

Effect of Fluorohydrocortisone on Gastrointestinal and Renal Excretion of Cations by the Dog.* (23585)

JOHN W. POUTSIKA, BERNARD G. H. THOMAS AND CHARLES R. LINEGAR
(Introduced by B. N. Craver) (With the technical assistance of Gerald J. Lockwood,
Desiderio P. Canales and Milton Nasveschuk)

Squibb Institute for Medical Research, New Brunswick, N. J.

The effect of adrenal cortical steroids on excretion of sodium and potassium by the kidney has been extensively studied. In contrast, there is relatively little information concerning the effect of corticosteroids on the elimination of cations via the gastrointestinal tract. The influence of the adrenal gland on the gastrointestinal transfer of sodium was first reported by Clark(1). In more recent studies, Berger(2) and Emerson(3) showed that administration of desoxycorticosterone acetate (DOCA) to rats or humans decreased fecal excretion of sodium, thereby indicating an increase in the gastrointestinal absorption of this cation. In their studies, an effect of DOCA on potassium transfer in the gut was not conclusively shown.

The present experiments performed on intact dogs demonstrated the chronic effect of large daily doses of nine-alpha-fluorohydrocortisone (FF), a synthetic analogue of hydrocortisone, on fecal and urinary excretion of sodium and potassium with particular emphasis on cation balance.

Materials and methods. Eight dogs (8 to 14 kg) from 4 different litters were used in this experiment. Of each pair from a given litter, one was the test subject and the other the control. The animals were housed individually in metabolism cages and offered a daily food ration consisting of 280 g of Gaines meal wetted with 300 ml of distilled water. By our analysis the dry meal contained 0.15 mEq of sodium and 0.22 mEq of potassium per g or 42 and 62 mEq per daily ration respectively. Since all dogs consistently ate the total ration, their daily cation intake remained uniform throughout the study. Drinking water containing less than 0.2 mEq of sodium or potassium per liter was

supplied *ad libitum*. The test animals were injected intramuscularly once daily for 22 consecutive days with FF alcohol (1 mg/kg) suspended in an aqueous vehicle. Controls received the aqueous vehicle alone on a similar regimen. Measurements of water consumption and urinary and fecal outputs for a 48 hour interval were made weekly. Each dog was catheterized at the end of this period and the urine withdrawn was added to the total voided specimen. The specific gravity of the sample was determined and an aliquot saved for analysis. Stools were removed from the cages as soon as they had been passed and were stored in screw cap jars. Blood for serum was taken from the jugular vein at the mid-point of each collection period. *Sodium or potassium balance* over 48 hours was calculated by subtracting the sum total of the cation voided in urine and feces from the total quantity of that cation ingested with food. Since metabolic water and evaporative fluid losses were not accounted for, the difference between measured fluid intake and output was not considered an accurate gauge of water balance. Therefore, the conditions of the skin and mucous membranes and changes in body weight were the criteria used for estimating fluid balance. *Sodium and potassium analyses* were made on the P & I flame photometer(4) using lithium sulfate as an internal standard. Serum and urine were atomized after appropriate dilution with double distilled water. Stools were prepared for analysis as follows: each total 48 hour specimen was transferred to a tared Waring Blendor jar and its moist weight obtained by difference. The sample was blended and a 1 g aliquot removed for moisture analysis. Double distilled water was then added to the stool in sufficient quantity so that the entire sample could be reblended to a homogeneous paste. A 2 g aliquot of the paste was weighed

* We wish to thank Dr. J. Fried of Squibb Institute for the nine-alpha-fluorohydrocortisone used.

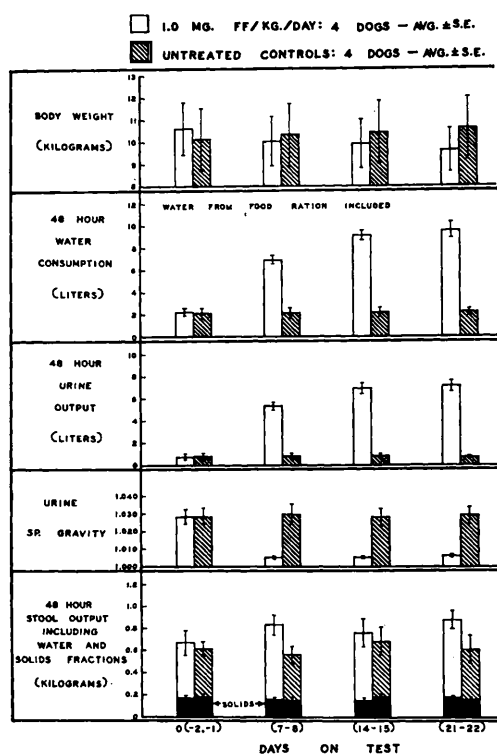


FIG. 1. Chronic effect of intramuscularly administered nine-alpha-fluorohydrocortisone (FF) on body weight, water consumption and urinary and fecal outputs of intact dogs.

in a 50 ml beaker, 10 ml of 20% chloride free nitric acid was added and the beaker covered with a short stem funnel. The sample was digested on a hot plate for about 2 hours or until the organic residue had a transparent, flocculent appearance. After cooling, the contents of the beaker were filtered quantitatively through prewashed Whatman #31 paper into a 100 ml volumetric flask containing the appropriate amount of lithium internal standard. The solution was diluted to volume and then atomized in the flame photometer. The significance of the data is evident from the graphs which include average values and their standard errors.

Results. The daily intramuscular administration of FF to dogs resulted in a striking increase in water consumption and urinary output and a decrease in urinary specific gravity (Fig. 1). Polydipsia and polyuria were well established by the end of the first week of dosage and increased during the

second and third weeks of treatment. Only a small increase was noted in the excretion of fecal water and there was no change in the quantity of fecal solids. The FF treated dogs exhibited no evidence of fluid retention; rather, at the completion of the 3 weeks' dosing they showed signs of mild dehydration such as loose, tacky skin and dry mucous membranes. Moreover these dogs sustained a 9% average loss in body weight as compared to a 5% gain for controls.

The chronic polyuria produced in dogs with daily doses of FF was associated with a significant increase in the urinary excretion of sodium and a concomitant decrease in the urinary excretion of potassium (Fig. 2). Conversely, the elimination of sodium in their

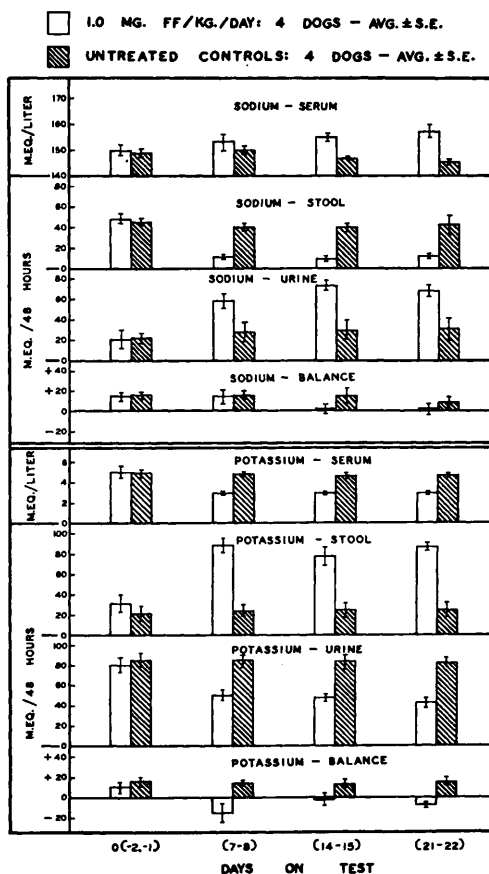


FIG. 2. Chronic effect of intramuscularly administered nine-alpha-fluorohydrocortisone (FF) on urinary and fecal excretions of sodium and potassium ions by intact dogs. Intake/48 hrs: sodium, 84 mEq; potassium, 124 mEq.

feces was sharply reduced and that of potassium was markedly increased. These changes resulted in a negative potassium balance which was reflected by an unequivocal drop in serum potassium and by slight muscular weakness. Alterations in sodium balance were not significant although directed toward the negative state. Despite the latter tendency, serum sodium levels in FF dogs showed a significant increase; this, in combination with their apparent dehydration, indicated a depletion of fluid in excess of salt.

Discussion. It is generally accepted that adrenal cortical hormones diminish the renal excretion of sodium and enhance the renal excretion of potassium. FF is reported to be extremely active in this respect (5,6). FF exerted a similar influence on sodium and potassium voidance from the gastrointestinal tract as attested to by the fecal cation changes sustained by test dogs in our experiments. Apparently, the urinary excretion of sodium and potassium in these animals was altered to offset the shift of fecal cations. Since, however, a negative potassium balance and hypokalemia with muscular weakness were produced in FF dogs, it would appear that their renal mechanism was unable to limit adequately the excretion of potassium; this effect may have been due to the profound diuresis also noted in these animals. Conversely, since no significant change was produced in sodium balance and serum sodium became elevated in the presence of dehydration, it would also appear that their renal mechanism limited the excretion of sodium,

despite the copious flow of urine. Thus, although an atypical urinary pattern of cations was observed in these experiments, it is considered that the effect of FF on cation transfer in the kidney was analogous to its effect on cation transfer in the gut; with both organs functioning to abase sodium and augment potassium excretion.

Summary. The daily intramuscular administration of large doses (1 mg/kg) of nine-alpha-fluorohydrocortisone (FF) to intact dogs resulted in a chronic state of polydipsia and polyuria with gross evidence of mild dehydration. With FF treatment the fecal excretion of sodium was reduced and that of potassium enhanced but the converse was true for urinary excretion. These changes did not significantly alter sodium balance although serum sodium was elevated, but resulted in a negative potassium balance which was indicated by a drop in serum potassium and muscular weakness.

1. Clark, W. G., *PROC. SOC. EXP. BIOL. AND MED.*, 1939, v40, 468.
2. Berger, E. Y., Quinn, G. P., and Homer, M. A., *ibid.*, 1951, v76, 601.
3. Emerson, K., Jr., Kahn, S. S., and Jenkins, D., *Ann. N. Y. Acad. Sci.*, 1953, v57, 280.
4. Process and Instruments Co., Brooklyn, N. Y.
5. Liddle, G. W., Pechet, M. M., and Bartter, F. C., *Science*, 1954, v120, 496.
6. Swingle, W. W., Baker, C., Eisler, M., Lebrrie, S. J., and Brannick, L. J., *PROC. SOC. EXP. BIOL. AND MED.*, 1955, v88, 193.

Received September 20, 1957. P.S.E.B.M., 1957, v96.

Thymus Specificity in Lethally Irradiated Mice Treated with Rat Bone Marrow. (23586)

N. GENGOZIAN,* I. S. URSO, C. C. CONGDON, A. D. CONGER, AND T. MAKINODAN
Biology Division, Oak Ridge National Laboratory,† Oak Ridge, Tenn.

The transplantation and repopulation of

*Public Health Service Research Fellow of the National Cancer Institute, N.I.H.

†Operated by Union Carbide Nuclear Co. for the U. S. Atomic Energy Commission.

erythrocytic, granulocytic, and platelet precursors in lethally irradiated mice injected with heterologous (rat) bone marrow has been demonstrated by immunohematologic, cytochemical, and chromosome marker tech-