Effects of Chlorothiazide on Specific Renal Functions in Hypertension

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Oral administration of chlorothiazide depresses glomerular filtration, increases blood urea, maintains sodium output in the face of decreased filtered sodium load, and paradoxically for a diuretic, in these and in tests done shortly after intravenous administration, increases the efficiency of water reabsorption.

A PREVIOUS report on the mechanism of action of chlorothiazide\(^1\) was based on observations on hemodynamic functions. Studies of specific renal functions were done concurrently in some of the patients and in others that were treated identically, except for the omission of some of the hemodynamic observations.

The results show that, in addition to its recognized saluretic and kaluretic properties,\(^2\) chlorothiazide in therapeutic doses may depress glomerular filtration, may increase blood urea, and causes a paradoxical increase in osmotic ceiling.\(^3\)

METHODS

Renal effects of chlorothiazide\(^*\) were studied in 33 patients. Eleven were given the drug in a dose of 1 Gm. twice daily for periods of 3 to 14 days. Their renal functions were measured before and at the end of the course. Renal function was tested in 4 patients just before and again 1 hour after the intravenous injection of 0.5 Gm. of this agent.

Renal plasma clearances of p-aminohippurate (\(C_{PAH}\)) and mannitol (\(C_M\)), and water and electrolyte outputs were measured by methods previously described.\(^3\) It is assumed that \(C_{PAH}\) is equivalent to effective renal plasma flow, and \(C_M\) times 1.1 (to correct for possible mannitol reabsorption or storage) is equivalent to glomerular filtration rate.

The tests were done during osmotic (mannitol) diuresis in 6 patients, in the prolonged and in all in the acute study; these conditions enabled measurements of stable excretion rates of electrolytes and calculation of tubular reabsorption of osmotically "free" water (\(T_{\text{osm}}\)). This function is an index of relative osmotic ceiling.\(^4\) The stimulus to water reabsorption was either fluid deprivation (4 cases) or intravenous infusion of Pitressin (6 cases). All functions are expressed in units per minute relative to 1.73 M\(^2\) body surface area.

Brachial arterial pressure was determined by auscultation during the tests. Ten of the 11 patients in the prolonged study were weighed daily on awakening. Supine and standing arterial pressures were measured 4 times daily in 8 patients undergoing the prolonged study. Five of the 11 patients receiving oral and 3 of the 4 given intravenous chlorothiazide continued treatment with the antihypertensive drugs which they had taken for many months.

RESULTS

Prolonged Administration

Renal Hemodynamics. During the control periods \(C_{PAH}\) ranged from 128 to 401 ml. Administration of chlorothiazide did not change effective renal plasma flow in 6 patients and was followed by slight decreases in 4 (table 1). Control levels of glomerular filtration rate ranged from 43 to 168 ml. in 11 and uniformly decreased during treatment with chlorothiazide (mean \(-29\) per cent, range \(-16\) to \(-50\)). Arterial pressure decreased at the time of the chlorothiazide clearance study in 5 patients; 4 of these demonstrated decreased renal vascular resistance and 1 an increase. Among the 5 showing no change in arterial pressure, renal vascular resistance decreased in 3 and was unchanged in 2. (Filtration fraction was decreased in all.)

Electrolyte and Water Excretions. These functions were studied during osmotic diuresis in 6 patients (table 2). During chloro-

\(^*\)Kindly supplied by Dr. John R. Beem, Merek Sharp & Dohme.
thiazide administration, glomerular filtration rate was depressed in all and osmolar clearance \((C_{osm})\) in 5. The absolute rate of tubular reabsorption of osmotically free water \((T_{W_{osm}})\) was decreased in 4 patients and increased in 2 who had received the drug for no more than 3 days. When this function was calculated in relation to simultaneously measured glomerular filtration rate \((T_{W_{osm}}/C_M \times 1.1)\) 100, the relative rate was found to be increased in 5 of 6 cases, the exception being the patient with the lowest initial glomerular filtration rate. Filtered sodium \((I_{Na})\) load, the product of glomerular filtration rate times serum sodium, was consistently decreased, as was the rate of sodium excretion \((U_{Na}V)\). However, the percentage of filtered sodium that was reabsorbed \((I_{Na}−U_{Na}V/I_{Na})\) 100 was unchanged or, in 1 case, increased. Potassium clearances were increased in 4 patients in whom this function was measured.

Other Observations. All patients lost weight during treatment. Venous hematocrit ratio rose slightly in all but 1. Serum
osmolality diminished in the 6 patients in whom it was measured. Blood urea concentrations rose in 6 of 8 patients. Serum creatinine concentration was measured in 4 cases and did not change, in spite of depressed filtration rates. Arterial pressures, supine and standing, decreased in 6 of 8 patients.

**Intravenous Injection**

One hour after intravenous injection of 0.5 Gm. of chlorothiazide, renal plasma flow (C_{PAH}) was depressed in 2 and glomerular filtration in 1 of the 4 patients.

The largest renal change observed was a consistent decrease in sodium reabsorption, with increases in the rate of sodium excretion, potassium clearance, and absolute and relative rates of free water reabsorption.

**DISCUSSION**

The renal vascular bed is responsive to changes in blood volume, cardiac output, and sodium balance. Acute hypovolemia, such as results from moderate bleeding, venous congestion of the extremities, and quiet standing, decreases renal plasma flow, has little effect on filtration rate, and increases filtration fraction. In contrast, during prolonged sodium restriction with resultant chronic hypovolemia, such as results from the rice diet, renal plasma flow is well maintained, glomerular filtration rate falls, and filtration fraction diminishes. The effects of prolonged administration of chlorothiazide on the renal vascular bed resemble those seen during low sodium dietotherapy. Since chlorothiazide causes depletion of sodium, water, and plasma volume, it would be premature to ascribe these changes in the renal circulation to sodium depletion as such. It may be that chronic hypovolemia leads to renal hemodynamic readjustments resulting in changes that have been attributed to sodium depletion alone. Supporting this view is the fact that in the nephrotic syndrome—a condition characterized, in part, by chronic hypovolemia—renal plasma flow may be unchanged or increased, filtration rate is usually depressed, and filtration fraction is consistently low. Against this interpretation is a study in 2 patients under treatment with the rice diet; in them infusion of salt-poor albumin did not increase filtration rate, while infusion of sodium lactate solution restored it to or towards control levels.

Since chlorothiazide is excreted in part by proximal tubular secretion, apparently along a pathway similar to that of p-aminohippu-
rate, it is not surprising that large intravenous doses depress renal extraction of p-aminohippurate in the dog. It is unlikely that this would account for the small decreases in plasma C_{PAH} in the tests done during oral administration, although it may account for the decreases observed in 2 patients after the intravenous injection.

The decreases in absolute rates of free water reabsorption observed during prolonged chlorothiazide administration obviously reflect depressed glomerular filtration. The increases in the relative rate of this function could be attributed to a dispersion of nephron function, such that glomerular filtration is largely in abeyance in some nephrons and persists in those nephrons whose longer tubules enhance their water reabsorptive function. However, both the absolute and relative rates of free water reabsorption increased after intravenous injection of the drug, without noteworthy changes in glomerular filtration. This suggests that the primary basis for the change in reabsorptive function, which implies an increase in renal "osmotic ceiling," may be increased osmolality of renal extracellular fluid in the regions of active water transport.

Changes in sodium and potassium excretion after intravenous injection of the drug confirm earlier observations. The changes in the prolonged experiments are of interest, in that decreased filtered sodium load usually stimulates sodium reabsorption. While this was observed in 1 patient of the prolonged series, the data indicate that chlorothiazide prevented increased sodium reabsorption in the others.

Changes in osmolality reflect the saluretic activity of the drug, and require no further comment. The increases of blood urea observed in some patients may be noteworthy, in that in some cases they seem to be greater than would be predicted from the concurrent decrease in filtration rate. One factor may be increased urea reabsorption, consequent on increased water reabsorption. However, this function was not measured. Another possibility is that chlorothiazide may indeed stimulate ammonia formation in the kidney, as may occur in hepatic cirrhosis, with the difference that this ammonia, in our subjects, could be converted to urea. This assumption implies a stimulation of glutaminase activity, but more evidence is required, both indirect from clearance studies and direct from studies of enzymatic activity.

**Summary**

In addition to its recognized saluretic and kaluretic properties, prolonged oral administration of chlorothiazide to hypertensive patients often depresses glomerular filtration, causes an increase in blood urea that may be disproportionate, and, in the face of decreased filtered sodium load, tends to maintain a normal rate of sodium reabsorption. It also causes an increase in free water reabsorption, which is evidenced only relatively in the prolonged experiments but which is also observed, as an absolute increase, in tests done shortly after intravenous injection of the drug. The
renal hemodynamic status during prolonged administration may be attributable to sodium depletion as such. However, by analogy with renal hemodynamic status in nephrosis, hypovolemia may be the primary factor.

**Summario in Interlingua**

A parte su reecognoscite proprietates saluretic e kaliuretic, le prolongate administration oral de chlorothiazido a patientes hypertensive deprime frequentemente le filtration glomerular, causa un augmento del urea in le sanguine (a grados que pote devenir disproportionalmente alte), e—in le presentia de un reducete carga de natrium filtrate—tende a mantenir un normal mesura in le reabsorption de natrium. Illo etiam causa un augmento del reabsorption de aqua libere. Iste facto es evidente solmente in manera relative in le experimentos prolongate, sed illo se observa etiam como un augmento absolute in tests effectuate brevemente post le injection intravenose del droga. Le stato del hemodynamic renal durante cursos de administration prolongate es forsane attribuibile al depletion de natrium per se. Tamen, per analogia con le stato del hemodynamic renal in nephrosis, il es possibile che hypovolemia es le factore primari.

**REFERENCES**

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