

## Effects of Triamcinolone and of Desoxycorticosterone on Renal Function in Sheep (39012)

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When dogs are treated for several days with a mineralocorticoid drug such as desoxycorticosterone acetate, the hypokalemic effects of the steroid are accompanied by a decrease in the kidney's capacity to elaborate a concentrated urine (1). These experimental results in dogs are similar to the changes in kidney function observed in potassium-depleted rats (2) and in humans with primary hyperaldosteronism (3). The effects of the glucocorticoids cortisone and cortisol on kidney function in the presence of adequate adrenal cortical secretion are less definitive, the results of their administration being complicated by striking species differences (4) as well as their inherent mineralocorticoid potential (5). The purpose of this series of experiments was to compare the effects of triamcinolone, a glucocorticoid with virtually no effects on renal electrolyte metabolism (5), with the effects of desoxycorticosterone on renal function in sheep.

**Materials and methods.** Eleven adult ewes, body weight 35–55 kg, were purchased from local sources and were maintained in the Animal Care Department under conditions of constant temperature and humidity. The sheep were given free access to water, high-quality alfalfa hay, grain (Omolene) and a salt mixture composed of a 1:1 ratio (w/w) of sodium chloride and sodium bicarbonate. Experiments were conducted only after the sheep had been allowed to adapt to the animal facilities for at least 4 weeks. Grain consumption averaged 2 lb/day/sheep, and preliminary studies on urea clearance indicated that the  $U/P_{\text{urea}}:U/P_{\text{inulin}}$  ratios during hyponatremia ranged from 0.40 to 0.77 when  $U/P_{\text{inulin}}$  was greater than 200. On the basis of these results, the diet can be characterized as an "adequate protein" diet (6, 7). Ingestion of the salt mixture varied greatly, some sheep consuming 2–3 lb/week while others consumed lesser amounts.

Experiments were performed in tandem,

each sheep serving as its own control. In three of the five experiments with triamcinolone and in five of the six experiments with desoxycorticosterone, the control period preceded the period of drug treatment. The remaining experiments were performed in the reverse order, the treatment period preceding the control. The sheep which were to be treated with and the two previously treated with triamcinolone were given daily intramuscular injections of 0.154 M NaCl solution for 10–17 days. The sheep which were to be treated with and the one sheep previously treated with desoxycorticosterone acetate were given daily intramuscular injections of corn oil during the control period of 10–17 days. A period of 10–14 days elapsed between the control renal-function studies and the start of the treatment period. With those sheep given the steroids first, the interval between the renal function studies and the start of the control period was 4–5 weeks. Desoxycorticosterone acetate (Nutritional Biochemicals Corp.) was suspended in corn oil and administered intramuscularly, 0.1 mg/kg body weight/day for 10 days (three sheep) or 17 days (three sheep). Triamcinolone acetate (Vetalog Parenteral, E. R. Squibb and Sons) was administered intramuscularly, 0.1 mg/kg body weight/day for 10 days (two sheep) or 17 days (three sheep).

Renal-function studies were performed twice in each sheep, once at the end of the control period and once at the end of the treatment period. The last injection of the drug or the vehicle was given at 8:00 AM, water was withdrawn and renal-function studies were performed the following day according to methods previously described (7, 8). After a 2-hr urine collection period, a solution of 20% mannitol in 0.154 M NaCl was given intravenously in increasing increments over a period of 2–2.5 hr.

Initial experiments had indicated that maximum free water clearance rates ( $T^{\circ}\text{H}_2\text{O}$ )

in sheep during mannitol-induced diuresis occurred when  $V$  (urine flow-rate) was approximately 16.0 ml/min. When  $V$  exceeded 18–20 ml/min, changes in  $T^{\circ}\text{H}_2\text{O}$  were erratic. In some experiments there were continued increases, in others no changes or even decreases. These results are quantitatively similar to other observations in sheep (9). Thus, the objective of the mannitol infusion was to attain three consecutive 15-min periods in which  $V$  was relatively stable at a rate greater than 14 and less than 20 ml/min. These periods were used for the determination of renal clearances during mannitol diuresis.

Glomerular filtration rate (GFR) as the inulin clearance, urine and plasma osmolality, osmolal clearance and free water reabsorption, and Na and K concentrations in plasma and in urine were determined according to methods previously described (8). The percent filtered Na and K which was excreted into urine was calculated according to the formula  $[(U_{\text{Na}} \text{ (or } U_{\text{K}}) \times V / P_{\text{Na}} \text{ (or } P_{\text{K}}) \times \text{GFR}] \times 100$ .

All sheep treated with desoxycorticosterone acetate became hypokalemic ( $P_{\text{K}} < 2.8$  mequiv/l) within 3–4 days, thereby providing an indication of the biological effectiveness of this dose. The biological effectiveness of the dose of triamcinolone acetate used was difficult to assess; for example, no changes in plasma electrolytes, urea or glucose concentrations were observed. However, other experiments in sheep have shown that the dose of triamcinolone acetate used reduced by 90% *in vitro* cholesterol synthesis by adrenal cortical tissue (10).

**Results.** Treatment with triamcinolone was not accompanied by significant changes in plasma concentrations of either K or Na (Table I). Treatment with desoxycorticosterone acetate was accompanied by a significant decrease in plasma K concentrations but no significant change in plasma Na concentrations (Table I).

An increase in GFR and a small increase in  $T^{\circ}\text{H}_2\text{O}$  during hydropenia were the significant changes that accompanied treatment with triamcinolone (Table II). Decreases in the percent filtered Na excreted into urine during mannitol diuresis were observed con-

TABLE I. PLASMA SODIUM AND POTASSIUM CONCENTRATIONS (MEQUIV/L) IN CONTROL, TRIAMCINOLONE AND DESOXYCORTICOSTERONE-TREATED SHEEP<sup>a</sup>

Plasma cation	Control	Treatment	Mean change
Triamcinolone ( $N = 5$ )			
Na	148.8±3.4	146.0±2.7	<sup>b</sup>
K	4.0±0.2	3.8±0.5	<sup>b</sup>
Desoxycorticosterone ( $N = 6$ )			
Na	146.8±3.9	150.1±2.0	<sup>b</sup>
K	4.3±0.3	2.1±0.1	-2.3±0.2 <sup>c</sup>

<sup>a</sup> All results in this and subsequent tables are expressed as the mean ± 1 standard error of the mean.

<sup>b</sup> No consistent changes, mean not determined.

<sup>c</sup> Significance of mean change:  $P(t) < 0.001$ .

sistently in the triamcinolone-treated sheep but with large variations in the magnitude of the changes (Table II). The relationship between urine flow and Na excretion during mannitol diuresis is shown in Fig. 1.

The changes in renal function accompanying desoxycorticosterone treatment are summarized in Table III. GFR increased and there was an increase in urine flow-rate when compared with control values. A highly significant decrease was recorded in the osmolality of urine after 24 hr of water deprivation. Two prominent changes in renal function were observed during mannitol diuresis in the desoxycorticosterone-treatment period: 1) A significant decrease in  $T^{\circ}\text{H}_2\text{O}$  and 2) a significant decrease in the percent filtered Na excreted into urine. The relationship between urine flow-rates and Na excretion is shown in Fig. 1.

**Discussion.** A clear definition of triamcinolone effects on renal function in sheep, other than the increase in GFR, has not been obtained. Some decrease in the ability to elaborate a concentrated urine may have been associated with triamcinolone treatment, but there was no decrease in  $T^{\circ}\text{H}_2\text{O}$  during mannitol diuresis. Triamcinolone, therefore, did not impair the kidney's capacity to concentrate urine.

There may also have been an increase in Na reabsorption during mannitol diuresis in triamcinolone-treatment periods when compared to control responses, particularly

TABLE II. EFFECTS OF TRIAMCINOLONE ON SEVERAL ASPECTS OF RENAL FUNCTION IN SHEEP ( $N = 5$ ).

Renal function	Control	Triamcinolone	Mean change
<b>Hydropenia</b>			
GFR (ml/min)	70 ± 7.9	101 ± 8.5	+31 ± 6.9 <sup>a</sup>
$V$ (ml/min)	0.22 ± 0.04	0.70 ± 0.26	+0.44 ± 0.28
$U_{osm}$ (mOsm/kg H <sub>2</sub> O)	2183 ± 263	1576 ± 378	-607 ± 361
$T^cH_2O$ (ml/min/100 ml GFR)	1.35 ± 0.15	1.82 ± 0.14	+0.47 ± 0.12 <sup>a</sup>
(Na excreted/Na filtered) × 100	0.25 ± 0.17	0.44 ± 0.12	<sup>c</sup>
(K excreted/K filtered) × 100	20.5 ± 10.4	31.9 ± 10.4	<sup>c</sup>
<b>Mannitol diuresis</b>			
GFR (ml/min)	77 ± 7.5	106 ± 9.7	+29 ± 6.2 <sup>b</sup>
$T^cH_2O$ (ml/min/100 ml GFR)	6.42 ± 0.60	7.20 ± 0.81	<sup>c</sup>
Na excreted/Na filtered) × 100	13.49 ± 2.77	5.65 ± 0.60	-7.84 ± 2.89
K excreted/K filtered) × 100	63.5 ± 20.1	50.7 ± 6.7	<sup>c</sup>

<sup>a</sup> Significance of mean change:  $P(t) < 0.02$ .

<sup>b</sup> Significance of mean change:  $P(t) < 0.01$ .

<sup>c</sup> No consistent changes, mean not determined.

when the increases in filtered Na are taken into consideration. Renal cells contain specific cytoplasmic receptors for glucocorticoid as well as mineralocorticoid hormones, and it has been proposed that glucocorticoid receptors may be involved with metabolic processes such as gluconeogenesis (11, 12). It is also possible that all "adrenal active" steroids whether glucocorticoid or mineralocorticoid stimulate Na reabsorption.

Desoxycorticosterone administration to sheep was accompanied by decreases in the extent to which urine can be concentrated and decreases in solute-free water reabsorption during mannitol diuresis, deficits in kidney function probably resulting from mineralocorticoid induced hypokalemia (1, 2, 3). In these aspects of renal function, sheep respond to desoxycorticosterone in a manner similar to other species.

No changes in urinary Na or K excretion were observed during the hydropenic periods in desoxycorticosterone treated sheep. It is likely that "escape" from mineralocorticoid-induced Na retention had occurred prior to the 10th day of continued desoxycorticosterone administration (4, 13, 14), and therefore urinary Na excretion could be comparable to control levels. That increased urinary K excretion was not observed does merit some notice. The rumen assumes a dominant role in electrolyte and water metabolism (15, 16), and it is possible that mineralocorti-

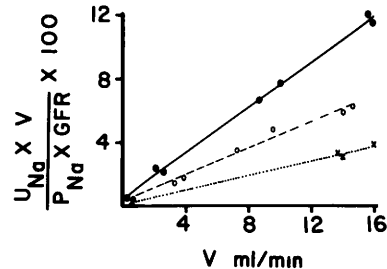


FIG. 1. Relationship between urine flow rates ( $V$ ) and Na excretion (expressed as the percent filtered Na excreted into urine) in control periods (solid circles, solid line) after treatment with triamcinolone (open circles, broken line) and after treatment with desoxycorticosterone ( $\times$ , dotted line) during mannitol diuresis.

coid-induced hypokalemia may result from steroid effects on the profuse salivary secretion (17) and on ion transport by ruminal as well as intestinal mucosa. The hypokalemia secondary to ACTH administration to sheep (presumably from the component of mineralocorticoid activity of the steroids secreted in response to ACTH) also was not accompanied by increased urinary K secretion (14). Although the experiments reported here are preliminary in nature, they indicate that changes in renal K metabolism may not be prominent effects of mineralocorticoid activity in sheep.

The results of the mannitol diuresis experiments revealed a prominent component of

TABLE III. EFFECTS OF DESOXYCORTICOSTERONE ON SEVERAL ASPECTS OF RENAL FUNCTION IN SHEEP ( $N = 6$ ).

Renal function	Control	Desoxycorticosterone	Mean change
Hydropenia			
GFR (ml/min)	67 ± 3.9	112 ± 8.8	+45 ± 9.9 <sup>a</sup>
$V$ (ml/min)	0.25 ± 0.02	0.77 ± 0.13	+0.53 ± 0.08 <sup>a</sup>
$U_{osm}$ (mOsm/kg H <sub>2</sub> O)	2246 ± 81	1125 ± 241	-1121 ± 246 <sup>a</sup>
$T^{\circ}H_2O$ (ml/min/100 ml GFR)	1.48 ± 0.21	1.32 ± 0.42	<sup>c</sup>
(Na excreted/Na filtered) × 100	0.13 ± 0.05	0.15 ± 0.07	<sup>c</sup>
(K excreted/K filtered) × 100	30.6 ± 9.9	35.3 ± 8.9	<sup>c</sup>
Mannitol diuresis			
GFR (ml/min)	79 ± 3.7	115 ± 10.0	+36 ± 12.0 <sup>b</sup>
$T^{\circ}H_2O$ (ml/min/100 ml GFR)	5.74 ± 0.81	2.33 ± 1.16	-3.41 ± 0.58 <sup>a</sup>
(Na excreted/Na filtered) × 100	14.25 ± 1.60	3.98 ± 0.95	-10.27 ± 1.46 <sup>a</sup>
(K excreted/K filtered) × 100	79.1 ± 16.9	131.4 ± 23.3	<sup>c</sup>

<sup>a</sup> Significance of mean change:  $P(t) < 0.01$ .

<sup>b</sup> Significance of mean change:  $P(t) < 0.05$ .

<sup>c</sup> No consistent changes, mean not determined.

Na retention during continued desoxycorticosterone administration. Despite the increased amount of filtered Na (a consequence of the increased GFR) a considerably larger percent of filtered Na and total quantity of Na had been reabsorbed against the heavy osmotic diuresis following desoxycorticosterone treatment than during the control periods. These results are consistent with the demonstration that hypersecretion of aldosterone in humans results in a degree of continued Na retention with expansion of the extracellular fluid volume (18) although "escape" from massive Na retention likely had occurred (13).

Mannitol diuresis unmasked Na-retaining effects of triamcinolone and to a greater extent of desoxycorticosterone not apparent in the hydropenic state. Thus glucocorticoid as well as mineralocorticoid hormones of the adrenal cortex may participate in expansion of the extracellular volume and, under appropriate circumstances, may be implicated in the genesis or maintenance of hypertension. Whether this Na-retaining effect is related to triamcinolone and desoxycorticosterone-induced increased GFR remains to be determined.

**Summary.** Sheep were treated for 10 or 17 days with triamcinolone acetate, 0.1 mg/kg body weight/day, or desoxycorticosterone acetate, 0.1 mg/kg body weight/day, and the results of renal function studies during

hydropenia and mannitol diuresis were compared with respective control periods. GFR was increased and urine concentration was unimpaired by treatment with triamcinolone. A consistent decrease in mannitol-induced Na excretion was observed, but with large variations in the mean change, in triamcinolone treatment periods. Treatment with desoxycorticosterone resulted in an increased GFR but with impaired urine concentrating capacity. The hypokalemia produced by desoxycorticosterone was not accompanied by an increase in urinary K excretion. During mannitol diuresis in sheep treated with desoxycorticosterone, there was a significant decrease in Na excretion when compared with control periods.

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