Effect of Amphotericin B on the Renal Clearance of Urea in Man (34947)

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Amphotericin B remains the sole effective therapy for certain fungal diseases. Detracting from its clinical usefulness is its deleterious effect on the kidney. Many investigators (1–4) have demonstrated that this antifungal agent reduces glomerular filtration rate and renal plasma flow. Renal biopsies (1–3) show thickening of the basement membranes, tubular swelling and degeneration, and marked calcification of the renal parenchyma. The extent of the renal damage correlates well with the amount of the drug administered (4).

Defects in the ability to concentrate (5–7) and acidify (6, 7) the urine have been described, suggesting that functional tubular damage may also result from treatment with this agent. On the other hand, the tubular maximum of para-aminohippurate (Tm_{PAH}) appears to decrease at the same rate as the renal plasma flow (7). The cause of the excessive urinary potassium loss and hypokalemia observed by some investigators (6–8) remains unexplained.

Some patients have failed to show any rise in blood urea nitrogen levels during therapy despite striking falls in inulin and PAH clearances (7). Others have been observed to develop elevated blood urea nitrogen levels early in the course of therapy with return toward normal levels before discontinuation of the drug (3, 4). Since the blood urea nitrogen does not appear to be a reliable measure of renal function in treated patients, the cause of this phenomenon was studied.

The purpose of this communication is to describe an aberration in the renal handling of urea observed to develop during the course of therapy with amphotericin B which would explain the failure of blood urea nitrogen levels to accurately reflect decreases in glomerular filtration rate.

Materials and Methods. The patients undergoing therapy were adult white males ranging in age from 36–66 years. All patients had been diagnosed as having either histoplasmosis, cryptococcosis, or coccidioidomycosis by biopsy and culture. The amount of amphotericin B administered every other day was increased up to 50 mg in all patients but J. A. who received a maximum amount of 30 mg. Clearance studies were performed before and during therapy at intervals of 2–6 weeks. These studies were repeated in one patient (G. P.) 2 months after discontinuation of therapy. The patients were hydrated with 20 ml of water per kg of body weight, and urine flows exceeded 10 ml/min in most studies. Priming loads of inulin and PAH were administered, and sustaining infusions started. After 30 min was allowed for equilibration of inulin and PAH plasma levels, urine samples were collected for three 20-min periods. The patients were allowed to void spontaneously in a standing position. Blood samples were collected at the midpoints of the first and third urine samples.

Determinations were made on all urine and plasma samples for urea using a commercial (Hycel, Inc.) urea nitrogen reagent, inulin (9), and PAH (10).

Results. The results in the first patient are shown in Fig. 1. Marked, nearly parallel decreases in inulin, PAH, and urea clearances were observed after only 390 mg of amphotericin B had been given over a 3-week period. Plasma urea nitrogen levels rose from 23 to 40 mg/100 ml. Little further change was observed during the next 3 weeks when total

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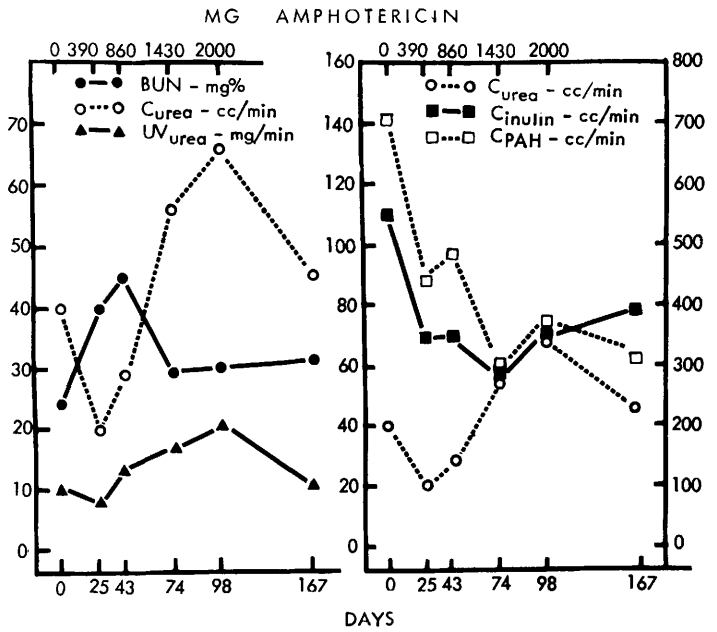

FIG. 1. On the left are serial plasma urea nitrogen levels, urinary urea nitrogen excretion, and urea clearances in a patient treated with a total of 2 g of amphotericin B over a 98-day period. On the right are the serial inulin, urea, and PAH clearances obtained simultaneously.

dosage reached 860 mg except that total urinary urea excretion and urea clearance increased slightly.

In two subsequent studies over the next 2 months when the total dosage of amphotericin B was carried to 2 g, marked increases in urinary urea excretion and urea clearances were observed, and plasma urea nitrogen levels fell. Only small changes in inulin and PAH clearances were observed. An increase in the urea clearance to inulin clearance ratio to unity was particularly noteworthy.

Two months after discontinuation of therapy, urinary urea excretion, urea clearance, and plasma urea nitrogen levels were similar to those observed in the pretreatment studies despite the fact that inulin and PAH clearances were still substantially below pretreatment levels.

Urinary sodium excretions remained unchanged, and total solute and potassium excretions fell slightly in this patient when pretreatment excretions were compared with those obtained 74 days after start of therapy. Since glomerular filtration rate decreased, there was an increase in solute excretion per unit of glomerular filtration rate suggesting a mild osmotic diuresis. However, when one compares the sodium and total solute excretion per unit of glomerular filtration rate in the latter study with one obtained 2 months after discontinuation of therapy, there were no differences despite a considerable drop in the urea to inulin clearance ratios. In one additional patient studied, urinary sodium and total solute excretion per unit of glomerular filtration rate decreased, and urea to inulin clearance ratios increased after therapy was instituted.

Table I shows the results of studies in this and four additional patients. With one exception (W. F.) who died before completion of his course of therapy, all showed early decreases in inulin and PAH clearances with little further change during subsequent studies. As therapy progressed, three patients increased urea clearances so that they exceeded their pretreatment clearances; in the other two patients, urea clearances remained depressed but not so severely as did the inulin clearances. In three of five patients, the urea to inulin clearance ratio reached unity.

TABLE I. Correlation of Urea, Inulin, and PAH Clearances in Five Patients Treated with Amphotericin B. Studies Were Performed Before, During, and, in One Case, After Therapy.

Patient	Amphotericin (mg)	UV_{urea} nitrogen (mg/min)	Plasma urea nitrogen (mg %)	C_{urea} (cc/min)	C_{inulin} (cc/min)	C_u/C_i	C_{PAH} (cc/min)
G. P.	0	9.5	24	40	105	0.38	707
	390	7.8	40	20	70	0.29	440
	860	12.8	45	28	70	0.40	481
	1430	16.8	30	56	57	0.98	301
	2000	20.4	30	68	70	0.97	376
	2 months	10.7	32	45	76	0.59	305
J. A.	0	6.0	14	42	86	0.49	265
	307	7.3	14	52	69	0.75	313
	640	7.6	17	45	47	0.96	209
	1400	8.6	12	76	57	1.33	239
W. F.	0	10.8	19	57	127	0.45	613
	435	16.8	28	60	113	0.53	754
	985[a]	9.8	14	87	137	0.64	867
T. T.	0	12.9	16	84	115	0.73	503
	500	8.3	19	46	46	1.00	364
W. W.	0	6.8	7	93	162	0.57	729
	350	8.8	15	59	100	0.59	540
	1000	8.8	12	79	114	0.69	536

[a] Died before next study performed.

In only a single study, in one patient (J. A.), did any ratio exceed unity. The changes in plasma urea nitrogen levels failed to adequately reflect the decreases in glomerular filtration rates.

While none of the additional patients showed the striking increases in urinary urea excretion that the first patient did, three of four patients did show some increase which could not be explained by mobilization of urea from body fluids.

Discussion. At urine flow rates above 2 cc/min, urea clearance is approximately 60% of the inulin clearance indicating that 40% of the filtered urea is reabsorbed while passing through the remainder of the nephron (11). Although urea transport in all other sites in the body is strictly by passive diffusion along concentration gradients, urea apparently is actively transported out of the collecting duct into the medullary interstitium against concentration gradients (12, 13). This explains how a large concentration gradient for urea can be generated in the medullary interstitium. Furthermore, transport of urea in the collecting duct is blocked by urea analogs, such as acetamide, and inhibitors of anaerobic metabolism, such as iodoacetate, suggesting block of an active transport mechanism.

The uniform increase in urea to inulin clearance ratios, reaching unity in three patients, suggests that urea in these patients was being filtered but not reabsorbed and that amphotericin B was in some way interfering with the generation of a concentration gradient for urea between the collecting duct and medullary interstitium. Since therapy with amphotericin B did not appear to produce any substantial increase in urinary sodium or total solute excretion per unit of glomerular filtration rate, this effect could not be attributed to any solute diuresis. We are unaware of previous reports of similar effects produced by other drugs or agents utilized in man.

At least two possible explanations exist to explain this failure to reabsorb urea and to generate a concentration gradient for urea. The first is that amphotericin B might block

the active transport of urea from the collecting duct into the medullary interstitium. Evidence for a possible disruption of active transport processes is provided by the histological examination of tubular tissue in patients treated with the antibiotic (2, 3).

Based on our understanding of the mechanism of action of amphotericin B, a second possibility appears more feasible. Lichtenstein and Leaf (14) showed that amphotericin B increases flux of urea across the toad bladder by its action on the dense diffusion barrier of the cell. Andreoli *et al.* (15) also have demonstrated that amphotericin B increases diffusibility of the membrane to small molecular weight substances such as urea. If the rate of back diffusion of urea into the collecting duct during a water diuresis increased sufficiently so that it matched the rate of active transport out of the collecting duct, no net urea reabsorption would occur. We are unable to determine, from these studies which of these two alternatives is correct.

Similar alternatives must be considered to explain the defect in hydrogen ion excretion or renal tubular acidosis observed in patients receiving amphotericin B (6). The inability to generate a hydrogen ion gradient between the tubular fluid and medullary interstitium could be due to either to a block in active hydrogen ion transport or to an increase in passive back diffusion of hydrogen ion from the tubular fluid into the interstitial fluid along the concentration gradient. Steinmetz and Lawson (16) recently have presented evidence using a toad bladder preparation to support the latter contention.

The block in urea absorption and inability to generate a concentration gradient in the medullary interstitium may be contributing to the vasopressin-resistant concentrating defect seen in these patients (6, 7). Possible effects on active sodium transport or back diffusion of sodium along concentration gradients in the medullary interstitium may also be contributing to the defect in concentrating ability (14, 15).

The increase in urea clearance was associated with an increase in urinary urea excretion in four of five patients with the patient illustrated in Fig. 1 more than doubling urea concentration on therapy but returning to pretreatment levels 2 months after discontinuation of therapy. The increase in urinary urea excretion cannot be explained by mobilization of urea from stores in various fluid compartments in the body and suggests increased catabolism. The common association of weight loss along with evidence that amphotericin B causes destruction of the mammalian erythrocyte (17) and damage to the renal tubular epithelial cells suggests the increased urea load may be due to increased endogenous protein catabolism.

Summary. Renal function studies were performed in five patients with disseminated fungous disease before, during, and, in one case, after treatment with amphotericin B. Early in the course of therapy, inulin and paraminohippurate (PAH) clearances decreased. The decreases in urea clearances were generally absent or less impressive than decreases in inulin clearances, and some increase in plasma urea nitrogen level was observed in each case. Later in the course of therapy, urea clearances increased often until they were similar to the inulin clearances, and plasma urea nitrogen levels fell with little change in other clearance measurements. These observations suggest that amphotericin B, in addition to its deleterious effect on glomerular filtration rate and renal plasma flow, may block reabsorption of urea and prevent establishment of a concentration gradient between the collecting duct and medullary interstitium.

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