Removal of Alpha-Methyldopa (Aldomet) in Man by Dialysis (35155)

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It has been generally acknowledged that some patients with reasonably well controlled hypertension developed an increase in blood pressure following hemodialysis or peritoneal dialysis. This phenomenon could be caused by delayed clearance of urea from the brain and cerebrospinal fluid, creating an osmotic gradient and resulting in cerebral edema (1). However, many of these patients had also been treated with alpha-methyldopa (Aldomet) for hypertension; thus, removal of the drug by dialysis could have contributed to the reemergence of hypertension. Because of the wide use of alpha-methyldopa in the treatment of hypertension in patients with renal failure (2) and because data concerning its dialytic removal are lacking, the present study was undertaken to determine the rate and the amount of the drug which would be removed *in vivo* by hemodialysis or peritoneal dialysis in patients with chronic renal insufficiency.

Methods. Patients Undergoing Hemodialysis. Four studies were carried out in three patients undergoing chronic hemodialysis; patient 1 was studied twice. Each dialysis lasted 6 hr. Patient 3 was receiving alpha-methyldopa, 125 mg by mouth three times a day, for hypertension. All subjects were given 20 μCi (1.7 mg) of ^{14}C alpha-methyldopa[3] by mouth, 1 hr prior to the dialyses. Blood specimens were collected from the arterial and venous side of the shunt before onset of dialysis and at hourly intervals during each dialysis.

Two dialyses were performed with a Travenol RSP artificial kidney, and two with a Travenol twin coil artificial kidney. The blood flow rate in these was maintained at 200 ml/min throughout the dialyses. The volume of the dialysates were measured at hourly intervals. Analyses of pH, BUN, osmolarity, and radioactivity were made on dialysates and plasma. Twenty-four-hr urine collections were collected on each patient for 3 days and only ^{14}C was determined. Relative dialysance (3) (sum of alpha-methyldopa and its metabolites) was calculated from the following formula:

$$\text{relative dialysance} = \frac{\text{dialysance of } ^{14}\text{C}}{\text{dialysance of Urea}} = \frac{(^{14}C_A - ^{14}C_V)/(^{14}C_A - ^{14}C_B)}{(\text{Urea}_A - \text{Urea}_V)/(\text{Urea}_A - \text{Urea}_B)},$$

where X_A, V, and B denote the concentration of a substance in the plasma of arterial blood (entering the bath), venous blood (returning from the bath), and the bath fluid, respectively.

Patients undergoing peritoneal dialysis. Two patients with terminal renal insufficiency undergoing 30-exchange (hourly interval; volume/exchange = 2 liters) peritoneal dialyses were given 1.7 mg of ^{14}C alpha-methyldopa by mouth, shortly after the second exchange. One of these subjects was also receiving 250 mg of alpha-methyldopa orally four times a day. Since both patients were seriously ill and had severe anemia, no blood specimens were obtained for determinations of ^{14}C.

Determination of radioactivity. ^{14}C was measured with an LS 250 Beckman liquid scintillation spectrometer. One ml of plasma, dialysate, or urine was added to 18 ml of counting medium made as follows: to 1 liter

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[3] Sp act 11.9 μCi/mg of alpha-methyldopa-2-^{14}C.

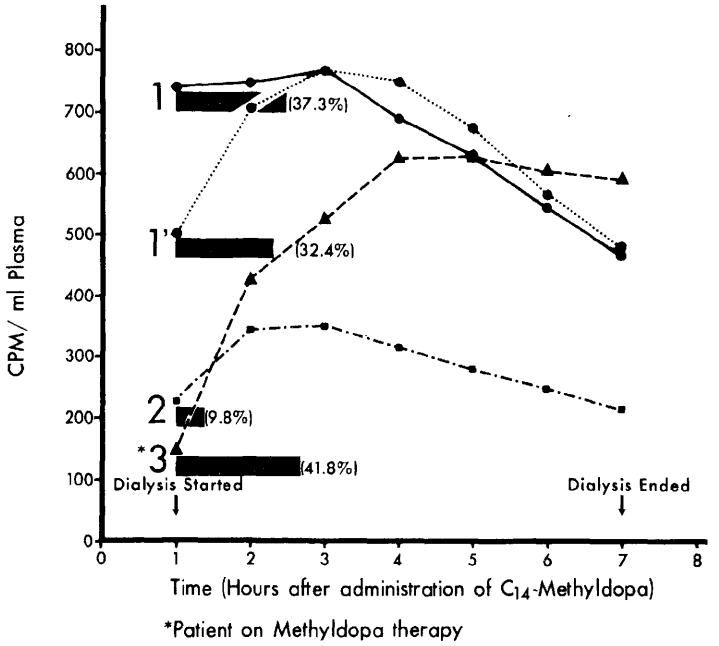

FIG. 1. ^{14}C in plasma (arterial); three patients, each of whom received 20 μCi of ^{14}C alpha-methyldopa at time zero. Patient 1 was studied twice (curves 1 and 1'). Hemodialysis started 1 hr after administration of the drug and ended 6 hr later. The amount of ^{14}C recovered for each study, expressed as percentage of the total administered dose, is shown as a horizontal bar on the left side of each curve. Patient was on alpha-methyldopa therapy when this study was carried out.

of toluene were added 7.0 g of PPO (2, 5-diphenyl oxazole) and 0.36 g of POPOP (1, 4-bis-2-(4-methyl-5-phenyl) oxazolyl benzene), followed by 200 ml of Biosolv (Beckman) BBS-3. ^{14}C in each specimen was counted to $\pm 2\%$. The background was compensated for automatically; counting efficiency was about 0.8.

Results. Patients undergoing hemodialysis. 1. Effects of hemodialysis on arterial pH, BUN, and osmolarity. As expected, blood pH of acidotic patients shifted to the alkaline side with dialysis. The mean arterial blood pH increased from 7.38 (7.35–7.40) to 7.44 (7.40–7.51).

The mean predialysis BUN was 55 mg/100 ml (44–67 mg/100 ml), which decreased to 17.5 mg/100 ml (14–22 mg/100 ml) in the immediate postdialysis period.

The mean plasma osmolarity decreased from 309 to 290 mOsm/liter with dialysis.

2. *Recovery of ^{14}C in the dialysate and in the urine.* Figure 1 shows the level of radioactivity of arterial blood plasma in this group of patients. The patterns of ^{14}C in plasma were similar in the duplicate studies carried out in patient 1. The radioactivity of plasma reached its peak between the second and the fourth hour after oral administration of the drug, then gradually declined.

The mean recovery of ^{14}C in the dialysate of all three patients was 30% of the dose given (6 μCi), but 42% (8.4 μCi) of the administered ^{14}C was recovered in the dialysate of the patient receiving prior alpha-methyldopa therapy.

The mean recovery of ^{14}C in the 72-hr urine specimen for the three patients was 3.4%. One patient in the diuretic phase of terminal glomerulonephritis excreted 8.2% of the ^{14}C dose during this period, while in the other three studies, less than 4% of the radioactivity was recovered in the 72-hr urine specimen. Table I summarizes these results.

3. *Relative dialysance of alpha-methyldopa* in vivo. At flow rate of 200 ml/min, the mean dialysance for urea was 143 (100–180) ml/min. The mean calculated relative dialysance

TABLE I. Recovery of ^{14}C in the Dialysate and 72-hr Urine of Three Patients on Chronic Hemodialysis.

Patient no.	Mean plasma radioactivity during dialysis (cpm/ml)	Total ^{14}C recovered (%) in		
		Dialysate	72-hr urine	Dialysate and urine
1	662	32.4	1.0	33.4
1′ (2nd study)	666	37.3	3.9	41.2
2	296	9.8	8.2	18.0
3[a]	529	41.8	0.6	42.4

[a] Study carried out while patient was receiving alpha-methyldopa (125 mg, po, t.i.d.) for hypertension.

of the sum of alpha-methyldopa and its metabolites was 0.34 (0.24–0.46).

Patients undergoing peritoneal dialysis. In the dialysate of the patient receiving alpha-methyldopa therapy, 39.3% of administered radioactivity was recovered; 22.3%, respectively, for the other patient.

Discussion. The following findings of Buhs *et al.* (4) are pertinent to our study: (i) *In vitro* experiments indicated that ^{14}C in plasma of patients given ^{14}C alpha-methyldopa was completely dializable. (ii) Only half (29–64%) of the drug was absorbed. (iii) The major metabolite, the *O*-methyl sulfate, was shown to be equal in potency to the parent drug. This conjugate is excreted in urine and accounts for a significant fraction of total plasma concentration. (iv) Delayed urinary excretion and prolonged plasma levels of drug occurred with azotemia; this may explain the prolonged duration of action in patients with renal failure.

In hemodialysis studies, we found that the amount of ^{14}C recovered in dialysate was a function of plasma ^{14}C concentrations, and that the mean relative dialysance was 0.34. Further, the peak level of ^{14}C appeared between 2 and 4 hr after oral administration, whereas Buhs *et al.* (4) reported a range of 3 to 6 hr. Correcting for the reported 50% average absorption, a mean recovery of 30% (9.8–41.8%) of the administered ^{14}C in the dialysate of our patients, indicates that about 60% of the absorbed drug was dialyzed over a 6-hr hemodialysis. The removal of alpha-methyldopa and its conjugate by hemodialysis, by shortening the duration of action of the drug, probably contributes to the reemergence of hypertension observed in some patients during the postdialysis period. ^{14}C was also recovered in peritoneal dialysates; these procedures were performed over a much longer period than hemodialysis. For this reason, removal of the drug by peritoneal dialysis probably constitutes a less acute problem than in hemodialysis.

Recently, Cameron *et al.* (5) have demonstrated the marked discrepancy between certain *in vitro* binding studies and removal of barbital in patients undergoing hemodialysis. Such results necessitate proof of dialytic removal of the drug *in vivo,* rather than reliance on predictions based on merely one type of *in vitro* experiments.

Summary. Dialytic removal of alpha-methyldopa (Aldomet) has been investigated in chronic uremic patients undergoing either hemodialysis or peritoneal dialysis, using ^{14}C tracer techniques. A mean of 60% of the estimated absorbed radioactivity was recovered in the dialysate of 3 patients undergoing 4 hemodialyses; the mean relative dialysance of radioactivity from alpha-methyldopa and its products was 0.34. A similar amount of radioactivity was recovered in the dialysate of 2 patients undergoing peritoneal dialysis.

The antihypertensive action of administered alpha-methyldopa and its major metabolite (a mono-*O*-sulfate conjugate) may be diminished by hemodialysis. This effect could contribute to the reemergence of hypertension occasionally observed in the postdialysis period in patients receiving alpha-methyldopa therapy.

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