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Localization of the Site of Action of Triamterene Diuretic.* (28356)

G. M. BALL AND J. A. GREENE, JR. (Introduced by W. S. Wilde)
Department of Physiology, University of Michigan Medical School, Ann Arbor

The pteridine compound triamterene has been reported to cause a sodium diuresis in rats, dogs(1) and man(2,3,4). The drug not only antagonizes the sodium retaining effect of 9α fluoro hydrocortisone and dl aldosterone (2,3), but also produces a sodium diuresis in adrenalectomized rats and dogs(1,4), presumably exerting its effect directly on the renal tubule by interfering with sodium reabsorption. The following studies were done to localize the site of action in the kidney of this agent using the stop flow method(5, 6).

Materials and methods. Eleven dogs weighing between 11-20 kg, anesthetized with pentobarbital 30 mg/kg body wt., were infused into the jugular vein at a rate of 10 ml/min with the following: mannitol, 20 g/100 ml; NaCl, 0.4 g/100 ml; and creatinine, 0.12 g/100 ml, all dissolved in Ringer's solution. The left ureter was exposed through a flank incision and urine collected from a polyethylene catheter pushed into the renal pelvis and tied securely in place. Eight minute ureteral occlusions were used. Mean aortic pressure was measured with a mercury manometer. Triamterene† dosage consisted of a single i.v. injection of 3 mg/kg body wt. followed by a sustaining infusion of 3 mg/kg body wt/hr incorporated into the mannitol infusion.

In 4 dogs a control occlusion was done just before drug administration and a second occlusion was done 45 minutes after the triamterene infusion was initiated. In 7 dogs an initial occlusion was done after 30 minutes of drug administration and was followed

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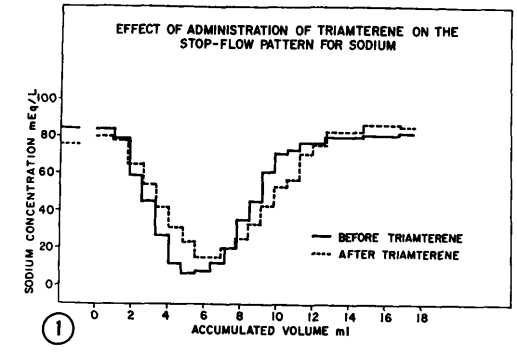

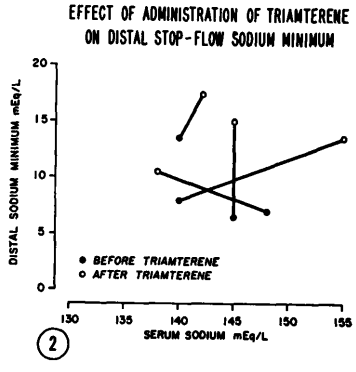

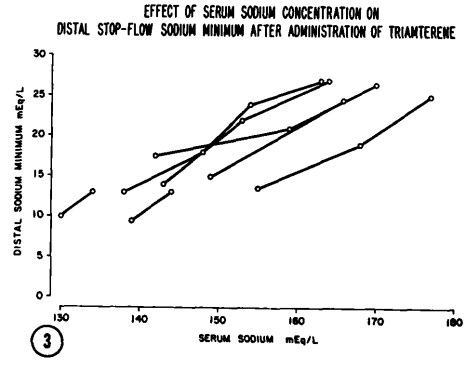

FIG. 1. Effect of triamterene on the stop flow Na pattern. Note elevation of Na minimum value from 6.5 meq/l to 15 meq/l with no corresponding change in free flow urine Na concentration or proximal tubular urine Na concentration.

FIG. 2. Distal sodium minimum concentration is increased 45 min after triamterene administration.

FIG. 3. Effect of elevation of serum Na concentration on the stop flow minimum Na concentration in dogs treated with triamterene.

by one to 3 successive occlusions each preceded by rapid intravenous administration of 80 to 120 ml 5% NaCl. Urine for 5 minute clearance was collected before each ureteral occlusion. Blood was taken at the midpoint of each clearance and at the midpoint of each stop flow ureteral occlusion. Sodium was determined by a Beckman direct reading flame photometer and creatinine was determined by the method of Bonsnes and Taussky(7).

Results. In 4 dogs in which 8 minute stop flow ureteral occlusions were done before and 45 minutes after triamterene was administered intravenously, there was an increase in the distal Na minimum concentration after drug. Fig. 1 shows the stop flow Na pattern before and 45 minutes after giving triamterene. Fig. 2 summarizes the sodium minimum data from the 4 experiments. Elevation in sodium minimum concentration averaged 5.5 meq/l urine with a range of 3.5 meq/l to 8.5 meq/l. There was no consistent change in the free flow urine Na concentration in these 4 experiments. Creatinine clearance also was unchanged. Mean aortic pressure remained constant.

When the serum Na concentration was progressively increased during the sustaining infusion of triamterene and successive 8 minute stop flow ureteral occlusions done, the distal Na minimum increased directly with serum Na concentration (Fig. 3). This was a significant increase and a consistent finding in all 7 dogs. The free flow urine sodium concentration also increased directly with serum Na concentration. Creatinine clearances showed small and inconsistent variations. Mean aortic pressure remained unchanged for any one experiment. The finding of increased Na minimum with increase in serum Na concentration during triamterene infusion is in contrast to the stability of the Na minimum concentration in untreated dogs when the serum Na is increased(8).

Discussion. These studies agree with those showing that the pteridine compound triamterene is capable of producing natriuresis(1, 2,3). It has been suggested that this compound has a direct effect on the distal tubule(3) where it antagonizes the action of aldosterone. The results presented here indicate that triamterene acted to increase Na minimum concentration. Elevation of Na minimum concentration during stop flow is evidence of a decreased ability of the distal tubule to reabsorb sodium. These studies

provide evidence to support the hypothesis that triamterene acts in the distal tubule to reduce Na reabsorption. While this drug acts in the same area of the tubule as aldosterone and causes effects on sodium reabsorption opposite to those attributed to aldosterone(9), competitive inhibition cannot be inferred. The fact that triamterene causes a natriuresis in adrenalectomized rats and dogs indicates that the drug acts by other mechanisms than aldosterone antagonism.

There were no consistent changes in urine flow rate, free flow urine Na concentration, and proximal urine Na concentration in 4 experiments where stop flow studies were done before and after triamterene. While proximal tubular events are not as easily assessed by the stop flow method(6), there is no evidence to support the idea of a proximal tubular action of the drug.

Summary. The pteridine compound triamterene was studied in 11 dogs using the stop flow method. These data support the hypothesis that the site of action of triamterene is the distal tubule of the kidney and that triamterene produces its natriuretic effect by reducing Na reabsorption in this area. No evidence was obtained for a proximal renal tubular effect.

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Effects on Smooth Muscle and Blood Vessels of Polypeptides Related to Bradykinin and to Kallidin. (28357)

BERNARD RUBIN, MARGARET H. WAUGH, ROBERT J. LAFFAN, ERIKA O'KEEFE AND BRADFORD N. CRAVER
The Squibb Institute for Medical Research, New Brunswick, N. J.

The physiological and pharmacological actions in experimental animals of synthetic or of naturally occurring bradykinin have been reviewed recently(1,2,3,4). Among the actions of bradykinin are transient vasodilatation of peripheral and coronary arteries, transient hypotension, increased capillary permeability, induction of edema, migration of leukocytes, production of pain after topical application to the base of a blister or after intra-arterial injection, bronchoconstriction in certain animal species, and stimulation or relaxation of excised gastrointestinal or uterine muscles.

Four of these actions (transient hypotension, coronary dilatation, increased capillary permeability, stimulation of excised uteri) provided the basis for comparing the actions of 9 synthetic analogues of bradykinin and one of kallidin.

Materials. Bradykinin and the 10 analogues were synthesized by members of our Organic Chemistry Section. Preliminary reports on the syntheses of these peptides as well as on their stimulant activities on excised rat uteri have appeared recently(5-9). The 10 peptides related to bradykinin or to kallidin were 1-citrulline bradykinin(5,6,8),