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EFFECT OF DEXAMETHASONE ON CITRATE METABOLISM

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SUMMARY

1. Dexamethasone treatment on a constant dietary intake induced a significant decrease in both plasma and urinary citric acid levels in normal subjects and patients with hypo- and hyper-parathyroidism. The decrease in the levels of urinary citrate occurred despite an increase in urinary calcium excretion.

2. Acute citrate infusions in three normal subjects after dexamethasone treatment demonstrated lower plasma and urinary citrate levels than the same infusion carried out during a control period.

3. The data indicated that glucocorticoids induced a change in citrate kinetics with a real or apparent increase in its volume of distribution and an increase in the fractional turnover rate without a change in total exchangeable citric acid mass.

4. Our data indicated that the effect of the synthetic steroid on citrate metabolism was apparently independent of the status of parathyroid function.

Citric acid concentration in plasma and urine has been shown to change in a variety of circumstances (Evans *et al.*, 1957; Crawford, Milne & Schribner, 1959; Gamble, Orten & Smith, 1961; Hara, Doherty & Williams, 1961). Henneman & Henneman (1958) demonstrated that adrenal steroids can influence citrate metabolism, inducing reductions in both urinary excretion and plasma concentration of citrate.

Since one of the mechanisms of parathyroid hormone (PTH) action in bone could be through a local increase in citric acid production (Neuman *et al.*, 1956), several investigators (Harrison, 1956; Canary *et al.*, 1961; Lichtwitz *et al.*, 1961) have postulated an interrelationship between citrate and calcium metabolism indicating that metabolic reactions which influence the calcium economy of the body can affect the accumulation of citrate in tissue (Harrison & Harrison, 1959).

Since PTH and glucocorticoids influence citrate metabolism, one wonders whether or not these actions are related. The present work was designed to study the influence of a synthetic

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potent adrenal steroid-dexamethasone (9α-fluoro-11β,17,21-tri-hydroxy-16 methyl-$\Delta^{1,4}$ pregnanedione-3,20-diene) upon citric acid metabolism and to verify a possible relationship between PTH and dexamethasone, as far as plasma and urinary citrate levels are concerned.

MATERIALS AND METHODS

Balance studies

Four normal controls (two males and two females, ages ranging from 22 to 28), two patients with post-surgical hypoparathyroidism (one male age 30 and one female age 35), one patient with primary hyperparathyroidism (adenoma) (female, age 38), and one patient with Cushing's syndrome (female, age 25) were on a metabolic balance programme, including a known constant diet containing 350 mg of calcium and 500 mg of phosphorus. Collections of urine were made throughout the experiment and the 48-hr urinary excretion of citric acid (collected with hydrochloric acid to a final concentration of 2%) and calcium were measured for each subject. Venous blood samples were drawn from the subjects each 48 hr, separated plasma immediately taken for calcium determination and the remainder precipitated with cold 20% trichloroacetic acid within 30 min of collection for citric acid which was measured by the method of Beutler & Yeh (1959) in plasma and urinary aliquots. Calcium was analysed by the method of Kramer and Tisdall modified by Clark & Collip (1923). All subjects after being on a control period for at least 10 days, were given dexamethasone in a dosage of 9–12 mg/day administered orally in four divided doses for 14 days and kept on the same programme with urine and plasma sampling.

Citrate infusions

Three normal subjects (two males and one female, ages ranging from 20 to 38), after an overnight fast, were infused intravenously with 12–20 ml of 2·5% sodium citrate solution. The infusions were performed over 3 min and venous blood samples were drawn immediately before the start of the infusion and 5, 10, 15, 20, 25, 30, 35, 40 and 45 min afterwards, being analysed for their citrate concentration. A 3-hr urine collection for citrate determination was obtained starting with the beginning of each infusion. In order to avoid bladder catheterization, the urinary flow of the subjects was kept above 6 ml/min by giving them a water load (20 ml/kg of body weight). After treatment with dexamethasone (12 mg/day) for at least 7 days, the same subjects were submitted again to the infusion above described.

Conceptual model for citrate dynamics. Citrate dynamics could be represented by a multicompartmental model, as shown in Fig. 1: a large rapidly equilibrating space probably represented by blood and remaining extracellular fluid (ECF), presenting at least three routes of loss or transfer, i.e. renal excretion, tissue metabolism and bone. To analyse such a system we have chosen the technique of a rapid citrate infusion. We were fully aware of the possibility that the results so obtained might be influenced by changes brought about by the citrate load. Other assumptions and limitations of this technique have already been discussed by Tashjian & Whedon (1963).

The analysis of the decay curve of plasma citrate concentration as a function of time, following the acute load, was restricted to the first 45 min, during which the model can be simplified to a single compartment system, cleared both by urinary excretion and transfer toward other

compartments (Fig. 1). In this condition, the variation of plasma citrate concentration (C_t) as a function of time (t) can be represented by an equation involving a minimum of one exponential term plus a constant:

$$C_t = C_0\, e^{-\lambda t} + A.$$

In this situation, the semi-logarithmic representation of C_t is figured by a straight line where the angular coefficient depends on the fractional turnover rate (λ). It should be mentioned that the single exponential model is replaced by a double one for the post-steroid analysis.

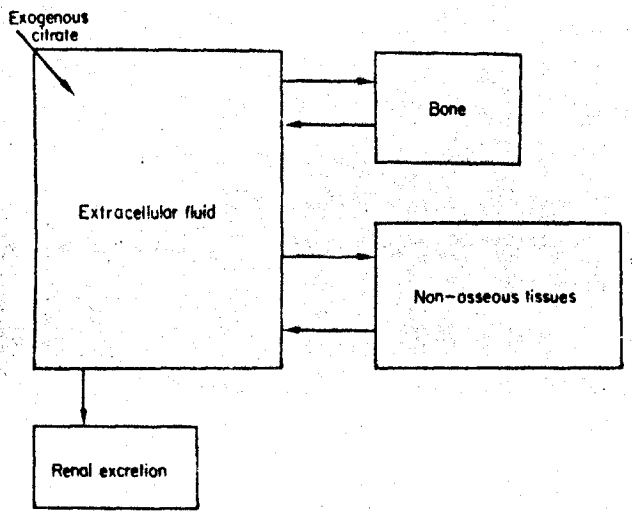

FIG. 1. Schematic representation of citrate metabolism (according to Tashjian & Whedon, 1963).

These models allow us to calculate some parameters. Symbols, definitions and units (taken from Tashjian & Whedon, 1963) are defined as follows:

Symbols	Definitions	Units
V	Volume of the initial equilibrating space of distribution of infused citrate	ml kg body weight (BW)$^{-1}$
M	Total mass of citrate corresponding to compartment of volume V	mg kg BW^{-1}
λ	Fractional turnover rate of initially equilibrating compartment	min^{-1}
λ_1, λ_2	Fractional turnover rates after dexamethasone	min^{-1}
F	Turnover rate of citrate that equilibrates during the experimental period	mg kg BW^{-1} 24 hr^{-1}

TABLE 1. Plasma and urinary citric acid and calcium levels in normal subjects, before and after dexamethasone treatment

	Urine				Plasma			
	Citric acid (mg/48 hr)		Calcium (mg/48 hr)		Citric acid (mg/100 ml)		Calcium (mg/100 ml)	
	Control	Dexamethasone	Control	Dexamethasone	Control	Dexamethasone	Control	Dexamethasone
No. of patients	4	4	4	4	4	4	4	4
No. of observations	12	12	12	12	12	15	10	10
Mean	456·66	226·66	306·8	454·6	2·03	1·22	10·2	10·5
Range	178–794	50–290	232–387	400–538	1·38–2·5	0·85–1·87	9·6–10·6	10·2–10·8
SD	222·54	44·75	60·1	48·3	0·385	0·295	0·4	0·2
P values		<0·01		<0·001		<0·001		>0·05

TABLE 2. Plasma and urinary citric acid and calcium levels in patients with parathyroid diseases and Cushing's syndrome

	Urine				Plasma			
	Citric acid (mg/48 hr)		Calcium (mg/48 hr)		Citric acid (mg/100 ml)		Calcium (mg/100 ml)	
	Control	Dexamethasone	Control	Dexamethasone	Control	Dexamethasone	Control	Dexamethasone
W.V.V.: Post-surgical hypoparathyroidism								
No. of observations	3	10	3	5	3	7	1	1
Mean	556·66	247·50	150·6	262·0	1·60	0·91	8·2	7·5
Range	457–623	163–357	146–156	200–338	1·60–1·60	0·85–1·00	—	—
SD	87·89	56·86	5·0	49·8	0	0·04	—	—
P value		<0·001		<0·01		<0·001		
I.M.D.: Post-surgical hypoparathyroidism								
No. of observations	5	4	3	3	3	4	1	1
Mean	232·80	169·20	109·0	162·3	1·97	1·27	7·7	7·6
Range	205–307	158–178	105–113	120–213	1·85–2·03	1·10–1·60	—	—
SD	42·54	20·30	2·0	47·1	0·1	0·23	—	—
P value		<0·025		>0·05		<0·005		
G.R.: Primary hyperparathyroidism								
No. of observations	3	4	3	3	1	1	1	1
Mean	611·66	367·00	610·0	831·3	3·10	2·35	14·2	12·0
Range	537–735	232–477	606–613	789–845	—	—	—	—
SD	107·6	106·33	3·8	37·4	—	—	—	—
P value		<0·05		<0·001				
W.M.S.: Cushing's syndrome								
No. of observations	3	—	3	—	5	—	3	—
Mean	130·00	—	618·3	—	1·04	—	10·4	—
Range	124–136	—	606–622	—	0·93–1·15	—	10·3–10·5	—
SD	6·00	—	15·5	—	0·087	—	0·1	—

The results after dexamethasone administration were analysed, accepting the load of citrate as a tracer technique with all analytical implications.

RESULTS

Balance studies

The mean urinary excretion for citrate and calcium for the whole group of normal controls in the last three 48-hr periods were 465·66 and 306·8 mg/48 hr respectively. These values decreased to 266·66 mg/48 hr for citrate and increased to 456·6 mg/48 hr for calcium, following the administration of dexamethasone. These differences were statistically significant ($P<0·01$) for citric acid and highly significant ($P<0·001$) for calcium. The mean plasma citric acid and calcium levels for the same group were 2·03 and 10·2 mg/100 ml, respectively, before steroid treatment. In the post-steroid period there was a statistically highly significant ($P<0·001$) fall in the mean citrate level to 1·22 mg/100 ml. However, no significant changes were noticed in plasma calcium levels ($P>0·05$). Table 1 summarizes these results.

The results concerning the patients studied by the balance technique are shown in Table 2. The two patients with hypoparathyroidism presented the same kind of response to the synthetic steroid in both plasma concentration and urinary excretion of citrate. These changes were statistically significant in both patients and similar to those shown by the normal controls under the same conditions. The patient with hyperparathyroidism presented a marked decrease in the urinary excretion of citrate after the drug, both the basal and post-steroid mean values being above the corresponding levels shown by the normal controls. Though only one determination was made before and after dexamethasone administration, the plasma citrate showed the same trend as in the normal controls, i.e. a fall, the levels being above the normal range. The patient with Cushing's syndrome had urinary excretion and plasma concentration of citrate overlapping the values observed in the normal controls receiving dexamethasone. All patients showed a significant increase in urinary calcium levels after steroid treatment.

Citrate infusions

The results of citrate infusions are shown in Table 3. As in the balance studies there was a marked decrease in urinary excretion of citrate during the infusion performed in the dexamethasone period.

The variation in plasma concentration of citric acid as a function of time, after the acute infusion of citrate, in both control and dexamethasone periods, were similar in three subjects studied. A representative study is shown in Fig. 2. According to the kinetic considerations previously presented, the experimental data from the control study were consistent with a single compartment. On the other hand, dexamethasone data, as shown in Fig. 2, were consistent with a two compartment model. Based on these criteria, the data were analysed allowing us to calculate the numerical values for the parameters defined above. They are given in Table 4.

The space of distribution of citrate (V) after dexamethasone doubled, approximately. Total exchangeable citrate (M) did not apparently change after steroid treatment in all cases, although it was distributed in a larger space, thus explaining the fall in plasma concentration. Two values for fractional turnover rate (λ_1 and λ_2) were calculated as a consequence of the existence of two

exponential terms corresponding to the plasma citrate curve after dexamethasone: λ_1 corresponds to the slow component and does not greatly differ from the λ value of the basal curve; on the other hand, λ_2 which was related to the rapid component, was approximately ten times greater.

The turnover rate of citrate (F) increased, in the subjects studied, after the administration of the glucocorticoid.

TABLE 3. Δ Plasma (individual plasma citric acid values minus basal plasma citric acid value) and urine citric acid levels after citrate infusion

Time (min)	E.L.P., male, 20 years, 68 kg		V.M., male, 28 years, 60 kg		R.V., female, 38 years, 60 kg	
	Control	Dexamethasone	Control	Dexamethasone	Control	Dexamethasone
Δ Plasma citric acid levels (mg/100 ml)						
5	1·34	3·50	2·75	4·5	2·95	3·60
10	1·20	1·42	2·42	2·3	2·40	1·53
15	1·05	0·76	1·98	1·4	2·05	1·08
20	0·88	0·52	1·73	0·97	1·75	0·85
25	0·80	0·43	1·50	0·83	1·52	0·70
30	0·70	0·35	1·27	0·70	1·35	0·56
35	0·60	0·29	1·03	0·60	1·05	0·48
40	0·52	0·26	0·89	0·62	0·9	0·36
45	0·45	0·20	0·78	0·44	0·78	0·30
Total urine citric acid (3 hr) mg excreted	72·20	23·45	116·50	36·00	74·30	39·40

TABLE 4. Results of compartmental analysis in patients E.L.P., V.M. and R.V.

	E.L.P.		V.M.		R.V.	
	Basal	Dexamethasone	Basal	Dexamethasone	Basal	Dexamethasone
V (ml kg body weight^{-1})	270	463	250	500	194	333
M (mg kg body weight^{-1})	6·06	6·02	5·00	5·50	4·85	4·67
λ (min^{-1})	0·0277		0·0330		0·0331	
λ_1 (min^{-1})		0·0356		0·0285		0·0420
λ_2 (min^{-1})		0·3180		0·2330		0·4600
F (mg kg body weight^{-1} 24 hr^{-1})	242	309	183	280	229	305

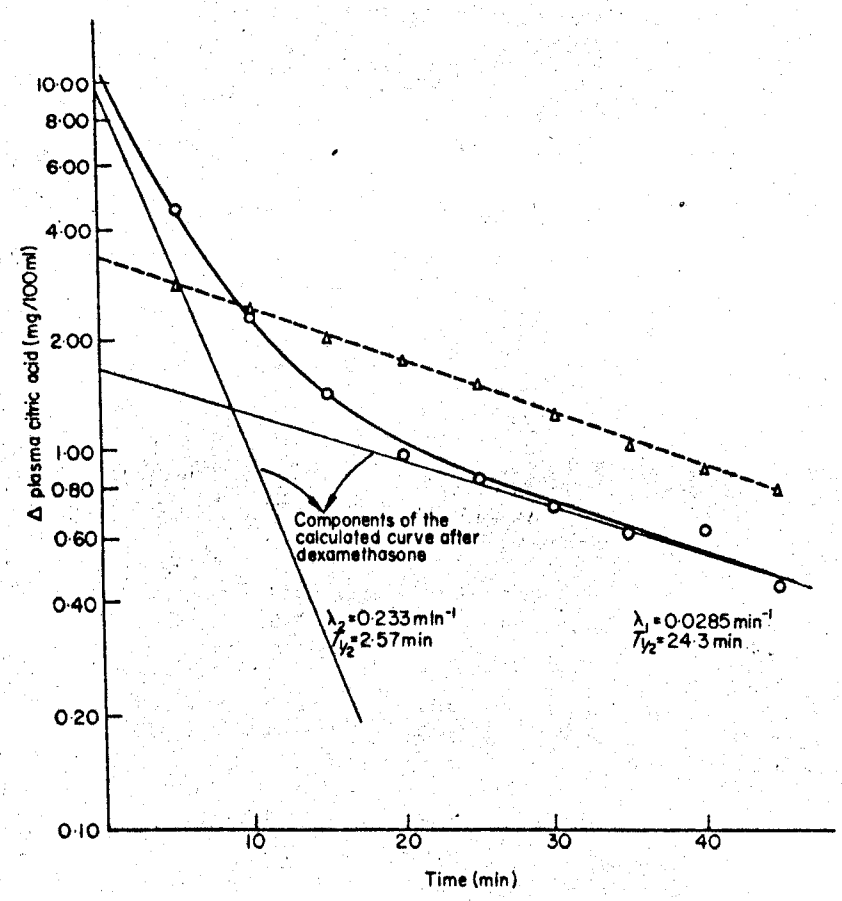

FIG. 2. Representative plasma citric acid curve after citrate infusion, before and after dexamethasone administration (patient V.M.). Δ, Observed control values; Δ - - - Δ, calculated control curve; O, observed values following dexamethasone; O——O, calculated curve after dexamethasone.

DISCUSSION

According to the literature, citric acid concentration in normal subjects varies within the limits of 2–5 mg/100 ml (Freeman, 1960; Rasmussen & Reifenstein, 1962). Our results obtained in four normal controls agree with these values (Table 1). This level is determined by the equilibrium of several factors acting simultaneously and thus may vary according to the predominance of one or more factors over the others (Freeman, 1960). Exogenous load, renal excretion and tissue metabolism are the major factors by which plasma concentration of citrate may change beyond the normal limits. Any drug inducing changes in the concentration of plasma citric acid must act primarily through one of these mechanisms. As demonstrated by Henneman & Henneman (1958) and confirmed by our own data, glucocorticoid administration is capable of changing both plasma concentration and urinary excretion of citrate in normals (Table 1).

The patient with Cushing's syndrome, whom we studied in the active phase of the disease, showed the same pattern as the normal control subjects receiving dexamethasone.

Our data show that steroid-induced decreases in the levels of citric acid occurred, despite a significant increase in urinary calcium—a situation which normally induces a prompt rise in urinary citrate (Henneman & Henneman, 1958).

The mechanisms by which the actions on citrate metabolism are carried out have been previously discussed by Henneman & Henneman (1958), Harrison & Harrison (1959), Lemon *et al.* (1960) and Tashjian & Whedon (1963). Our own balance data would fit one of the following mechanisms operating alone or together:

(1) Decreased production of citrate due to diminished conversion of pyruvate to acetyl CoA (Henneman & Henneman, 1958), as suggested by the pattern of blood concentrations of carbohydrate metabolites in Cushing's syndrome and induced hypercortisonism (Henneman & Bunker, 1957; Hennes *et al.*, 1957), but there is no evidence that corticosteroids have a direct effect on pyruvate dehydrogenase (Weber *et al.*, 1965).

(2) Decreased cellular membrane permeability to citrate from the cell to the extracellular fluid (intracellular sequestration) (Harrison & Harrison, 1959; Lemon *et al.*, 1960).

(3) Increased tissue degradation (Tashjian & Whedon, 1963). Our balance data exclude the possible participation of the excretory function of the kidneys, as urinary excretion was also reduced during dexamethasone administration (Table 1).

As far as the acute citrate infusions are concerned, only the earliest stages of citrate distribution can be analysed. At this phase the kinetic characteristics in the basal studies are different from those after dexamethasone treatment.

The lack of appreciable change in citrate mass (M) (Table 4) with an increase in its volume of distribution (apparent or real) (Table 4) and a fall in plasma and urinary levels (Table 3) suggests two possible explanations:

(a) The steroid induces changes in the cell membrane characteristics leading to a real expansion in the physical space of distribution of citrate. This expansion would be equivalent to the formation of a new space of distribution with extremely rapid rate of transfer.

(b) The fall in plasma citrate levels does not depend on a real increase in its physical space of distribution, but to the division of the original space into two sub-compartments with large differences in concentration of citric acid. These differences would explain mass constancy associated with a drop in plasma concentration of citric acid, without an increase in its real space of distribution. The lack of information regarding citrate production and consumption does not allow us to draw absolute conclusions, but this hypothesis agrees with Harrison's (1959) experimental evidence that cortisol increases intracellular citrate, perhaps by decreasing cellular permeability to permit the egress of citrate from the cell to the extracellular fluid.

Similar changes in plasma and urinary citric acid concentration were induced by dexamethasone in the absence of significant endogenous PTH activity as evidenced by the patients with hypoparathyroidism, and in the presence of PTH hyperactivity as shown by the patient with hyperparathyroidism (Table 2). These data suggest that the action of dexamethasone upon citrate metabolism is not mediated through PTH. It has been suggested that the changes induced by adrenal corticosteroids upon biological systems are usually opposed to those induced by PTH (Wajchenberg *et al.*, 1965), whatever the mechanisms involved.

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SUMÁRIO

1. Dexametazona determinou em indivíduos normais e em pacientes portadores de hipo e hiperparatireoidismo mantidos em dieta constante, um decréscimo significativo dos níveis de ácido cítrico plasmático e urinário. O decréscimo do ácido cítrico plasmático e urinário. O decréscimo do ácido cítrico urinário manifestou-se malgrado um aumento da excreção urinária de cálcio.

2. Três indivíduos normais em tratamento com dexametazona, acusaram níveis plasmáticos e urinários inferiores aos observados durante um período de contrôle, quando submetidos a infusão aguda de citrato.

3. Os resultados obtidos sugerem que os glucocorticoides determinam uma mudança na cinética do citrato, caracterizada por um aumento real ou aparente de seu espaço de distribuição e por um incremento no ritmo de renovação, sem variação simultânea da massa total de citrato permutável.

4. Os resultados indicam que o efeito dos esteroides sintéticos sôbre o metabolismo do citrato é, aparentemente, independente do estado funcionam paratireoidismo.