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Effects of Chlorothiazide on Renal Ammonia Production, Plasma Electrolytes and Acid Base Balance in Acute Renal Failure. (28551)

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The metabolism of the anuric kidney has not been studied systematically. It has been postulated that the anuric kidney is in a state of hibernation, the low oxygen consumption being accounted for by metabolic processes unrelated to glomerulo-tuberlar metabolism (1). Recent investigations have suggested that the major part of renal oxygen consumption is needed for reabsorption of filtered sodium(2,3). If this is correct and oxygen consumption by the anuric kidney is very low it is necessary to assume that filtration must have ceased in the anuric kidney. More recently higher values of oxygen consumption by the anuric kidney have been reported(4) and the hypothesis of the 'resting' state has been questioned. Therefore, it was decided to see if the anuric kidney produced ammonia and to determine the effect of chlorothiazide in renal ammonia production, plasma electrolytes and acid base balance in patients with acute renal failure. Measurements were made either before or after treatment by haemodialysis and the same intravascular catheters were used for metabolic determination and for haemodialysis.

Methods. Five patients with acute oliguric renal failure were studied during the first week of the onset of oliguria. Endogenous creatinine clearances were less than 1 ml per minute on the day of the study and no urine was voided during the study or for the subsequent 16 hours. Renal blood flow was measured using a constant infusion of indocyanine green (IG) into the renal artery(5) following its catheterisation under fluoroscopic control by a percutaneous femoral arterial radiopaque teflon catheter(6) and the catheterisation of the corresponding renal vein following femoral vein puncture. A loading dose of IG 0.3 mg per kg body weight was given intravenously and it was then infused at 0.5 mg per minute (in a volume of 1 ml) into the renal artery catheter by a Sigma constant infusion pump. After a 20-minute equilibration period, samples were obtained anaerobically from the renal vein and femoral arterial catheters (allowing for dead space sampling times). Two control samples were obtained (minus 10 minutes and 0 time), then 1000 mg of chlorothiazide were administered intravenously in a volume of 50 ml. Subsequent samples were obtained at 10 and 20 minutes after chlorothiazide administration. Arterial and renal venous blood were analysed for IG(7), ammonia (NH_3)(8), oxygen content(9) and arterial blood for pH, bicarbonate and pCO_2 (10) and plasma sodium and potassium using an E.E.L. flame photometer. Renal blood flow (RBF) was calculated for one kidney from the renal venous-arterial IG difference and infusion rate of IG using the indirect Fick principle(5). The renal venous-arterial NH_3 difference and RBF were used to calculate renal vein NH_3 release ($\mu g/min/1.73M^2$) and renal oxygen consumption (ROC) was obtained from RBF values and arterial-renal venous oxygen content difference $(A\text{-}RV)O_2$.

TABLE I. The Effect of Chlorothiazide on Renal Vein Ammonia Production, Serum Electrolytes and Acid Base Balance in 5 Patients with Acute Renal Failure.

Case No.	Time, min	Renal blood flow (right), ml/min/1.73M²	Arterial NH_3, μg/ml	Renal vein NH_3, μg/ml	Release of NH_3 into renal vein, μg/min/1.73M²	A-RO_2, ml/100 ml	ROC, ml/min/1.73M²	Serum Na, mEq/l	Serum K, mEq/l	Arterial pH	Arterial HCO_3, mEq/l	Arterial pCO_2, mm Hg
PP	—10	250	1.61	2.54	232	1.5	3.7	135	5.0	7.41	24	32
	0*	250	1.52	2.26	185	1.3	3.3	130	5.1	7.41	24	32
	+10	300	1.60	2.30	210	1.5	4.5	130	5.0	7.41	24	32
	+20	280	1.55	2.45	196	1.4	3.9	135	5.0	7.43	24	30
EL	—10	270	1.50	2.01	157	1.3	3.6	130	4.5	7.38	20	33
	0*	330	1.44	1.90	152	1.1	3.6	135	4.7	7.38	19	31
	+10	260	1.83	2.18	103	1.2	3.1	130	4.4	7.38	20	32
	+20	260	1.63	2.30	200	1.3	3.4	130	4.6	7.42	20	28
JH	—10	150	.95	1.40	68	1.3	1.9	140	4.0	7.38	23	40
	0*	160	1.00	1.39	62	1.4	2.2	140	4.1	7.37	22	39
	+10	150	1.05	1.40	53	1.4	2.1	140	4.0	7.38	22	38
	+20	160	1.00	1.40	64	1.1	1.7	140	4.0	7.36	22	40
RR	—10	130	.83	1.49	86	1.5	2.0	140	4.0	7.42	23	33
	0*	140	.94	1.66	103	1.4	2.0	130	4.1	7.41	23	34
	+10	160	.85	1.53	100	1.5	2.5	135	4.1	7.41	23	34
	+20	160	.88	1.55	109	1.4	2.2	145	4.1	7.44	23	34
JK	—10	200	.80	1.21	82	1.3	2.6	140	6.0	7.30	15	28
	0*	250	.79	1.30	127	1.1	2.7	130	6.1	7.32	16	27
	+10	220	.81	1.35	118	1.2	2.6	135	6.2	7.30	15	28
	+20	230	.85	1.30	103	1.1	2.5	140	6.2	7.31	15	29
Mean control values		213 ±66	1.014 ±.336	1.716 ±.442	125.4 ±55.5	1.32 ±.47	2.76 ±.23	135 ±5.4	4.76 ±.79	7.378 ±.047	20.9 ±3.28	32.9 ±4.1
Mean post chlorothiazide values		218 ±57	1.203 ±.400	1.766 ±.468	125.6 ±56.0	1.31 ±.48	2.85 ±.87	136 ±1.6	4.76 ±.84	7.381 ±.047	20.8 ±3.10	32.5 ±4.1
t		.58	1.75	.03	.008	.012	.25	.59		.20	.068	.218
p		.5<p<.6	.1<p<.2	.9<p	.9<p	.9<p	.8<p<.9	.5<p<.6	.9<p	.8<p<.9	.9<p	.8<p<.9

* 1000 mg chlorothiazide I.V. ± = 1 standard deviation. A-RO_2 = arterial renal venous oxygen difference. ROC = renal oxygen consumption.

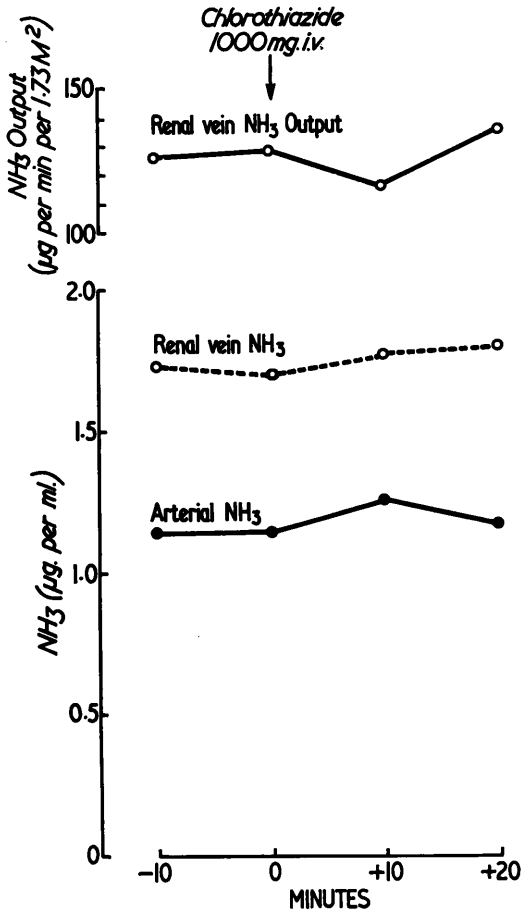

FIG. 1. Mean renal arterial NH_3, renal vein NH_3 and renal vein ammonia release in 5 patients with acute renal failure before and after administration of 1000 mg of chlorothiazide I.V. The drug had no significant effect upon these parameters.

Results. (Table I, Fig. 1). The mean renal vein NH_3 release averaged 125 $\pm$ 55 μg per minute per 1.73M^2 ($\pm$ = 1 Standard Deviation), during the control period and did not alter significantly in the 20 minutes following intravenous infusion of 1000 mg of chlorothiazide (Fig. 1). Chlorothiazide had no effect on renal blood flow, renal oxygen consumption, arterial or renal vein NH_3 levels, nor did it affect serum potassium or sodium levels, or arterial blood pH, pCO_2 or bicarbonate values.

Discussion. The ability of the renal tubules to produce ammonia during the stage of oliguric renal failure has not previously been reported. This observation suggests that metabolic work is proceeding in the renal tubule in anuria and affords evidence against the 'resting kidney' hypothesis. In the functioning kidney it has been shown that an increase in renal vein NH_3 release occurs following intravenous chlorothiazide administration(11). The increase can be attributed to a shift of ammonia from urinary excretion into renal vein output(11) following an acute rise in urinary pH and redistribution of ammonia diffusion on a nonionic basis(12). The failure of chlorothiazide to increase renal vein NH_3 release in the anuric kidney is explained by the absence of urinary NH_3 excretion excluding a shift of ammonia from the urine to the renal vein. The failure of chlorothiazide to influence serum potassium levels or acid base balance in the absence of renal function confirms previous reports of the observation in nephrectomised animals(13,14) and casts doubts on the original report of a hypokalaemic effect of chlorothiazide in nephrectomised dogs(15). These observations suggest that chlorothiazide exerts its major influence in the human by a renal effect.

Summary. It has been demonstrated that the renal tubule produces ammonia during the oliguric phase of acute renal failure. Chlorothiazide had no effect on renal blood flow, oxygen consumption, and ammonia production, nor did it affect the serum electrolytes or acid base balance. It is suggested that chlorothiazide exerts its main action in man by a predominantly renal effect.

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Humoral Regulation of Erythropoiesis XII. Effect of Erythropoietin and Iron on Cell Size in Iron Deficiency Anemia.* (28552)

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High doses of exogenous erythropoietin, when given to normal or hypertransfused rats, result in production of short-lived macrocytes (1-3). Similarly, after intense erythroid stimulation from bleeding, phenylhydrazine anemia or exposure to hypoxia, there is a macrocytosis, presumably mediated by high levels of endogenous erythropoietin(4). We have suggested that the macrocytic response is due to shortening of maturation time with a resultant skipped division(1-3). Iron deficient animals, of course, produce microcytes; the effect of erythropoietin on cell size in iron deficient animals has not been studied, although it has been shown that treatment with iron in the face of substantial anemia results in macrocytic response(5). This report concerns the effect of erythropoietin in the iron deficient animal and the relationship of iron to production of macrocytes.

Materials and methods. Weanling Sprague-Dawley females were placed on a milk powder diet to which essential vitamins and minerals with the exception of Fe were added. Control groups received a similar diet but with the addition of 200 mg of $FeCl_3$/kg. Animals were treated by adding 0.2-1.0 g of Fe/kg of diet or by parenteral injection with 5 mg of Fe as Imferon.† Erythropoietin was obtained by alcoholic extraction from the urine of a patient with a hypoplastic anemia; it was assayed in the starved rat and compared with the standard of Erythropoietin A(6). Standard techniques were used for measuring red cell values. The frequency distribution of red cell size was measured with a Coulter model B Counter and graphout. Differential centrifugation was used to separate out mixed cell populations(3) where the frequency of one cell population was sufficiently low that it could be detected from distribution curves on whole blood.

Results. After 3 months the animals receiving the iron deficient diet had a severe hypochromic microcytic anemia; the hemoglobin values were 4-5 g%; mean corpuscular volume (MCV), 35-42 μ^3; mean corpuscular hemoglobin concentration (MCHC), 21-24%; compared to values for Hgb. of 13-15 g%; MCV, 52-57; and MCHC of 32-36% in animals receiving Fe supplemented diets. There was a significant macrocytic response when 35 units of erythropoietin were given every 12 hours, for a total of 175 units, to animals on iron supplemented diets (Fig. 1). In contrast a similar amount of erythropoietin had no significant effect on cell size distribution in the iron deficient animal (Fig. 1).

When iron deficient animals were treated by supplemental dietary iron, in amounts equivalent to that in the control diet, there was a normocytic response. Blood was separated by differential centrifugation in an effort to detect any small proportion of macrocytic cells which might be present. None were found. The pre-treatment microcytes, however, were seen in the upper fraction of the centrifuged column of blood, while the post-treatment normocytes with a higher MCHC

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