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The Effect of Dexamethasone on Urinary Acidification (39089)

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(Introduced by Murray Epstein)

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It is well recognized that mineralocorticoids enhance renal acid excretion (1, 2). The effect of glucocorticoids on urinary acidification, however, has not received much attention. In two studies (2, 3) acute administration of large doses of prednisolone and hydrocortisone was associated with a rise in urine pH and decreased net acid excretion. On the other hand, it has been suggested that glucocorticoids, either of endogenous or exogenous origin, can induce metabolic alkalosis which implies, in part, an increase in urinary acid excretion. For example, chronic cortisone acetate administration may induce a metabolic alkalosis (4), and patients with Cushing's syndrome often develop a similar abnormality (5). Since the glucocorticoid compounds whose effects on renal acidification have previously been studied (2–4) all have some mineralocorticoid activity (6), the present study was designed to evaluate renal acidification in normal subjects after acute and chronic administration of moderately large doses of dexamethasone, a glucocorticoid steroid with little or no mineralocorticoid activity.

Methods. Seven healthy volunteers, ages 18 to 39, without clinical or laboratory evidence of renal, cardiovascular, endocrine, gastrointestinal, or psychiatric disease, were selected for study. No subject had hypokalemia, clinical or laboratory evidence of urinary tract infection, or was taking medications known to influence urinary acidification. All were outpatients following their customary diet and activities.

Six subjects underwent evaluation of renal acidification before and at the end of one week's ingestion of dexamethasone, 1.5 mg three times a day. One-third of the total dose was administered personally by one of the investigators; pill counting also indicated excellent patient compliance. During dexamethasone administration the subjects were weighed and interviewed daily. Serum creatinine and electrolytes were measured at the beginning and end of the week.

Renal acidification was evaluated with a short duration oral NH_4Cl acid-load test previously described (7). The patients were water restricted overnight and urine specimens were obtained by spontaneous voiding starting at 8:00 AM and were collected under mineral oil. At 8:00 AM arterial and venous blood samples were drawn for baseline measurements. Over the next hour NH_4Cl in gelatin capsules was ingested at a dose of 0.1 g/kg of body weight. Venous blood was obtained 2 and 6 hr after the completion of NH_4Cl administration, and urine was collected hourly for 6 hr with the subjects remaining supine throughout except to void.

In a separate study, four subjects were given dexamethasone intravenously. Eight weeks previously, three of the four had received dexamethasone for 1 week as already described. Starting at 7:00 AM, urine was collected hourly for 9 hr as described above. At 9:00 AM, 7.5 mg of dexamethasone sodium phosphate were given intravenously. Blood samples were collected as before. A study without dexamethasone (control) had been performed in identical fashion in each subject on the previous day.

Signed informed consent was obtained from each subject after the nature of the procedures had been fully explained. The study was approved by the Committee on Human

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Experimentation of the Miami Veterans Administration Hospital. There were no adverse effects.

Determinations of the pH and P_{CO_2} of blood and urine were completed within 5 min of collection using a Radiometer Acid-Base Cart ABC-1. All urine and venous blood samples were measured for concentrations of sodium, potassium, phosphorus, creatinine, and total solutes, and urinary titratable acid (TA) and ammonium (NH_4) content were also measured by methods previously reported (7). Blood bicarbonate concentrations (HCO_3) were calculated from the Henderson–Hasselbalch equation assuming a pKa of 6.10 and a solubility coefficient of 0.0301; urine bicarbonate concentrations were calculated similarly using a pKa of $6.33 - 0.5\sqrt{\mu}$ and a solubility coefficient of 0.0309 (8). Net acid excretion ($U_{NA}V$) was calculated as the sum of ammonium ($U_{NH_4}V$) and titratable acid ($U_{TA}V$) less bicarbonate ($U_{HCO_3}V$) excretion: $U_{NA}V = U_{NH_4}V + U_{TA}V - U_{HCO_3}V$.

Student's t test (9) was used to compare all the values before and after dexamethasone administration. Mean pH values reported are the direct arithmetic mean. Mean pH data were also calculated by converting individual pH values into hydrogen ion concentration, taking this arithmetic mean and then converting back into pH. Statistics were done both with pH and with hydrogen ion concentration. Since the results were not different using the two methods of calculation, the data are presented in pH units.

Results. Acid-loading before and after oral dexamethasone. There were no significant changes in body weight, blood urea nitrogen, serum electrolyte concentrations, and endogenous creatinine clearance following dexamethasone administration for 1 week. There was a slight but statistically significant decrease in serum sodium concentration (Table I).

In all subjects the control baseline arterial and venous pH, P_{CO_2} and (HCO_3) were within the normal range. After dexamethasone, baseline arterial and venous blood gases revealed a tendency towards an increase in pH and a decrease in P_{CO_2} and bicarbonate concentration (Table II). When the individual arterial values after dexamethasone were plotted on an acid-base diagram, they all fell into the range of chronic respiratory alkalosis.

Prior to NH_4Cl administration, baseline urine pH was higher ($P < 0.05$) after dexamethasone, while the baseline excretion rates of NH_4, TA and NA were similar (Table III). Baseline urinary bicarbonate, although trivial (2.6 ± 1.1 μEq/min), was higher ($P < 0.05$) after dexamethasone than it was before (0.9 ± 0.5 μEq/min). After adequate systemic acidification (Table III), urine pH decreased normally to 5.3 or less in every subject both before and after dexamethasone, and there were no significant differences in the minimal urine pH achieved or in the maximal excretion rates for TA, NH_4 and NA.

Effect of intravenous administration of dexamethasone on urinary acid and electrolyte excretion. Fig. 1 shows the effect of a single intravenous dose of dexamethasone on the hourly urine pH. After dexametha-

TABLE I. BODY WEIGHT AND LABORATORY VALUES BEFORE AND AFTER ORAL DEXAMETHASONE IN SIX HEALTHY VOLUNTEERS

	Before dexamethasone	P value	After dexamethasone[a]
Weight (kg)	70 ±7	NS[b]	71 ±7
BUN (mg/100 ml)	13 ±2	NS	14 ±3
Serum phosphorus (mg/100 ml)	3.2 ±0.2	NS	3.6 ±0.1
Serum sodium (mEq/liter)	141 ±0.3	<0.01	139 ±0.5
Serum chloride (mEq/liter)	101 ±1	NS	97 ±1
Serum potassium (mEq/liter)	4.6 ±0.1	NS	4.6 ±0.1
Blood bicarbonate (mEq/liter)	25 ±1	NS	24 ±1
Creatinine clearance (ml/min)[c]	146 ±12	NS	146 ±12

[a] Daily dose of 4.5 mg for 1 week. Values are mean ± SEM.

[b] NS = statistical difference nonsignificant, $P > 0.05$.

[c] Average of four collection periods for each patient during acid-loading.

TABLE II. BASELINE ARTERIAL BLOOD ACID-BASE STATUS AND CHANGES IN VENOUS BLOOD IN RESPONSE TO NH_4Cl BEFORE AND AFTER ORAL DEXAMETHASONE IN SIX HEALTHY VOLUNTEERS

		Venous			Arterial		
		pH	P_{CO_2} (mm Hg)	HCO_3 (mEq/liter)	pH	P_{CO_2} (mm Hg)	HCO_3 (mEq/liter)
Before dexamethasone	B[a]	7.31 ± 0.01	51 ± 2	25 ± 1	7.38 ± 0.01	38 ± 2	22 ± 1
	A[a]	7.24 ± 0.01	50 ± 2	21 ± 1	—	—	—
After dexamethasone	B[a]	7.34 ± 0.01[b]	46 ± 3[c]	24 ± 1	7.39 ± 0.01	33 ± 2	19 ± 1[c]
	A[a]	7.26 ± 0.01	46 ± 2	20 ± 1	—	—	—

[a] B = before acid-loading and A = lowest value after acid-loading. Values are mean ± SEM.
[b] $P < 0.02$ before vs after dexamethasone.
[c] $P < 0.05$ before vs after dexamethasone.

sone, the maximum increase of urine pH was 1.86 ± 0.20 above baseline. This increment was significantly greater ($P < 0.05$) than that resulting from diurnal variation observed on the control day (1.20 ± 0.30). Thus, the maximal urine pH on the day of dexamethasone administration (7.09 ± 0.20) was significantly higher ($P < 0.02$) than on the control day (6.18 ± 0.20).

At the time of the highest urine pH, the venous pH, P_{CO_2}, and (HCO_3), and the urine flow rate, osmolality, and creatinine clearance were comparable on the two days (Table IV). After dexamethasone, serum phosphorus decreased and urine potassium increased significantly, and there was a tendency for serum potassium concentration and urinary sodium excretion to increase and for the excretion of phosphorus, titratable acid, and ammonium to decrease, although these changes did not achieve statistical significance (Table IV).

Discussion. After 1 week of dexamethasone administration, the renal response to acid-loading in the present study was unchanged both in terms of ability to lower pH and to excrete acid. To our knowledge, there are no previous reports in the literature on the effects of glucocorticoids on the renal response to a standardized acid-loading test.

Chronic dexamethasone administration was associated with the development of mild respiratory alkalosis. Although we have no apparent explanation for this finding, similar changes were found in both arterial and venous blood samples and were evident in each of the patients when the individual data were plotted on an acid-base diagram. Of

TABLE III. URINARY CHANGES IN RESPONSE TO NH_4Cl BEFORE AND AFTER DEXAMETHASONE IN SIX HEALTHY VOLUNTEERS

		pH	$U_{TA}V$ (μEq/min)	$U_{NH_4}V$ (μEq/min)	$U_{NA}V$ (μEq/min)
Before dexamethasone	B[a]	5.75	10	25	33
		±0.22	±3	±8	±10
	A[a]	4.94	19	62	80
		±0.08	±3	±11	±13
After dexamethasone	B[a]	6.02	9	24	30
		±0.17[b]	±2	±3	±4
	A[a]	4.94	27	56	82
		±0.06	±3	±7	±9

[a] B = before acid-loading and A = maximal or minimal value after acid loading. Values are mean ± SEM.
[b] $P < 0.05$ from before dexamethasone.

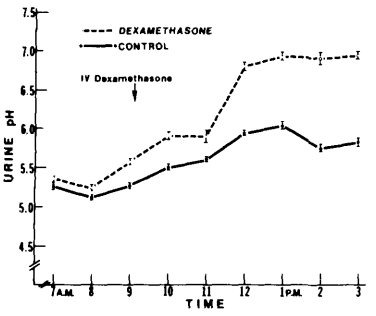

FIG. 1. Urinary pH changes following the intravenous administration of 7.5 mg of dexamethasone phosphate in four healthy volunteers. Open circles connected by broken lines represent the experimental (dexamethasone) day and closed circles connected by solid lines are those from the previous (control) day. Vertical bars show ±1 SD. The mean difference achieved statistical significance in the last 2 hr; $P < 0.025$ (for the preceding 2 hr, $0.1 > P > 0.05$).

TABLE IV. EFFECT OF THE INTRAVENOUS ADMINISTRATION OF DEXAMETHASONE ON SERUM AND URINARY ELECTROLYTES IN FOUR HEALTHY VOLUNTEERS[a]

	Before dexamethasone	*P* value	After dexamethasone
Urine volume (ml/min)	1.6 ± 0.3	NS[b]	1.9 ± 0.4
Urine osmolality (mOsm/Kg H_2O)	341 ± 60	NS	430 ± 53
Creatinine clearance (ml/min)	120 ± 18	NS	132 ± 16
Sodium excretion (μEq/min)	109 ± 18	NS	228 ± 86
Potassium excretion (μEq/min)	31 ± 10	$P < 0.05$	67 ± 10
Phosphorus excretion (μg/min)	466 ± 68	NS	195 ± 90
$U_{TA}V$ (μEq/min)	5 ± 3	NS	0
$U_{NH_4}V$ (μEq/min)	18 ± 2	NS	14 ± 2
Serum phosphorus (mg/100 ml)	4.1 ± 0.2	$P < 0.005$	3.5 ± 0.3
Serum potassium (mEq/liter)	3.9 ± 0.2	NS	4.1 ± 0.2
Venous pH	7.34 ± 0.01	NS	7.34 ± 0.01
Venous Pco_2 (mm Hg)	50 ± 3	NS	46 ± 1
Venous (HCO_3) (mEq/liter)	26 ± 1	NS	24 ± 1

[a] At the time of the highest urine pH. Values are mean ± SEM.
[b] NS = statistical difference nonsignificant, $P > 0.05$.

interest, another steroid compound, progesterone, is known to increase alveolar ventilation (10).

Acute intravenous administration of dexamethasone produced a significant increase in urine pH and a trend towards a decrease in ammonium and titratable acid excretion without changes in arterial blood gas values, creatinine clearance, or urine flow rate. After acute dexamethasone administration, urine potassium increased and serum phosphorus decreased significantly, as previously reported after hydrocortisone administration (3).

There are few studies concerning the effect of glucocorticoids on urinary acidification. Mills *et al.* (3) studied the acute effect of hydrocortisone given intravenously at different times of the day upon the excretion of sodium, potassium, and acid by the kidney. They noted increased urine pH and potassium excretion and decreased sodium excretion and suggested that glucocorticoids promote tubular sodium reabsorption in exchange for secreted potassium, with a decline in total hydrogen ion secretion. Aldosterone, on the other hand, facilitated renal acid secretion (3).

Similar findings were reported by Bartter and Fourman (2) with prednisolone. These authors showed that the acute intravenous administration of prednisolone to healthy volunteers, in dosages approximately equivalent in glucocorticoid effect to those of dexamethasone used in the present study, was associated with a decrease in urinary titratable acid and ammonium and a rise in urine pH. Again, an opposite effect resulted from the administration of mineralocorticoids. In the present study using a corticosteroid almost devoid of mineralocorticoid activity, the changes seen were similar in nature to those of the previously reported studies (2, 3) with prednisolone and hydrocortisone.

We have no adequate explanation for the rise in urine pH after acute dexamethasone administration. Since potassium excretion also increased after dexamethasone, the possible relationship between tubular hydrogen and potassium secretion should be considered. The infusion of potassium salts is known to induce bicarbonaturia (12). This presumably is the result of a shift of potassium into and hydrogen ion out of renal tubular cells, with subsequent decreased hydrogen ion secretion (13). This situation may not be comparable in the present study, however, since the simultaneous rise in both serum and urinary potassium is more consistent with an exit of potassium from cells, which would be expected to result in a lowering of intracellular and urinary pH. On the other hand, if a rise of the pH of the distal tubular fluid were the primary process, this

would enhance potassium secretion at the same site (14).

A recent study (15) suggests that dexamethasone, like aldosterone, stimulates acidification of the urine in the isolated urinary bladder of the Colombian toad. This observation, however, may not be relevant, since the toad bladder preparation cannot discriminate between the effects of glucocorticoids and mineralocorticoids on sodium transport (16).

Although chronic administration of glucocorticoids has been shown to cause metabolic alkalosis (4, 17), the interpretation of these studies is complicated again by the mineralocorticoid activity of the glucocorticoid preparations used. Similarly, in Cushing's syndrome, the degree of metabolic alkalosis observed correlates best with the production of desoxycorticosterone, a corticosteroid with predominantly mineralocorticoid activity rather than with the secretion of cortisol (18). Furthermore, the metabolic alkalosis present in states of corticosteroid excess is usually associated with potassium deficiency, which is believed to be a prerequisite for the renal generation of metabolic alkalosis (19).

It should be noted that after dexamethasone administration our subjects did not excrete increased amounts of ammonium, the mechanism suggested to be responsible for the renal generation of an alkalotic state after hydrocortisone administration (20). The increase in ammonium excretion, in addition to being determined in part by hypokalemia, may be related more to mineralocorticoid than glucocorticoid activity, since we have shown (21) that patients with mineralocorticoid deficiency without renal insufficiency have impaired excretion of ammonium, and similar findings have been reported in experimental animals (22).

Summary. Although it is well recognized that mineralocorticoids enhance renal acid excretion, the effect of glucocorticoids on renal acidification is unclear. Oral administration of dexamethasone to six healthy volunteers for 1 week at a daily dose of 4.5 mg was associated with mild respiratory alkalosis and a small but statistically significant increase in baseline urine pH. However, neither the ability to lower urine pH nor to excrete titratable acid and ammonium after NH_4Cl acid-loading was altered. Administration of a single intravenous dose of dexamethasone sodium phosphate (7.5 mg) was associated with a significant rise in urine pH and potassium excretion and decreased titratable acid, ammonium, and phosphorus excretion in the absence of changes in blood acid–base status, creatinine clearance, or urine flow.

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