Kidney as a Source of Blood Ammonia: Effect of Chlorothiazide.* (25366)

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Elevated blood ammonia values have been observed following oral administration of chlorothiazide to patients with liver disease (1,2). However, the source of this increment of blood ammonia has not been identified. Recent studies indicate that the kidney is largely responsible for hyperammonemia which follows intravenous administration of the potent carbonic anhydrase inhibitor, Diamox®(3). Since chlorothiazide also increases urine pH and decreases urine ammonia excretion through carbonic anhydrase inhibition(4), the present study was undertaken to determine the effect of intravenous chlorothiazide on arterial ammonia concentration and release of ammonia into the renal vein.

Methods. Seven patients with Laennec's cirrhosis were studied. All were hospitalized males ranging in age from 28 to 49 years. None of the patients exhibited neuropsychiatric abnormalities or evidence of progressive hepatic deterioration. Renal function and serum electrolytes were normal. Patients were studied in recumbent position after overnight fast. A constant intravenous infusion (Bowman pump), delivering 14 to 16 mg of para-amino hippurate (PAH)/min. was maintained throughout and was preceded by a priming dose of PAH calculated to provide plasma levels of about 2 mg/100 ml. Each subject ingested 1000 ml of water at onset of study to initiate water diuresis. This was subsequently maintained by intravenous infusion of 5% Dextrose and water at 15 to 20 ml/min. Arterial and renal-venous blood was obtained from a brachial artery and a catheterized right renal vein. Control sampling was followed by intravenous administration of 500 mg of chlorothiazide. Subsequent samples were withdrawn at 10, 20, 30, 45, and 60 min. Voided urine specimens were obtained whenever possible. Arterial and renal-venous blood were analyzed for ammonia (NH_3), PAH, pH, CO_2 content, and O_2 saturation by previously described methods(3,5,6). Renal blood flow (RBF) was calculated from the arterial-renal venous (A-RV) PAH difference, using the indirect Fick principle of Bradley (7). The A-RV ammonia difference and RBF were used to calculate renal vein ammonia release (μg/min)(3).

Results. The effect of intravenous chlorothiazide on arterial ammonia concentration, renal vein ammonia release, and urine pH are shown in Fig. 1.

Mean arterial ammonia concentration progressively increased following chlorothiazide and was significant ($p = <0.01$) at 45 and 60 min. periods when compared with resting values. Signs of early pre-coma appeared in one subject, whose arterial ammonia concentration increased from 165 to 194 μg%.

The resting A-RV ammonia difference was negative in each subject, mean = −37 μg%, indicating release of ammonia into renal vein. Ten min. after chlorothiazide administration, mean renal vein ammonia release increased from control value of 1154 μg/min. to 1992 μg/min., $p = <0.01$, and remained essentially unchanged throughout 60 min. observation. No alterations in renal blood flow were observed, mean control = 1475 ml/min., 10 min. = 1571 ml/min., 20 min. = 1688 ml/min., 30 min. = 1444 ml/min., 45 min. = 1460 ml/min., and 60 min. = 1430 ml/min. Increase in quantity of ammonia released into the renal vein was associated with rapid and significant increase in mean urine pH, $p = <0.05$ and <0.01 at 10 and 60 min., respectively.

Arterial and renal-venous pH, CO_2 content and the calculated pCO_2 remained essentially unchanged throughout the study, as did A-RV oxygen differences and calculated renal oxygen consumption.

Discussion. The present data demonstrate that intravenous administration of chlorothiazide to patients with liver disease with or with-

* Work supported (in part) by U. S. Public Health Grant.

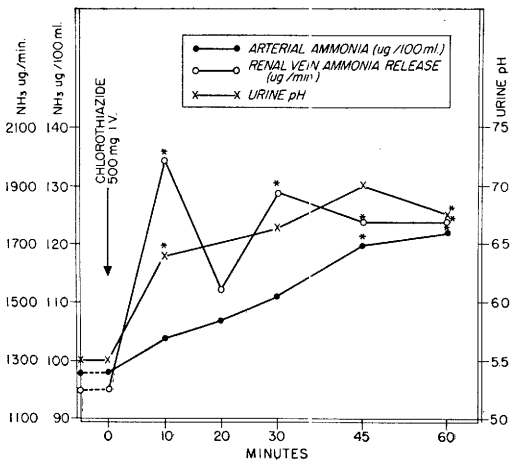

FIG. 1. Arterial ammonia concentration, release of ammonia into renal vein and urine pH before and after intrav. chlorothiazide. Mean values in 7 cirrhotic patients. * denotes significance.

out hyperammonemia results in a rise in arterial ammonia concentration, and that this rise is accompanied by an increased renal release of ammonia into the circulation. Indeed, increased release of ammonia into the renal vein could theoretically account for 360 μg% rise in extracellular fluid ammonia concentration at the 60 min. period, if one assumes a uniform distribution into a 14 liter fluid volume and an unchanged tissue uptake. Since the observed increase in arterial ammonia concentration was 22 μg%, it seems likely that the kidney represents the major source of increased increment of blood ammonia which followed intravenous chlorothiazide. The present results parallel those previously reported when Diamox® was given to patients with liver disease(3). In addition, the magnitude of increased release of ammonia into the renal vein which followed Diamox® could be correlated with degree of increase in urine pH and decrease in urine ammonia excretion. Thus, the post-Diamox® data suggested that urine pH is not only an important determinant of urinary ammonia excretion but also influences the amount of ammonia liberated into the renal vein(3). In this study, urine pH promptly rose after I.V. chlorothiazide in association with the increase in release of ammonia into the renal vein. These observations lend additional support to the concept that the kidney is a significant source of blood ammonia and that factors which influence urine pH also influence this contribution.

Summary. The effect of intravenous chlorothiazide on arterial ammonia concentration and release of ammonia into renal vein was studied in 7 patients with Laennec's cirrhosis. Rapid and significant increases in quantity of ammonia released into the renal vein were observed along with progressive rise in arterial ammonia concentration. The data demonstrate the kidney's importance in the pathogenesis of hyperammonemia which follows intravenous chlorothiazide.

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Received September 14, 1959. P.S.E.B.M., 1959, v102.

Effect of Lysergic Acid Diethylamide and Bufotenine on Performance of Trained Rats. (25367)

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The psychogenic activity of lysergic acid diethylamide (LSD) has long been recognized. It has been reported that a condition resembling schizophrenia can be produced in humans by administration of only 1 μg of LSD/kg(1). Winter and Flataker(2) demonstrated that