Effects of Chlorothiazide on Plasma Electrolytes in the Nephrectomized Dog. (25644)

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Chlorothiazide and structurally related compounds, orally effective diuretics, are widely used as antihypertensive agents. It has been suggested that chlorothiazide lowers blood pressure by means other than sodium excretion(1), but a definite mechanism has not been demonstrated. It was considered therefore, to be of interest to evaluate the effects of chlorothiazide on plasma electrolytes in the nephrectomized animal.

Methods. Fifty adult mongrel dogs were anesthetized with sodium pentobarbital (35 mg/kg) and arterial blood pressures were measured with a mercury manometer recording on a smoked drum. Acute bilateral nephrectomies were performed on all dogs from a ventral approach. Blood samples were taken prior to nephrectomy immediately prior to administration of experimental drugs, and 1, 1½ and 2 hours following beginning of drug injection. Blood hematocrits were determined, and plasma was analyzed for potassium and sodium with a Beckman flame photometer, and for pH with a Beckman pH meter. A control group of 8 animals received 10 ml 5% glucose in water one hour after nephrectomy followed by a 30 minute infusion of 50 ml 5% glucose. All experimental animals received a like amount of 5% glucose, and the second group of 9 animals had in addition 20 mg/kg chlorothiazide (Diuril) initially and in the 30 minute infusion. The third group of 13 animals were given 2.5 mg/kg mercury in the form of mercaptomerin (Thiomerin) as a prime dose and a like amount during the 30 minute infusion. The fourth group of 10 animals received 2 doses of 2 mg/kg hydrochlorothiazide (Hydrodiuril)* given in a like manner, and the last group of 10 animals similarly received a prime dose of 10 mg/kg acetazolamide (Diamox) and a 30 minute infusion of 10 mg/kg acetazolamide.

* Diuril and Hydrodiuril supplied by Merck, Sharp and Dohme, Inc.

Results. Table I summarized effects observed on plasma potassium and sodium concentrations of all drugs tested. There was no change in plasma sodium induced by any of the compounds. Plasma potassium values during the test period were unaltered in control animals, and in animals which received mercury or acetazolamide. However, in animals receiving chlorothiazide and hydrochlorothiazide there is a significant decrease in plasma potassium one hour after drug administration was started. This lowered potassium level continued for at least 2 hours after drug administration.

Fig. 1 presents graphically the change in plasma potassium seen in the 5 groups. At the 1½ and 2 hour post-treatment periods, potassium concentrations were decreased approximately 15% in both chlorothiazide and hydrochlorothiazide treated animals. Statistical treatment of the change in potassium values reveals that in these groups a significant ($P = <0.05$) reduction occurred when compared to changes seen in other groups.

There were no other significant differences between groups in the parameters studied. Mean arterial blood pressures of all animals averaged 126 mm Hg after nephrectomy and a mean decrease of 18 mm pressure was found after 2 hours. Decreases were similar in all groups. Hematocrits rose an average of 3% during the test period, with no intergroup differences found. Venous blood pH did not vary significantly in any group.

Discussion. A previous study from this laboratory(2) indicated that chlorothiazide decreases vascular reactivity in the anesthetized dog. The effect was not unique with chlorothiazide, being seen also with acetazolamide, dichlorphenamide and mercaptomerin (3).

The present results strongly suggest that chlorothiazide and hydrochlorothiazide have some effect on potassium distribution in the nephrectomized dog, an effect not shared by

TABLE I. Plasma Electrolyte Values in Nephrectomized Animals.

Group & No. animals	Control	Time in hr after drug 1	1½	2
		K, meq/l		
Control 8	3.70 ± .23†	3.52 ± .21	3.50 ± .24	3.60 ± .18
Chlorothiazide 9	3.98 ± .15	3.50 ± .05*	3.32 ± .14*	3.25 ± .17*
Mercury 13	3.75 ± .17	3.71 ± .20	3.67 ± .19	3.78 ± .20
Hydrochlorothiazide 10	3.74 ± .11	3.30 ± .13*	3.21 ± .11*	3.31 ± .11*
Acetazolamide 10	3.70 ± .19	3.74 ± .17	3.70 ± .16	3.75 ± .19
		Na, meq/l		
Control 8	141.4 ± 1.8	140.91 ± 2.1	141.94 ± 1.8	140.47 ± 1.9
Chlorothiazide 9	142.4 ± 2.5	143.61 ± 2.8	145.07 ± 2.6	142.54 ± 3.9
Mercury 13	147.7 ± 1.6	148.3 ± 2.8	147.7 ± 1.4	147.8 ± 1.1
Hydrochlorothiazide 10	148.0 ± 1.2	147.39 ± 1.2	146.76 ± 1.8	149.81 ± 1.2
Acetazolamide 10	148.9 ± 1.4	149.4 ± 1.5	148.5 ± 1.5	149.1 ± 1.6

* Significantly different from control values, P = <0.01. † ± stand. error.

mercaptomerin or acetazolamide. Whether this extrarenal effect is pertinent to observations that chlorothiazide reduces blood pressure in human hypertensives without necessarily altering body sodium, as reported by Winer(4), must be determined by future studies. These effects on potassium levels are observed using high doses of chlorothiazide and hydrochlorothiazide, and thus an easy extrapolation to the clinical situation is not possible. Acetazolamide, a potent carbonic anhydrase inhibitor, had no observable effect on plasma potassium, therefore the known carbonic anhydrase inhibition produced by high doses of chlorothiazide(5) is not considered responsible for the potassium changes.

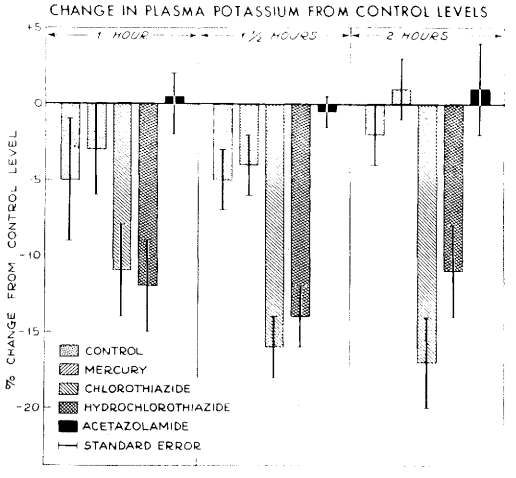

FIG. 1.

Summary. Chlorothiazide and hydrochlorothiazide significantly lowered plasma potassium levels in the nephrectomized dog after intravenous administration. Mercaptomerin and acetazolamide had had no such effect. Plasma sodium concentrations were not altered and no differential effects on pH, hematocrit, or blood pressure were seen in any groups of animals. These findings suggest that chlorothiazide and hydrochlorothiazide have an extrarenal effect not shared by mercaptomerin or acetazolamide.

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