The Toxic Effects of Amphotericin B in Man

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• **Studies of 47 patients with intravenous amphotericin B revealed some impairment of renal function in all cases. Azotemia developed in 46 cases. Microscopic examination in eight cases showed damage to the distal renal tubule. Profound hypokalemia was recognized in two cases; and symptoms suggesting hypokalemia, which were generally ameliorated by potassium administration, were noted in most cases. It is postulated that the initial potassium loss is due to a "tubular leak" and that subsequent potassium depletion leads to further tubular damage.**

Mild to severe anemia developed in all cases during therapy. Serial red cell indices, bone marrow examinations and red cell survival studies indicated that hemolysis, rather than bone marrow depression, was responsible.

The decision to treat, to modify therapy or to terminate treatment must be made on the basis of severity of disease, probability of progression, and renal status.

UNTIL RECENTLY it has been customary to express little concern about the nephrotoxic effects of intravenous amphotericin B.[3,11] At present there is greater concern for the kidney when this drug is used in the treatment of deep mycotic infections; however, there is still lack of understanding as to the mechanisms by which renal damage occurs and the best techniques to minimize the damage.[1,2,10]

A preliminary report of our early observations was made in 1961.[7] Further observations and analysis of data have confirmed and clarified many of our findings. Hence we believe a more detailed report will be of value at this time.

These observations were made in 47 cases of disseminated coccidioidomycosis in which the patients were treated wtih intravenous amphotericin B for a minimum of four weeks and treatment was extended to three months or longer in 31 cases. All patients were treated six days each week. Forty-one adults received a dose of 1 mg per kilogram of body weight daily. Six children received a dose of 1.5 mg per kilogram of body weight daily for three months. The drug was given by infusion over a period of not less than three hours in a concentration of 10 mg per 100 ml of 5 per cent dextrose in water with 10 to 20 mg of heparin added.

Forty-one of the patients had received no previous treatment. Six of the adults had received repeated courses of therapy. Total dose of amphotericin B was not calculated in the six children because of wide variation in body weight. Total dose, including previous treatment, in the adults was as follows:

4 to 14 grams of amphotericin B—6 cases.

2.5 to 3.9 grams of amphotericin B—29 cases.

Less than 2.5 grams of amphotericin B—6 cases.

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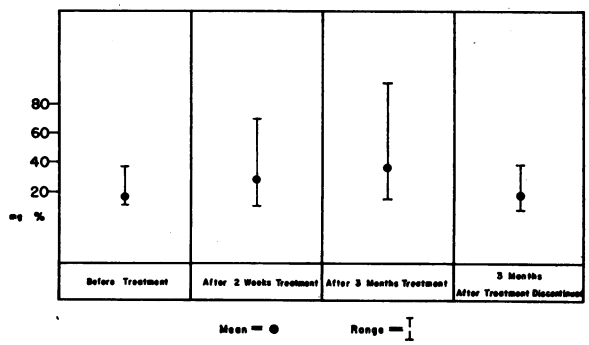

Chart 1.—Blood urea nitrogen in 47 patients, before, during and after treatment with amphotericin B.

OBSERVATIONS

Azotemia developed in 46 of the 47 cases (Chart 1). The 15-minute phenolsulfonphthalein excretion test showed pronounced impairment after two to three months of treatment in all cases (Chart 2). With one exception the Fishberg concentration test showed significant alteration after two weeks of therapy and in all cases after two to three months

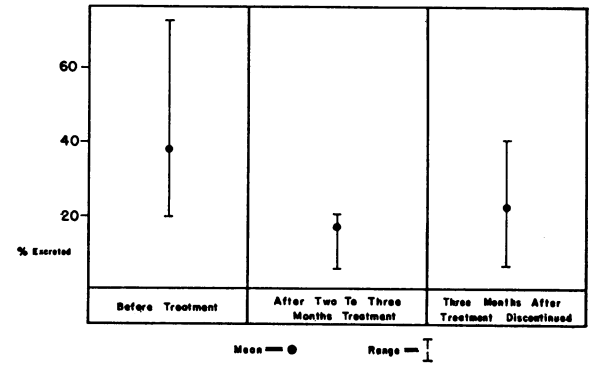

Chart 2.—Phenolsulfonphthalein excretion in 47 patients before, during and after treatment with amphotericin B.

(Chart 3). Three months after treatment was terminated the blood urea nitrogen and the Fishberg concentration test had returned to near pre-treatment values (Charts 1 and 3). However, the 15-minute phenolsulfonphthalein excretion test still revealed significant decrease of renal function (Chart 2).

Six patients died during treatment—none of them in renal failure—and necropsy was carried out. Two of these patients received about 3.5 grams of amphotericin B each; the others received 4.8, 8.8, 12 and 13.3 grams. Kidney biopsy was performed after two months of therapy in two additional cases. Each of these patients had received 2 to 2.5 grams of amphotericin B. No consistent pattern of histopathological change could be demonstrated in the glomerulus. In all eight cases there was necrosis of the epithelium of the distal renal tubule (Figures 1, 2 and 3) and calcinosis (Figure 1) was seen in two cases. Vacuolation of the tubular cells (Figure 3) was a prominent feature.

Ninety per cent of the patients complained of generalized muscular cramps and some weakness. It is also noteworthy that almost all the patients under treatment had an insatiable appetite for fruits and fruit juices.

Profound hypokalemia developed in the two cases reported below. Since then, serum potassium determinations have been done routinely in all patients during therapy and supplemental potassium has been administered. Hence no further data as to the incidence of hypokalemia is available in this series.

CASE 1. A 35-year-old white woman who ate an adequate diet, but who shunned fruits, complained of severe muscular weakness after receiving a total of 2.0 gm of intravenous amphotericin B in a two-month period. The serum potassium was found to be 2.2 milliequivalents per liter. She was much improved after vigorous replacement of potassium by mouth was begun and felt entirely well within 48 hours. At no time did this patient receive any corticosteroids.

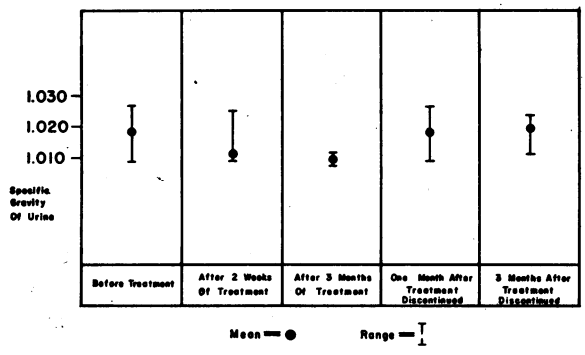

Chart 3.—Fishberg Concentration Test in 47 patients before, during and after treatment with amphotericin B showing loss of concentrating power during therapy.

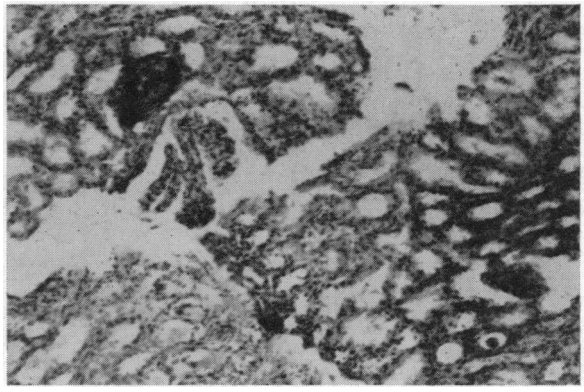

Figure 1.—Photomicrograph (×100) of kidney after amphotericin B therapy. Note extensive tubular damage and calcinosis. H & E stain.

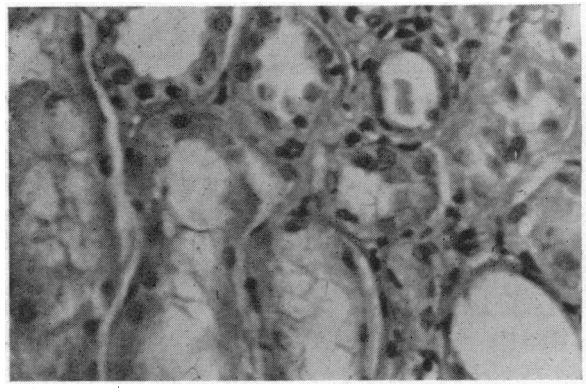

Figure 2.—Photomicrograph (×400) of kidney, showing more clearly the necrosis of tubular epithelial cells. H & E stain.

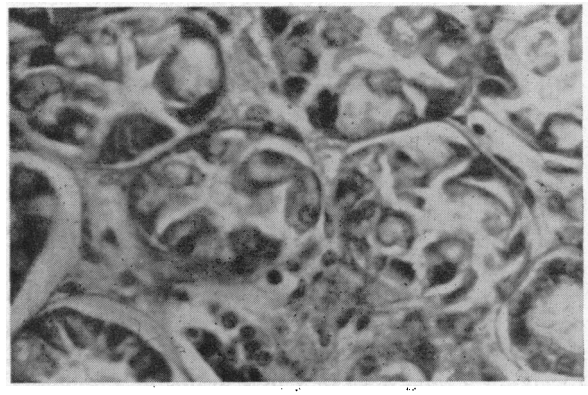

Figure 3.—Photomicrograph (×400) of kidney after amphotericin B therapy. Note vacuolation of tubular epithelium. H & E stain.

CASE 2. A five-year old Mexican boy became very lethargic and appeared moribund after receiving amphotericin B intravenously for 20 days. At no time had he received any corticosteroids. The serum potassium was 2.4 milliequivalents per liter. He responded rapidly to vigorous intravenous potassium replacement.

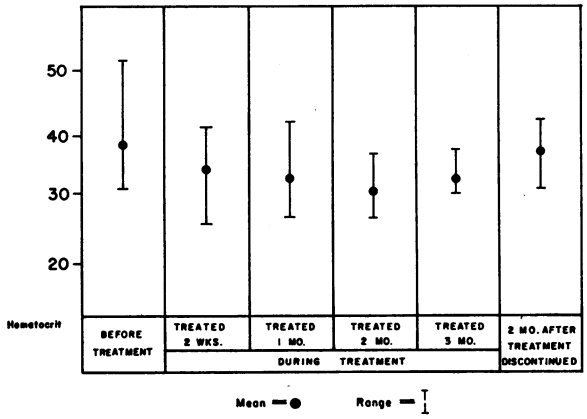

Chart 4.—Hematocrit (per cent) in 47 patients, before, during and after treatment with amphotericin B.

Anemia developed in all cases (Chart 4). Bone marrow examinations were performed before, during and after therapy in 20 cases. There was no significant change except hyperplasia during or after treatment. Red cell indices before, during and after treatment revealed no significant change. Red cell survival time was studied in six cases and there was a significant decrease during the second week of therapy (Chart 5).

Like many other observers,[8,11] we had much difficulty with nausea, vomiting, chills and fever. These symptoms were ameliorated, but not completely controlled, by the use of diphenhydramine and prochlorperazine intramuscularly and salicylates by mouth. Thrombophlebitis, a well known problem,[8,11] was minimized by the use of a fine needle in a peripheral vein as recommended by Winn.[11] It was further reduced when no drugs except heparin were added to the intravenous amphotericin solution.

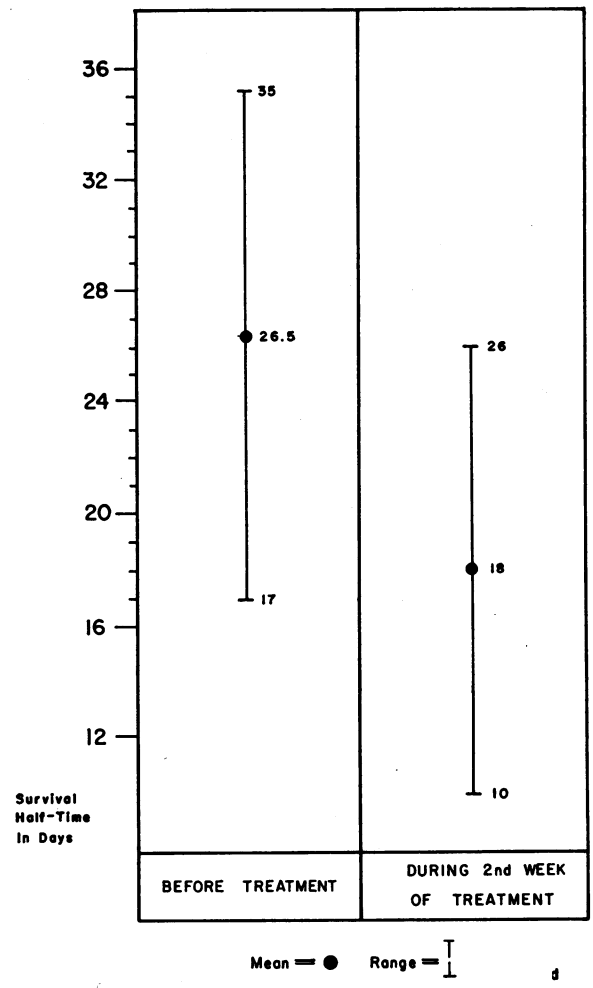

Chart 5.—Red cell survival studies using Cr^{51} labeled red cells in six patients before and during treatment with amphotericin B.

COMMENTS

The anemia observed during treatment with amphotericin B appears to be hemolytic rather than due to bone marrow depression.

In this series some impairment of renal function developed in all patients under treatment, including six who were treated for only four to eight weeks, receiving a total dose of 1 to 2 grams of amphotericin B each. These six patients, as well as those treated for more prolonged periods, had significant impairment of 15-minute phenolsulfonphthalein excretion three months after treatment was terminated. Histopathological studies in eight cases revealed damage to the distal renal tubule. Two of the patients with such damage had received less than 3 grams and three had received less than 5 grams of amphotericin B. In the hospital at which the present study was carried out, one patient died with renal failure while under treatment with amphotericin B, but was excluded from the series because autopsy was not done. We assume that his death was due to amphotericin B, but in the absence of pathological studies we can not prove the absence of other renal disease.

Profound hypokalemia occurred in two cases and has since been noted in other cases not included here. It should be emphasized that the serum potassium is not a good index of total body potassium, and that severe potassium depletion is present when the serum level falls below normal limits.[5] Presumably potassium loss is due to a renal tubular "leak."[4] Sections of pathological specimens of the kidney revealed vacuolation of tubular cells, suggesting that the severity of tubular damage is increased by potassium depletion.[9]

We think the following factors probably influence the severity of renal damage in any individual case:

1. Individual differences in susceptibility.

2. Pre-existing renal disease or lower urinary tract obstruction.

3. Daily dose of amphotericin B.

4. Lapse of time between doses.

5. Total dose administered.

6. Potassium depletion.

On the basis of these assumptions we recommend:

1. Careful selection of patients for therapy, balancing the risk of the disease against the risk of the drug in each case.

2. Early treatment of severe coccidioidal infections, since presumably larger amounts of amphotericin B will be required if the disease is permitted to progress. (Generally we use 1 mg per kilogram of body weight every other day, the amount depending on the clinical status of the patient.)

3. The administration of small doses once every one to two weeks where prolonged suppressive therapy is required, as recommended in an earlier article.[6]

4. More extensive use of local rather than systemic treatment in localized lesions. (Irrigation of chronic lesions has produced satisfactory results in our hands, provided provision is made for washing "through and through" the lesion rather than simply injecting the drug.)

5. Administration of supplemental potassium during therapy with frequent serum potassium determinations and serial electrocardiograms.

Since amphotericin B is the only drug that has been shown to be effective in the treatment of coccidioidomycosis[6] it should be administered in severe coccidioidal infections despite its nephrotoxicity. Until such time as a more effective and less toxic agent is available, further studies clarifying the mechanism of kidney damage and means of averting this damage are urgently needed.

ADDENDUM: Recent studies done by other investigators of patients treated for long terms with amphotericin B therapy suggest that there is consistent glomerular damage.

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