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Effect of salt supplementation on amphotericin B nephrotoxicity

ALEJANDRO LLANOS, JAVIER CIEZA, JOSE BERNARDO, JUAN ECHEVARRIA, ITALO BIAGGIONI, RAMZI SABRA[1], and ROBERT A. BRANCH[1]

Instituto de Medicine Tropical "Alexander Von Humboldt", Universidad Peruana Cayetano Heredia, Lima, Peru, and Division of Clinical Pharmacology, Vanderbilt University, Nashville, Tennessee, USA

Effect of salt supplementation on amphotericin B nephrotoxicity. It has been suggested that salt loading protects against amphotericin B-induced nephrotoxicity. The influence of saline loading on the nephrotoxic response to amphotericin B (50 mg/dose given i.v. over 4 hr 3 ×/week for 10 weeks) was assessed in two groups of ten patients each who were diagnosed with mucocutaneous leishmaniasis. Patients were randomized to receive either 1 liter of 0.9% saline or 1 liter of 5% dextrose in water, administered i.v. over one hour in a double-blinded manner, directly prior to amphotericin B administration. Renal function was monitored on a weekly basis two days after the last dose of amphotericin B. Baseline characteristics were similar in both groups except for a slightly higher serum creatinine concentration (Cr) in the saline group (0.8 ± 0.05 vs. 0.6 ± 0.04 mg/dl). Baseline sodium (Na) excretion was relatively high (262 ± 23 mmol/day in the dextrose group and 224 ± 17 mmol/day in the saline group). None of the patients sustained an increase in Cr to values greater than 1.7 mg/dl. Although mean Cr remained within normal, there was a significant difference between the two groups over the ten week period, with the dextrose group sustaining a significant increase in Cr and the saline group remaining unchanged. Serum potassium (K) levels fell in both groups necessitating oral K supplementation. The saline group required significantly greater amounts of K supplementation to maintain a normal serum K. Amphotericin B caused a rapid reduction in the acidification ability of the kidney in response to an ammonium chloride load. Under these conditions, the saline group had a poorer ability to acidify the urine. Urine volumes were not different between the two groups, and the specific gravity of the urine sustained a significant and similar decrease in the two groups. Neither plasma trough amphotericin B levels nor tissue concentrations at the site of the lesion were different between the two groups, suggesting that the effect of salt is probably not on the basis of pharmacokinetic changes. This study supports the hypothesis that salt loading confers protection against reductions in renal function by amphotericin B, but does so at the expense of enhancing K loss. The lower overall incidence of nephrotoxicity in comparison to prior published experience could be due to racial variation in responsiveness, the high baseline salt intake, or lack of coadministration of other nephrotoxic drugs.

Nephrotoxicity has been recognized as a serious and common complication of amphotericin B use since the introduction of this drug in the 1950's. Early reports indicated that as many as 80 to 90% of patients who received the drug developed some degree of renal dysfunction [1–3]. The clinical presentation of nephrotoxicity includes azotemia, renal tubular acidosis, impaired concentrating ability, and renal sodium, potassium and magnesium wasting, with consequent dehydration, hypokalemia and hypomagnesemia. The decrease in GFR may be so severe as to necessitate discontinuation of therapy, leading to progression of the underlying disease and extension of the hospital stay. Therefore, any maneuver that decreases the frequency and/or severity of amphotericin B-associated nephrotoxicity will aid the therapeutic use of this drug. This is especially true considering the increasing frequency of fungal infections, which is now reported at between 5 and 12% of hospitalized patients [4].

Several manipulations have been proposed to try and minimize amphotericin B-induced nephrotoxicity. Mannitol coadministration was once suggested as protective based on anecdotal, observational reports [5, 6]. A small prospective and randomized trial, however, did not support a protective effect [7]. More recent reports suggest that liposomal preparations of amphotericin B may have a wider margin of safety [8–10], but the drug has not been approved for use yet, and more definitive statements on its superiority to conventional formulations await larger controlled trials.

The maneuver that has received attention involves administration of a salt load in association with the amphotericin B dose. Unfortunately, there has not been a prospective, randomized, placebo-controlled trial that would provide a convincing argument for the routine use of such a protective measure. All previous studies have been either case reports [11], retrospective studies [12, 13] or prospective non-controlled studies [12, 14]. Major difficulties are faced in attempting to interpret the results of these studies, namely, that they were uncontrolled, and that certain bias may have been introduced on the basis of selection of patients, their underlying diseases, and the administration of other drugs. The randomized, placebo controlled study would overcome these difficulties and provide a more solid basis to make an informed clinical decision.

Studies of the influence of salt loading on amphotericin B nephrotoxicity in the population of patients receiving the drug in the U.S.A. have presented some difficulties in the evaluation of such an intervention, since they involved patients who were

[1] Present address is: Center for Clinical Pharmacology, University of Pittsburgh School of Medicine, 623 Scaife Hall, Pittsburgh, Pa 15261, USA.

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severely ill with systemic diseases that diminish baseline renal function, were immunocompromized, or were receiving concomitant potentially nephrotoxic therapy. The ability of amphotericin B to eradicate the parasite in mucocutaneous leishmaniasis offers a unique opportunity to assess the efficacy of salt supplementation in a population of patients with this disease. These patients were relatively healthy, nonimmunocompromized, with normal baseline renal function, suffering from a localized disease not involving the kidney which responds to amphotericin B as a sole agent. In this paper, we report the results of such a trial. The present report focuses on changes in renal function, although measures of hematologic and hepatic function were also assessed.

Methods

The study was conducted at the Instituto de Medicine Tropical "Alexander Von Humboldt", of the Universidad Peruana Cayetano Heredia, in Lima, Peru, where investigators have been using amphotericin B to treat patients with mucocutaneous leishmaniasis, an endemic disease in the jungle areas of inner Peru. Part of the assays and the data analyses were done at the Division of Clinical Pharmacology, Vanderbilt University.

Patients with mucocutaneous leishmaniasis, 14 to 70 years old, were considered for entry. This form of the disease, produced by *Leishmania braziliens*, is confined to the nasal mucosa, and is associated with destruction of the nasal septum and facial disfigurement, but has no systemic involvement. The subjects were otherwise healthy. Exclusion criteria included: underlying diseases that prevented the administration of an intravenous salt load; patients with serum Cr > 2 mg/dl; and patients receiving other medications. Twenty male patients were entered into the study, and were randomized to either a saline group or a dextrose group. All patients received amphotericin B administered three times per week for 10 weeks, starting with 15, 35, and 50 mg/dose the first week, and then maintenance on 50 mg/dose for the remainder of therapy. The drug was diluted in 0.5 liter 5% dextrose in water (D/W) and administered intravenously over four hours, on Mondays, Wednesdays, and Fridays. It was preceded by an infusion of 1.0 liter of either 0.9% sodium chloride (NaCl) or 5% D/W. Both saline and D/W were precoded so that both patients and investigators were blinded to the treatment received.

Initial pre-treatment evaluation included a history, physical examination, and a disease activity score based on the extent of the lesion. Blood samples were obtained for serum creatinine (Cr), blood urea nitrogen (BUN), electrolytes, calcium (Ca), magnesium (Mg), phosphorus (P), proteins, liver function tests, prothrombin time, complete blood count, reticulocyte count and platelets. In addition, a 24-hour urine collection was obtained for volume, Cr, electrolytes, Ca, Mg, specific gravity, and urinalysis. From these values creatinine clearance and urinary excretion rates were calculated. Urinary acidification ability was assessed using the ammonium chloride (NH_4Cl) loading test. The patients received 0.1 g/kg NH_4Cl orally and urine was collected hourly for three hours thereafter. If the pH of the urine decreased below 5.5, the test was considered normal. A baseline electrocardiogram was also obtained in all patients.

Therapy was monitored on a weekly basis with assessment of disease activity score, and repeat of the above-mentioned measurements except for the hematologic, hepatic and cardiac evaluations, which were made on a bi-weekly basis. A plasma sample was also obtained every week for measurement of amphotericin B levels by HPLC. The collection of plasma samples for monitoring of therapy was performed on Monday mornings, prior to the subsequent dose of amphotericin B. Similarly the 24-hour urine collection were started on Sunday morning, approximately 40 hours after the last dose of the drug, and ended on Monday morning of each week, before the administration of the Monday dose. Finally, tissue samples from the diseased area were obtained, when possible, on weeks 1, 5 and 11 to test for the presence of the parasite and for measurement of amphotericin B concentrations. Nephrotoxicity of sufficient severity to cause withdrawal from the study was defined as an increase in serum Cr to greater than 2 mg/dl. In such cases, the decision had been made to withold the subsequent dose of amphotericin B until the serum Cr returned toward baseline. In addition, potassium (K) supplementation was to be instituted when serum K levels fell to below 3 mmol/liter, and the magnitude of the supplement would be determined by the amount required to maintain K levels above 3 mmol/liter.

Patients remained hospitalized for the duration of the study (12 weeks) and were fed a constant diet ad libitum. Water was also unrestrained.

Values are reported as means ± SEM. Statistical analysis was conducted using the Number Cruncher Statistical System (NCSS, Kaysville, Utah, USA). Comparisons within one group were done using one-way analysis of variance (ANOVA), followed, when appropriate, by Duncan's range test to compare individual time points. Comparison between the two groups was done using ANOVA with repeated measures, one factor being the weekly cumulative doses of amphotericin B (11 levels), and the other factor being the treatment groups (2 levels, NaCl or D/W). Finally, life survival analysis was conducted using the Cox/Mantel test. All null hypotheses were two tailed, and the criterion for significance was $P < 0.05$.

Results

All patients responded to therapy with amphotericin B with remission of the disease as assessed by histologic examination, with no difference between the two groups in the therapeutic response. The patients reported symptomatic improvement as early as the first week of therapy. All but two patients completed the whole course of therapy. One patient withdrew early in the course of therapy for personal reasons and another replaced him in the same arm of the study; the former's data are not included in the analysis. Another patient was withdrawn after a cumulative dose of 1000 mg (week 7), when he developed cardiac arrhythmias.

The randomization procedure was successful in creating two similar groups with respect to most parameters studied (Table 1). The only significant observation was a small difference in serum Cr levels. The saline group had a higher baseline mean serum Cr concentration than did the dextrose group (0.8 ± 0.05 vs. 0.6 ± 0.04 mg/dl, $P < 0.01$), although all subjects in both groups were within normal limits (Fig. 1). The reason for this difference is not clear. The urinary Na excretion rates were relatively high compared to the usual population of patients

Table 1. Baseline characteristics in the control and saline groups ($N = 10$ in each)

	Dextrose	Saline	P value
Age *years*	32.5 ± 3.3	38.5 ± 2.8	NS
Weight *kg*	53.4 ± 2.3	52.3 ± 1.2	NS
Urine flow *ml/day*	1687 ± 217	1545 ± 193	NS
Serum Cr *mg/dl*	0.60 ± 0.04	0.80 ± 0.05	<0.01
C_{Cr} *ml/min/1.73 m²*	111.6 ± 6.3	99.1 ± 4.9	NS
Urinary Na excretion *mmol/day*	262 ± 23	224 ± 17	NS
Serum K *mmol/liter*	4.4 ± 0.2	4.1 ± 0.2	NS
Urinary K excretion *mmol/day*	51.0 ± 7.7	59.4 ± 11.0	NS
Serum Ca *mg/dl*	8.3 ± 0.4	8.6 ± 0.2	NS
Ca excretion *mg/day*	189 ± 35	181 ± 31	NS
Serum Mg *mmol/liter*	1.55 ± 0.06	1.54 ± 0.04	NS
Urinary Mg excretion *mmol/day*	2.48 ± 1.41	4.78 ± 1.08	NS
Serum P *mg/dl*	3.8 ± 0.3	4.1 ± 0.3	NS
Specific gravity	1011 ± 1	1014 ± 1	NS

receiving this drug in the USA [11], but no difference existed between the two groups.

Analysis of serum Cr over time revealed that the responses were significantly different between the two groups. The mean serum Cr increased over time in the dextrose group, but remained unchanged in the saline group (Fig. 2). The greatest increase occurred during the first week and the last three weeks of treatment. The mean maximal increase in serum Cr during therapy was significantly greater in the dextrose group ($P = 0.01$, Fig. 1). Similarly, Cr clearance decreased in the dextrose group, but remained unchanged in the saline group, resulting in a significantly different response over time ($P < 0.05$ by ANOVA, Table 2). There was no change in weight in either group over time. None of the patients sustained a failure event as defined by an increase in serum Cr to >2 mg/dl. However, using more stringent criteria for defining a nephrotoxic event, that is, a ≥100% increase in serum Cr, life table analysis confirmed the presence of a significant difference between the two groups (Fig. 3), with four patients in the dextrose group, and none in the saline group, meeting this criterion. Since the increase in serum Cr was small, the drug was not withdrawn in any of the four patients.

Urinary Na, K, Ca and Mg excretion rates are presented in Table 2. Despite the fact that these collections were started two days after the last dose of drug and intervention, there was a greater urinary Na excretion in the saline group over time. Urinary K excretion was not different in the two groups and did not change with time, while Ca excretion decreased in both groups in a similar fashion. Urinary Mg excretion also decreased in both groups in a similar fashion, although this decrease was not significant in the dextrose group because of large variations in the baseline value.

Serum Na, Ca, P and Mg levels did not change over time in either group. Serum K, however, sustained a significant decrease within the first two weeks of treatment ($P < 0.0001$ for effect of dose, but no difference between groups, Fig. 4A). When K levels reached 3 mmol/liter, K supplementation therapy was instituted. This was successful in maintaining normal or near-normal levels. Analysis of the K supplement itself revealed marked differences between the two groups, with the saline group requiring significantly higher supplements than the dextrose group, being approximately 70 mmol/day higher at the end of the study ($P < 0.0001$, Fig. 4B).

Assessment of the specific gravity of the urine over time revealed a significant and similar decrease in the two groups ($P < 0.0001$). Both groups sustained a slight but non-significant increase in the basal urinary pH. Life table analysis of the response to an acid load showed a faster loss of acidification in the saline group, where all subjects failed after the first week of therapy. In the dextrose group, only 4 of 10 failed during the first week, and by the second week all had failed. One patient in the dextrose group regained acidification ability in the fifth week. Statistical comparison of these two responses revealed a significant difference with $P < 0.005$.

Plasma trough amphotericin B concentrations are depicted in Figure 5. No differences were observed between the two groups. Steady state was achieved in approximately eight weeks, indicating an approximate half-life of two weeks. Samples of tissues received for measurement of amphotericin B levels were not obtained from all patients due to practical considerations of obtaining biopsies from healed lesions, and repeat samples were not always from the same patients. However, each tissue sample measured did have a concurrent measure of plasma amphotericin B concentration. Analysis of tissue levels revealed wide variations in values, and no significant difference was observed between the two groups (Table 3). The plasma to tissue ratios revealed that levels in plasma were approximately 20-fold higher than in the nasal mucosa, and that the ratio at one week of treatment was similar to that at the end of the course of therapy (Table 3).

Discussion

For approximately 30 years, nephrotoxicity, especially azotemia, has been regarded as a major and sometimes invariable consequence of amphotericin B therapy. Early studies reported an incidence of 80 to 90% [1]. A more recent report suggested that almost all patients develop azotemia, with a reduction of GFR of 20 to 60% initially, later stabilizing at 40% of baseline values [15]. Several risk factors have been suggested, including age [16], total dose [1, 17], frequency of dosing [18, 19], underlying renal disease, co-administration of other potentially nephrotoxic agents [13], and dehydration or a salt conserving state [11, 12]. One of the major manipulations that has been suggested as protective against amphotericin B nephrotoxicity is salt supplementation [20]. However, most of the information about the efficacy and effectiveness of this measure has been derived from case reports, retrospective studies, or prospective observational studies. The present report is the first to test the hypothesis that salt supplementation protects against amphotericin B-induced nephrotoxicity in a prospective, randomized, and controlled manner.

A limiting factor in the interpretation of many previous reports involves the complexity of the populations that were studied. In general, patients receiving amphotericin B in the U.S.A. are usually suffering from severe systemic fungal infections. These are frequently a consequence of debilitating diseases (AIDS, cancer, diabetes) or therapeutic measures (anticancer chemo- or radio therapy, cyclosporine) that result in immunosuppression. Thus, many of these patients have other causes of, or predisposing factors for, renal failure that may act

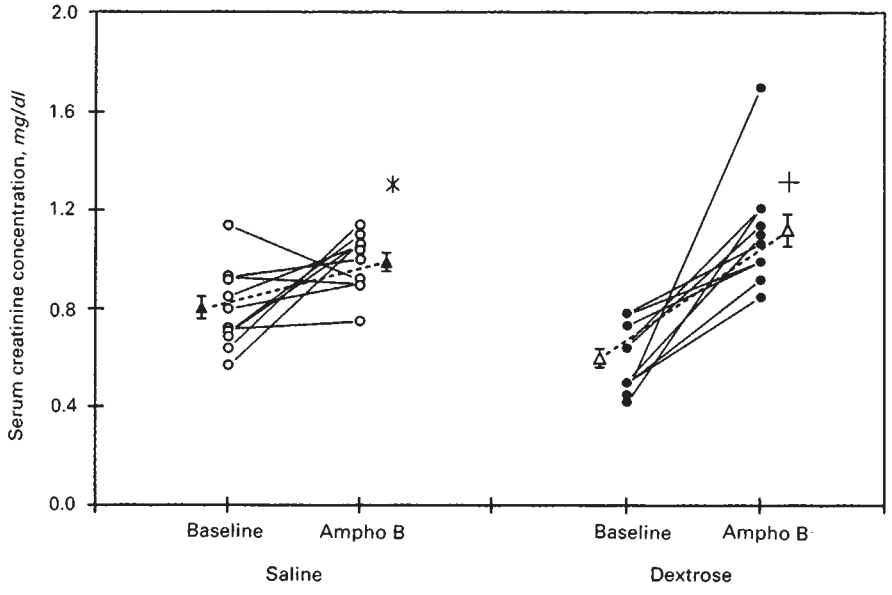

Fig. 1. *Baseline and maximum serum creatinine concentrations achieved in two groups of patients receiving amphotericin B (150 mg/wk) for 10 weeks.* $*P < 0.05$ compared to baseline; $+P < 0.0001$ compared to baseline. Comparison of the maximal change in serum Cr in the two groups gave a $P = 0.01$.

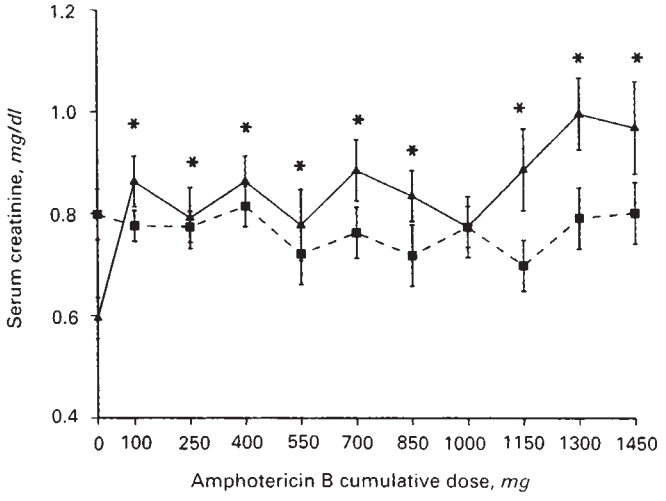

Fig. 2. *Serum creatinine levels in dextrose (▲—▲) and saline (■----■) treated groups receiving amphotericin B at 50 mg/dose 3 times weekly for 10 weeks (N = 10 in each).* Two-way ANOVA revealed $P < 0.01$ for interaction of intervention and dose on the response. $*P < 0.05$ compared to baseline.

as confounding variables when amphotericin B nephrotoxicity is assessed. This is particularly true of patients receiving concomittant antibacterial therapy with potentially nephrotoxic drugs such as aminoglycosides or vancomycin. The population of patients studied in this trial differ from the population receiving the drug in several respects. Firstly, they suffer from a localized, non-life threatening disease, which although severely disfiguring, has virtually no systemic effects. Thus, the patients are relatively healthy and have normal baseline renal function. Secondly, since the disease is responsive to amphotericin B as a sole agent, they do not require administration of other potentially nephrotoxic agents. Therefore, this population of patients offers a unique opportunity to examine the effects of this drug and the possible benefit from salt supplementation, free from the bias that would be introduced were a conventional population chosen. However, this population also presents some disadvantages in that it is composed of native Peruvians who are ethnically different from the populations in whom the drug has been most extensively studied (Caucasians). This limits our ability to draw comparisons with previous studies. In addition, as the results show, basal salt intake in the two groups was relatively high, as reflected by the high baseline urinary Na excretion rate. This may be expected to minimize the benefit that would be derived from salt supplementation.

The results of this study are interesting. Despite a cumulative dose of 1450 mg, none of the patients in either group sustained a nephrotoxic response as defined by an increase in serum Cr to >2 mg/dl. This is in contrast to reports of 60 to 70% in cases where no salt supplementation was administered [1, 12, 15, 21], and 0 to 12% where it was [12–14]. The explanation for the absence of a marked decrease in GFR may relate to several factors. As the baseline data show, the initial Na excretion, which should reflect Na intake, was high in this population, being 262 ± 23 mEq/day in the dextrose group and 224 ± 17 mEq/day in the saline group. This exceeds usual values for Na excretion reported for the U.S.A. population by approximately 100 mEq/day [11]. Thus, if salt supplementation is protective, as suggested by previous studies, this already elevated Na intake may have accounted for the low frequency of nephrotoxicity in the dextrose group. It should be noted that this native Peruvian population has relatively lower body weights than an age matched population in the U.S.A., and therefore their serum Cr concentrations are generally lower. Therefore, an increase in serum Cr to above 2 mg/dl may reflect a greater loss of renal function than a similar increase in the American population. When nephrotoxicity was defined as a 100% increase in serum Cr above baseline, a clear difference between the groups was observed, with four patients in the dextrose group and none in the saline group developing nephrotoxicity. This finding, in appropriately matched groups, does support the

Table 2. Influence of amphotericin B (150 mg/week) on creatinine clearance (C_{Cr}), serum levels of Ca, P and Mg, urinary excretion rates of Ma, K, Ca and Mg, specific gravity and flow rate of urine over 10 weeks in 2 groups of patients receiving 1 liter of either 0.9% NaCl or 5% D/W i.v. prior to the amphotericin B dose (N = 10 in each)

		Amphotericin B				*P* value	
	Baseline	Week 1	Week 4	Week 7	Week 10	One way ANOVA[a]	Two way ANOVA[b]
C_{Cr} *ml/min/1.73 m²*							
Dextrose	111 ± 6	88 ± 9[c]	87 ± 5[c]	94 ± 9[c]	76 ± 7[c]	<0.01	<0.05
Saline	99 ± 5	90 ± 7	80 ± 9	70 ± 6	91 ± 9	NS	
Serum Ca *mg/dl*							
Dextrose	8.3 ± 0.3	8.3 ± 0.3	8.2 ± 0.3	8.5 ± 0.2	8.4 ± 0.2	NS	NS
Saline	8.6 ± 0.2	8.4 ± 0.2	8.7 ± 0.3	8.4 ± 0.3	8.3 ± 0.2	NS	
Serum Mg *mEq/liter*							
Dextrose	1.5 ± 0.6	1.4 ± 0.1	1.3 ± 0.1	1.5 ± 0.1	1.1 ± 0.1	NS	NS
Saline	1.5 ± 0.4	1.5 ± 0.2	1.4 ± 0.2	1.4 ± 0.2	1.4 ± 0.1	NS	
Serum P *mg/dl*							
Dextrose	3.8 ± 0.3	3.8 ± 0.2	3.9 ± 0.2	3.8 ± 0.2	3.6 ± 0.2	NS	NS
Saline	4.1 ± 0.3	4.4 ± 0.2	3.8 ± 0.2	3.7 ± 0.3	3.8 ± 0.2	NS	
Urinary Na exc. *mmol/day*							
Dextrose	262 ± 23	241 ± 25	198 ± 24	208 ± 25	180 ± 35	NS	<0.05
Saline	224 ± 17	215 ± 26	222 ± 43	220 ± 33	270 ± 34	NS	
Urinary K exc. *mmol/day*							
Dextrose	55 ± 7	48 ± 3	48 ± 7	53 ± 6	49 ± 9	NS	NS
Saline	61 ± 10	43 ± 5	45 ± 6	49 ± 5	64 ± 7	NS	
Urinary Ca exc. *mg/day*							
Dextrose	189 ± 35	138 ± 19[c]	81 ± 12[c]	98 ± 9[c]	82 ± 9[c]	<0.0001	NS
Saline	168 ± 31	142 ± 15	101 ± 12[c]	99 ± 14[c]	95 ± 13[c]	0.03	
Urinary Mg exc. *mmol/day*							
Dextrose	2.5 ± 1.4	0.8 ± 0.5	1.3 ± 1.1	0.1 ± 0.1	0.2 ± 0.1	NS	NS
Saline	4.8 ± 1.1	1.4 ± 0.6	0.5 ± 0.2	0.3 ± 0.1	0.2 ± 0.1	<0.0001	
Urine flow rate *liter/day*							
Dextrose	1.7 ± 0.2	2.2 ± 0.2	2.5 ± 0.3	2.6 ± 0.3	2.8 ± 0.3	NS	NS
Saline	1.5 ± 0.2	2.3 ± 0.2	2.8 ± 0.3[c]	2.9 ± 0.3[c]	3.1 ± 0.3[c]	<0.0001	
Specific gravity							
Dextrose	1011 ± 1	1011 ± 1	1008 ± 1[c]	1007 ± 1[c]	1005 ± 1[c]	<0.0001	NS
Saline	1014 ± 2	1009 ± 1[c]	1006 ± 1[c]	1006 ± 1[c]	1005 ± 1[c]	<0.0001	

[c] $P < 0.05$ compared to baseline using Duncan's range test, performed following a significant difference using one way ANOVA[a]
[b] Interaction of time and intervention (saline or dextrose) on the response

hypothesis that salt supplementation protects against amphotericin B-induced reductions in the GFR.

Other factors which may have contributed to the absence of a marked decrease in the GFR could relate to ethnic differences between the native Peruvian and American populations, or to the fact that the drug was administered on an alternate day schedule. A previous study in dogs [19] and a case report in humans [18] have suggested that alternate day therapy is associated with a lower frequency and severity of azotemia, though this issue has not been addressed in a controlled randomized study. Finally, one should consider the possibility that the intrinsic toxicity of this agent to the kidney is actually low when given to healthy individuals as a sole agent. It may be that the very high incidence reported in the literature merely reflects the contribution of the several factors mentioned previously to the development of nephrotoxicity, most importantly, the presence of an underlying systemic disease and the co-administration of potentially nephrotoxic agents. In addition, early reports which indicated frequencies of 80 to 90% [1, 16, 17] were of patients treated with excessively high doses reaching up to 5 g, which are rarely used at the present time.

The observation that salt loading conferred protection on renal function is in agreement with previous studies. In 1983, a series of five patients were reported who developed azotemia when amphotericin B was administered [11]. Four of these had prior identifiable salt-conserving states. Upon receiving salt supplements, all five lowered their serum Cr and BUN levels, and amphotericin B was restarted with no further deterioration

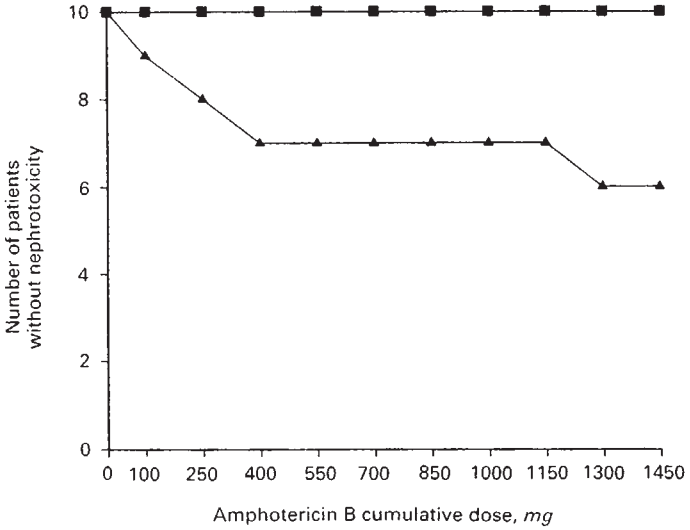

Fig. 3. *Life table analysis for patients developing nephrotoxicity defined as a 100% increase in baseline serum Cr level.* Symbols are: (■) saline; (▲) dextrose. $P < 0.03$ by Cox/Mantel test.

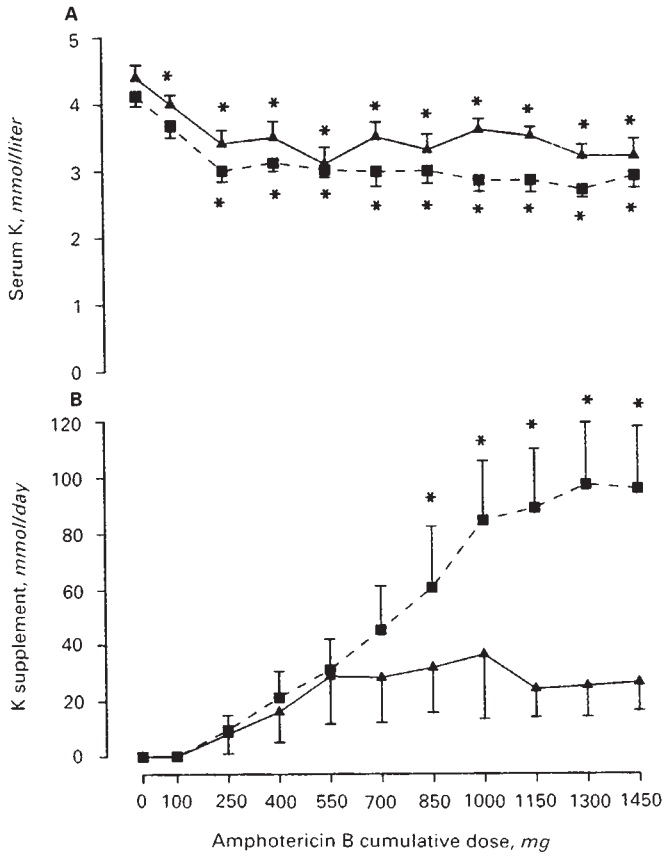

Fig. 4. *Serum K concentrations* (**A**) *and K supplementation given to maintain serum K at or above 3 mmol/liter* (**B**), *in the dextrose* (▲——▲) and saline (■----■) groups (N = 10 in each). (**A**). $P < 0.0001$ for dose only. (**B**). $P < 0.0001$ for effect of dose and intervention on response. *$P < 0.05$ compared to baseline.

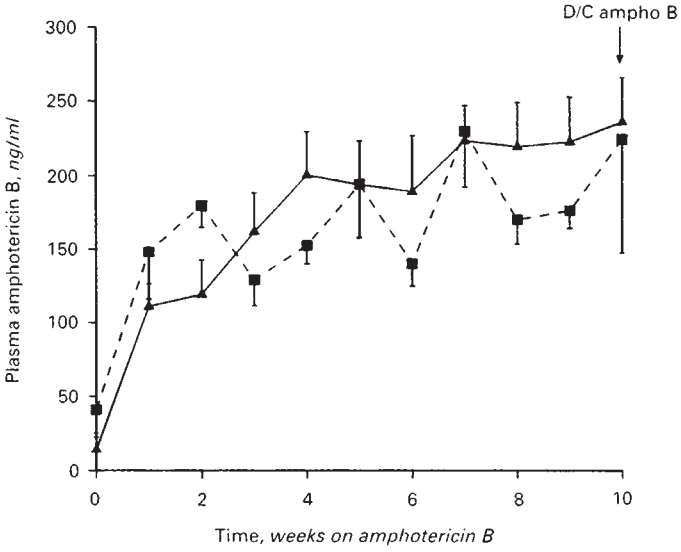

Fig. 5. *Plasma trough amphotericin B concentrations in the dextrose* (▲——▲) *and saline* (■----■) *groups* (N = *10 in each*). No significant difference between groups was observed.

in renal function. Another study reported that only 12% of patients receiving ticarcillin, with its obligatory Na load of 156 mEq/day, in conjunction with amphotericin B developed nephrotoxicity, compared to 67% in those not receiving ticarcillin [12]. In a companion study to the above, 2 of 20 patients receiving 1 liter 0.9% NaCl routinely with every dose of amphotericin B developed nephrotoxicity. Finally, a recent report indicated that of 37 patients receiving amphotericin B with 50 to 100 ml of 10% NaCl i.v., none developed nephrotoxicity defined as an increase in serum Cr to >2 mg/dl [14].

The beneficial effect of salt loading, however, occurs at the expense of hypokalemia and, perhaps, worsening tubular function. The saline group required significantly higher amounts of K supplementation to maintain a normal serum K level. This could reflect greater damage to the tubular cells, or simply be the result of increased Na delivery to the distal tubule, which itself stimulates K secretion. The absence of differences in the urinary K excretion rate probably relates to the fact that the urine collections were begun at least 40 hours after the last dose of amphotericin B and the intervention. Thus, there must have been an acute increase in urinary K excretion immediately following each dose of amphotericin B.

Both groups sustained a similar decrease in the specific gravity of the urine, suggesting a decreased ability to concentrate the urine. However, no specific challenge test was done to assess this. The NH_4Cl loading test revealed a faster loss of acidification in the saline group. While this may reflect greater tubular toxicity in that group, it could also be a consequence of increased potassium excretion. The greater the hypokalemia, the greater the renal ammonia production, which with a pK of 9, interferes with maximum urinary acidification upon NH_4Cl administration. In contrast, Ca and Mg excretion rates decreased similarly in both groups, with no change in serum Ca or Mg levels. Once again, caution is required in interpretation of these results since the urine collections were obtained two days after the last dose of drug and intervention.

The plasma concentrations of amphotericin B were similar in the two groups, as were the tissue concentrations. These results suggest that the differences observed in renal function between the two groups are probably not on the basis of a pharmacokinetic interaction between the drug and the sodium supplement. However, an interaction at the level of the kidney cannot be ruled out. Animal studies have shown that while plasma concentrations of amphotericin B are similar in salt-loaded and salt-depleted rats treated for three weeks, the kidney to plasma ratios are severalfold higher in salt-depleted rats which sustained greater deterioration in GFR [22]. Since the kidney is not a major route of excretion for this drug [23, 24], this difference is presumably not a result of the greater decrease in GFR in that group of rats. Rather, it suggests an interaction at the level of an uptake process in the kidney, whereby the accumulation of the drug in the renal tissue is not simply a passive process reflecting plasma concentrations.

In summary, this study shows that the frequency and severity of nephrotoxicity (as assessed by decreased GFR) in this generally healthy population of patients receiving amphotericin B is exceedingly low. Nevertheless, the slight deterioration in GFR that did occur was more pronounced in the non-salt supplemented group, supporting the protective effect of salt on

Table 3. Concentrations of amphotericin B in biopsied tissue from the site of the lesion, and its plasma-to-tissue ratios in the two groups of patients

	Dextrose		Saline		
	Week 2 ($N = 4$)	Week 10 ($N = 4$)	Week 1 ($N = 5$)	Week 2 ($N = 3$)	Week 10 ($N = 6$)
Tissue concentration *ng/g*	7.3 ± 1.7	19.4 ± 6.6	8.8 ± 2.2	5.1 ± 2.3	20.6 ± 3.4[a]
Plasma: tissue ratio	23.5 ± 3.4	16.6 ± 4.1	21.9 ± 5.8	26.5 ± 4.9	13.2 ± 5.2

[a] $P < 0.05$ compared to weeks 1 and 2

glomerular function. Although measures of tubular function were significantly better in the dextrose group, these differences, except for hypokalemia, were mainly during the first two to three weeks of treatment, and probably are not of practical clinical significance. Therefore, based on the results of this and previous studies, we recommend routine salt supplementation with administration of amphotericin B, with special attention being paid to serum potassium concentrations.

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Reprint requests to Dr. Robert A. Branch, Center for Clinical Pharmacology, University of Pittsburgh School of Medicine, 623 Scaife Hall, Pittsburgh, Pennsylvania 15261, USA.

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