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Pharmacodynamics of Chlorothiazide (Diuril), An Orally Effective Non-Mercurial Diuretic Agent.* (23277)

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The following report is concerned with chlorothiazide (Diuril)† a diuretic agent of low toxicity, which is well absorbed by the oral route(1) and is equally as potent as meralluride (given parenterally).

Methods and materials. The acute renal hemodynamic responses to doses up to 10 mg/kg of chlorothiazide (Diuril) given intravenously were observed in anesthetized dogs employing methods and technics described previously(2). The acute effect on water and electrolyte excretion was also observed in unhydrated dogs(3).

The clinical studies were done on 10 male patients who had been in mild heart failure but who at the time of the study were free of edema. The technic for evaluation of diuretic agents has been described previously(4,5). The subjects of the study were ambulatory, hospitalized patients maintained on a metabolic ward, eating a diet containing 50 mEq of sodium per day, and drinking 3,000 ml of distilled water per day. After a suitable period of adjustment to the diet the patient's urinary sodium was approximately 90% of the dietary intake, *i.e.*, about 45 milliequivalents per 24 hours. When this point was reached, the drug was given as a single dose at 6 a. m. and observations were made of subjective and objective signs of toxicity as well as of the urinary sodium excretion, analyzed with the use of a Beckman flame photometer. After another suitable interval (5 to 7 days) for equilibration, the next dose was given and so forth. The drug was administered 10 times at each dose and the results subjected to appropriate statistical analysis as justified by previous studies(4).

Results. Following intravenous administration of chlorothiazide (Diuril) to dogs there was a significant increase in water excretion associated with an increase in sodium, potassium, and chloride excretion which was generally proportional to the dose (Fig. 1A and 1B). The diuretic threshold dose was less than 0.5 mg/kg body weight. The diuretic effect was not due to an increase in glomerular filtration rate since renal blood flow and glomerular filtration rate were not increased (Fig. 2). This leads to the conclusion that the increase in water and electrolyte excretion is due to a direct tubular effect of the chlorothiazide which blocks the reabsorption of these substances. Mean blood pressure was not altered.

The particular electrolyte excretion pattern associated with administration of a single 2000 mg oral dose of chlorothiazide to a typical patient is presented in Fig. 3. The greatest increase in cations was in the excretion of sodium but potassium excretion was also increased temporarily. There was a moderate decrease in ammonia excretion following administration of the drug. Among the anions observed, the greatest increase in excretion rate was in chloride with a significant but temporary increase in bicarbonate. Total in-

* Supported in part by Houston Heart Assn.

† 6-chloro-7-sulfamyl-1,2,4 - benzothiadiazine-1, 1-dioxide. Supplied as Diuril by Merck, Sharp & Dohme, West Point, Pa.

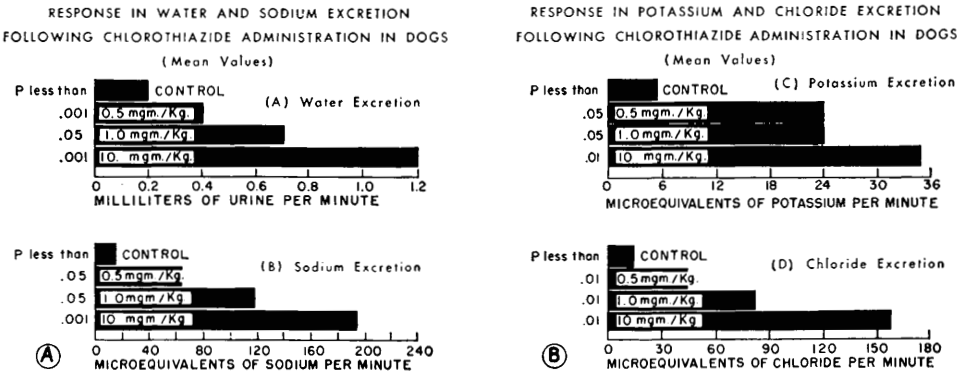

FIG. 1 (A & B). Responses in excretion of water, sodium, potassium, and chloride are proportional to dosage of the drug admin. to dogs intrav.

crease in excretion of bicarbonate per 24 hours was of a small order (Fig. 3).

The response to oral administration as compared to the same dose administered intravenously was observed in several patients. The effect on sodium excretion in one such study is presented in Fig. 4. There was a greater initial response following intravenous administration but following oral administration the response persisted for a longer period of time than it did after the intravenous route. Consequently, total increase in excretion of sodium over a 24-hour period was greater after the oral route of drug administration.

A summary of the natriuretic response to 2000 mg of chlorothiazide given to 10 patients is presented in Table I. Doses in excess of this amount of drug produced very little additional diuresis or natriuresis.

TABLE I. Response of 10 Patients in Sodium Excretion following Oral Administration of 2000 mg of Chlorothiazide (mEq/24 Hr).

	Control	Drug	Increase
	43	167	124
	41	138	97
	45	162	117
	48	145	97
	42	174	132
	45	130	85
	47	147	100
	46	142	96
	41	143	102
	47	137	90
Avg	45	149	104
P value*			<.001

$$* t = \frac{\bar{x}}{\sqrt{\frac{n(n-1)}{Sx^2}}}.$$

There was no significant toxicity noted in the patients who received doses up to 2000 mg per day. Nausea and vomiting were not observed. Two patients complained of mild weakness and lethargy.

Discussion. Chlorothiazide is an effective orally administered diuretic agent which is a non-mercurial and apparently is not toxic. It is a potent inhibitor of the renal tubular reabsorption of sodium. It causes a minimal increase in excretion of bicarbonate (Fig. 3) and a considerable increase in excretion of chloride. An oral dose has a rapid onset of action (2 hours) and a short duration (12 hours) of effect. In current trials, it maintains its effectiveness when administered daily (in contrast to carbonic anhydrase inhibitors). It is slightly more effective after oral than after intravenous administration (Fig. 4) indicating complete or at least adequate absorption by the oral route. A 2 dose daily schedule is optimal. The maximum effect appears to be achieved at a dose of 2000 mg daily (1000 mg at breakfast and supper). No toxicity was observed in 20 patients who received the drug daily for 3 months. Calculation of "potency"(4,5) reveals that it is equivalent to 1 cc of meralluride (Mercuhydrin) given intramuscularly (Fig. 5) at a dose of slightly more than 1000 mg administered orally and at a dose of 2000 mg given orally in 2 divided doses, it is nearly as potent as 2 cc of meralluride (Fig. 5).

In comparing chlorothiazide to other oral diuretic agents (Fig. 5) at the maximum clini-

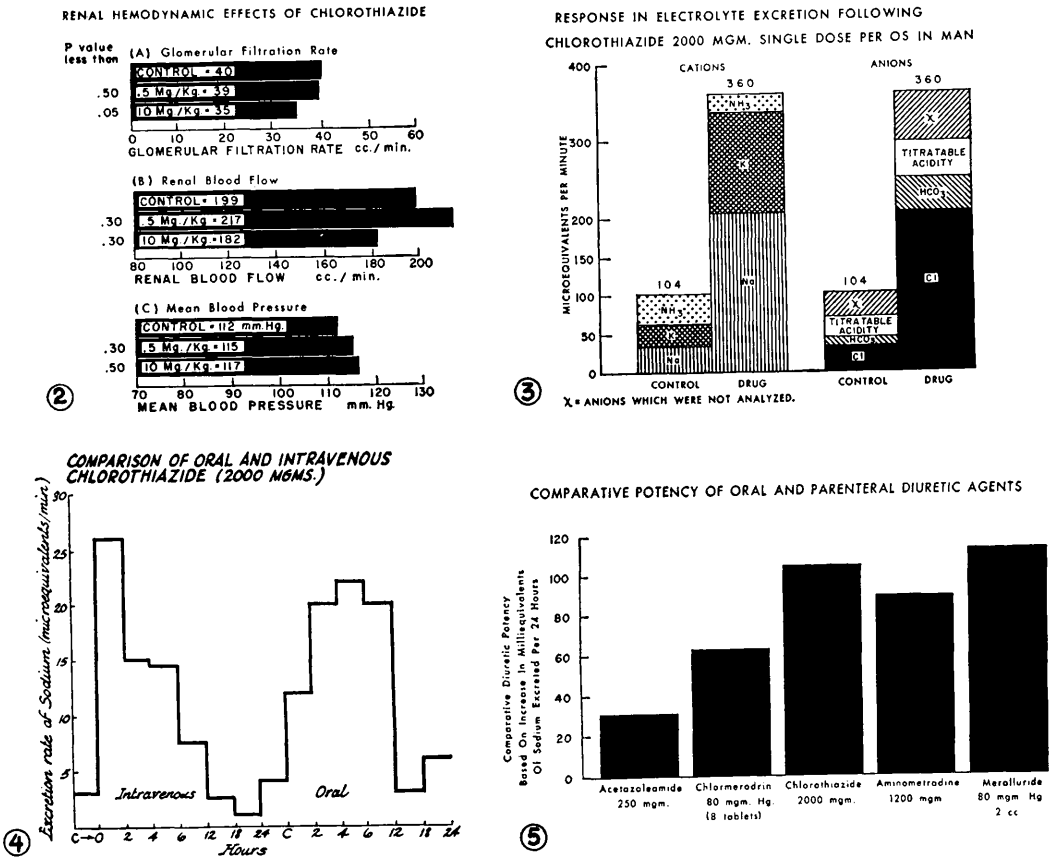

FIG. 2. When chlorothiazide is admin. to dogs intrav., there is no significant effect on renal hemodynamics.

FIG. 3. Electrolyte excretion pattern following oral admin. of chlorothiazide to man is characterized mainly by increase in excretion of sodium and chloride with lesser effects on potassium, bicarbonate and titratable acidity.

FIG. 4. Comparison of response to chlorothiazide given orally and intrav. Immediate response in sodium excretion after intrav. admin. was greater but total 24 hr increase in sodium was greater after oral admin.

FIG. 5. In producing an increase in excretion of sodium (as a measure of potency) chlorothiazide appears to be more powerful than chlormerodrin (Neohydrin) and acetazoleamide (Diamox). Doses larger than 250 mg of Diamox produce no greater effect. Doses in excess of 80 mg (8 tablets) of Neohydrin produce diarrhea or nausea in over 25% of the patients. A dose of 2000 mg of chlorothiazide is nearly as potent as 2 cc (equivalent to 80 mg Hg) of meralluride (Mercuhydrin) given intrav.

cally tolerated doses and employing the technic of potency estimation as previously described(4,5), it appears to be more potent in causing an increase in sodium excretion than chlormerodrin (Neohydrin) and acetazoleamide (Diamox).

Conclusions. Chlorothiazide at a daily dose of 2000 mg (500-2000 mg range) is effective as an oral diuretic agent with no demonstrable toxicity.

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