were noted for 32 (15%) infusions in six (22%) patients. No patient exhibited a temperature rise of >1°C. We conclude that, in doses of up to 0.9 mg/kg, AMB does not appear to induce asymptomatic ventricular dysrhythmias when administered over 1 h to patients with creatinine clearances of >25 ml/min.

Despite its potential to cause significant systemic toxicity and the recent development of alternative antifungal agents, amphotericin B (AMB) remains the mainstay of therapy for serious fungal infections (6). In order to minimize infusion-related toxicity, many authorities recommend a prolonged infusion duration of 4 to 6 h (3, 9). In the current era of cost containment and emphasis on outpatient antibiotic administration, it is desirable to administer AMB over as short a period as possible.

In a previous study, we showed that the incidence or severity of infusion-related toxicity of AMB with a 1-h infusion rate was no different from that with a 4-h rate (8). However, because of sporadic reports of ventricular fibrillation (2, 4, 5, 7) occurring in patients given rapid infusions of AMB, concern regarding the safety of a 1-h AMB infusion remains.

We addressed this concern by performing continuous, two-lead electrocardiographic (Holter) monitoring during 1-h infusions of AMB.

(This work was presented in part at the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlanta, Ga., 23 October 1990.)

All patients 18 years of age or older with creatinine clearances greater than 25 ml/min, who were treated with AMB, were eligible for enrollment. Patients giving voluntary informed consent, as required by SECONVINST 3900.39B, were enrolled for up to 10 maintenance infusions of AMB (Fungizone; E. R. Squibb & Sons, Princeton, N.J.) at a maximum concentration of 0.1 mg/ml. Each infusion was administered over 1 h.

Hydrocortisone (20 mg) and sodium heparin (1,000 U) were added to each infusion. All patients were premedicated with acetaminophen and diphenhydramine. In order to establish a baseline for comparison purposes, each patient was evaluated by Holter monitor (Cardiadata, Northboro, Mass.) for a minimum of 4 h prior to the first study infusion.

Following baseline monitoring, patients were monitored during each 1-h maintenance infusion of AMB. Tracings obtained during the 1-h infusions were compared with those obtained during baseline monitoring to detect any proarrhythmic effect of AMB. Temperature, heart rate, and blood pressure were obtained prior to each infusion and every 15 min thereafter. Patients were observed by a physician for signs of systemic toxicity. Renal function and serum electrolytes, including potassium and magnesium, were closely monitored.

Twenty-seven patients received 213 (mean, 7.9) 1-h infusions of AMB. The mean age of patients was 44 years (range, 18 to 78 years), and 21 were male and 6 were female. Nine (33%) of the 27 patients met the Centers for Disease Control case definition for AIDS. The mean maintenance dose of AMB administered was 0.53 mg/kg of body weight per day (range, 0.27 to 0.89 mg/kg/day).

Symptomatic toxicity (nausea and/or rigors) occurred during 32 (63%) of 51 infusions administered to 6 (22%) of the 27 patients (nausea, 20 infusions [9.4%] in four patients [14.8%]; rigors, 14 infusions [6.9%] in three patients [11.5%]). There were no temperature elevations of greater than 1°C. A decrease in systolic blood pressure of >20 mm Hg or a decrease in diastolic blood pressure of >15 mm Hg occurred in 3 (10%) of 30 infusions in an additional three patients (decrease in systolic blood pressure, two infusions in two patients; decrease in diastolic blood pressure, one infusion in one patient).

The Holter monitor tape was unavailable for one patient whose vital signs remained unchanged throughout his 10 study infusions. One patient exhibited frequent multifocal premature ventricular contractions during 10 1-h AMB infusions that were also present during baseline monitoring. There were no induced ventricular dysrhythmias during an additional 193 1-h infusions of AMB administered to 25 patients.

The impressive systemic toxicity that can occur with AMB administration has been previously reviewed (3, 6, 9). The first reported case of ventricular fibrillation during AMB infusion occurred in 1957 in a patient given 25 mg of AMB.
over 40 min (7). Subsequent 50-mg doses of a “newer, water soluble salt of AMB” given over 6 to 8 h were well tolerated. Butler et al. showed that dogs given AMB at doses between 5 and 15 mg/kg over 15 s to 5 min developed lethal hyperkalemia and ventricular dysrythmias which led to death within 15 min (2). Subsequently, reports of ventricular fibrillation during AMB infusion have been noted only with patients with hyperkalemia and severe renal failure when they were given large doses of AMB over short intervals. Craven and Gremillion described a case in which ventricular fibrillation developed in an anuric, dialysis-dependent patient with a potassium concentration in serum of 8.4 meq/liter who received 50 mg of AMB (1.4 mg/kg) over 45 min (4). DeMonaco and McGovern reported a semicomatose elderly patient with candida septicemia, renal failure, and elevated potassium and digoxin levels who developed transient asystole and cardiovascular collapse on two occasions during AMB infusion (5). On the other hand, Barreuther et al. did not find any serious dysrythmia during continuous electrocardiographic monitoring during the initial 1-h outpatient infusion regimen (1). We were unable to document any cases since Littman’s initial report in 1957 of hemodynamically significant ventricular dysrythmias in patients with preserved renal function and normal potassium levels in serum.

We did not observe significant asymptomatic ventricular dysrythmias in patients with creatinine clearances of greater than 25 ml/min who received maintenance doses of AMB of up to 0.9 mg/kg over a 1-h period. The vast majority of patients who require long-term therapy with AMB will fall into this category. With these patients, consideration may be given to 1-h infusions of AMB, thereby reducing nursing time and cost and enhancing patient satisfaction.

The Chief, Navy Bureau of Medicine and Surgery, Washington, D.C., Clinical Investigation Program sponsored this study, no. 89-16-2505-00.

REFERENCES