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The acute effect of chlorothiazide on serum-ionized calcium. Evidence for a parathyroid hormone-dependent mechanism.

M M Popovtzer, … , E B Reeve, R W Schrier

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Research Article

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The Acute Effect of Chlorothiazide on Serum-Ionized Calcium

EVIDENCE FOR A PARATHYROID HORMONE-DEPENDENT MECHANISM

MORDECAI M. POPOVTZER, VIBRAT L. SUBRYAN, ALLEN C. ALFREY, ERNEST B. REEVE, and ROBERT W. SCHRIER

From the Department of Medicine, University of Colorado School of Medicine and Veterans Administration Hospital, Denver, Colorado 80220

ABSTRACT The acute effects of chlorothiazide (CTZ) on total (TSCA) and ionized (SCA^{+2}) serum calcium concentrations were studied in three groups of people: (*a*) eight subjects with normal parathyroid function; (*b*) six patients with hypoparathyroidism; and (*c*) two patients with hyperparathyroidism. Most subjects were studied on four occasions; at least 3 days intervened between studies on an individual subject. During each experiment the subject received an i.v. infusion of 5% dextrose in water at 1 ml/min from 8 a.m. to 4 p.m. Additions to the infusions were (*a*) none; (*b*) CTZ to deliver 3.33 mg/kg/h; (*c*) parathyroid extract to deliver 1 U/kg/h; or (*d*) both CTZ and parathyroid extract at the rates previously indicated. CTZ, when used, was added to the infusion at 10 a.m., parathyroid extract at 8 a.m. When CTZ was infused, the diuretic-induced losses of Na and water were replaced by i.v. infusion. In normal subjects 2 h after the start of CTZ infusion, there was a transient increase in SCA^{+2} which coincided in time of day with a transient decrease in SCA^{+2} in control experiments. At that time of day SCA^{+2} was 4.18±0.12 mg/100 ml in control experiments and 4.56±0.08 in experiments with CTZ, $P < 0.025$. The corresponding values for (TSCA) were 9.32±0.15 and 9.80±0.30, $P < 0.01$. Such differences were not observed in the group with hypoparathyroidism. In the two patients with hyperparathyroidism, CTZ produced sustained increases in TSCA and SCA^{+2}. In normal subjects and those with hypoparathyroidism, CTZ plus parathyroid extract infusion resulted in sustained increases in both SCA^{+2} and TSCA throughout the periods of observation when compared to experiments in which only parathyroid extract was infused, $P < 0.01$ in all instances. The results suggest that the acute hypercalcemic action of CTZ requires the presence of circulating parathyroid hormone.

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Address reprint requests to Dr. M. Popovtzer, Department of Medicine, Temple University, Philadelphia, Pa. 19140.

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INTRODUCTION

The mechanism of thiazide-induced hypercalcemia has been the subject of numerous investigations (1–8). Although hypercalcemia has been noticed primarily in patients with high rates of bone turnover (2, 3, 5), significant increases in serum calcium concentration were also reported in normal individuals treated with thiazide diuretics (1, 7).

Because changes in total serum calcium concentration may reflect alterations in serum protein concentration without real changes in calcium metabolism (9), the direct measurement of serum ionized calcium is most desirable for an accurate determination of changes in calcium homeostasis. In this regard the correction of the measured total calcium concentration for the changes in serum protein concentration may not be entirely satisfactory since thiazides may alter the binding power of serum proteins for calcium (6). Furthermore, changes in the ultrafiltrable calcium concentration may not necessarily correlate closely with changes in ionized calcium concentration (9) and therefore cannot be used as a perfect substitute for ionized calcium.

Several mechanisms by which thiazides may affect calcium metabolism are worth brief comment. Contraction of the extracellular fluid volume may affect serum calcium concentration both by increasing the protein bound fraction and by augmenting tubular reabsorption of calcium (2, 5, 7, 10). In addition thiazides may act directly on the kidney to enhance tubular reabsorption of calcium (11).

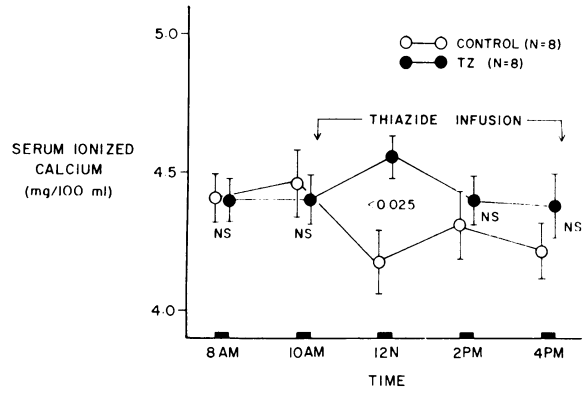

FIGURE 1 The acute effect of CTZ on SCA^{+2} in normoparathyroid subjects. The results are presented as mean ±SE. The *P* values refer to the comparison of the control with the corresponding experimental periods.

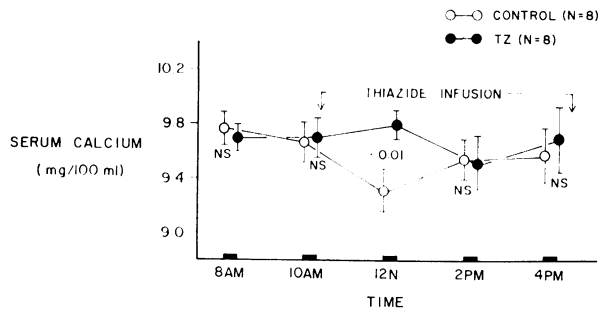

FIGURE 2 The acute effect of CTZ on TSCA in normoparathyroid subjects. The *P* values refer to the comparison of the control with the corresponding experimental values.

Mobilization of mineral from the bone has been proposed as another mechanism for the thiazide-induced increase in serum calcium (3, 5). This mechanism was considered to be most effective in states of rapid bone turnover, such as hyperparathyroidism, or during an intake of large dose of vitamin D (2, 3, 5).

All the previously reported findings in man were during chronic administration of thiazide diuretics and without a rigid replacement regimen for the urinary losses of sodium and water. The present study was undertaken to evaluate the acute effect of chlorothiazide (CTZ)[1] on serum calcium concentration, with an emphasis on changes in the ionized fraction. Prompt i.v. replacement of urinary losses of sodium and water helped maintain constant extracellular volume.

METHODS

Three groups of patients were studied. Group 1: Eight subjects with normal parathyroid function, four males and four females, with ages ranging from 38 to 52 yr (average 46 yr). Group 2: Six patients with hypoparathyroidism. The diagnosis was idiopathic hypoparathyroidism in three and surgical in the remainder. Three patients were male and and three female with ages ranging from 36 to 58 yr (average 49 yr). All six were treated and well controlled with oral vitamin D_2 (ergocalciferol) at the dose of 2.5 mg per day. Group 3: Two patients with surgically proved hyperparathyroidism. One with parathyroid adenoma and the second with chronic renal disease (creatinine clearance of less than 5 ml/min) and severe secondary hyperparathyroidism.

The patients were admitted and studied at the Clinical Research Center. Throughout the study the patients were maintained on balance regimen with diets containing constant amounts of calcium, sodium, and phosphorus in quantities similar to those present in their regular diets, as determined by the dietary histories, and received no medications other than those mentioned above. All patients received four infusions which were separated from one another by at least a 3-day interval and were given in the following sequence: (*a*) Control infusion (5% D/W [dextrose in water], 1 ml/min) was given from 8:00 a.m. until 4:00 p.m. (*b*) CTZ[2] (20 mg/kg body weight) was dissolved in 5% D/W and delivered by a constant infusion (1 ml/min) from 10:00 a.m. until 4:00 p.m. (*c*) Parathyroid extract[3] (1 U/kg body weight/h) dissolved in 5% D/W and infused at a constant rate from 8:00 a.m. until 4:00 p.m. (*d*) Combined parathyroid extract and CTZ infusion. As in (*c*), the infusion of parathyroid extract was started at 8:00 a.m. and continued until 4:00 p.m. CTZ infusion as in (*b*) was started at 10:00 a.m. and continued until 4:00 p.m.

During all infusions containing CTZ urinary electrolytes and water were measured at 1-h intervals and replaced quantitatively by a continuous infusion containing sodium and water in the same proportion as in the voided urine after subtraction of the corresponding control amounts of sodium and water. Two patients in group 1 and both patients in group 3 received only the control and CTZ infusions. The patients remained supine throughout the infusion periods except for assuming upright position for voluntary voiding. Urine was collected at hourly intervals and blood samples were withdrawn with minimal stasis into

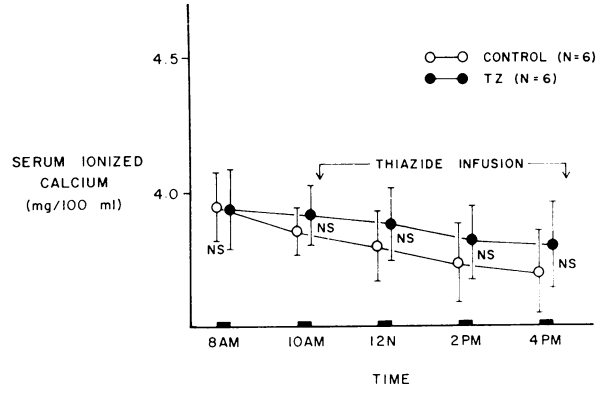

FIGURE 3 The acute effect of CTZ on SCA^{+2} in hypoparathyroid subjects.

[1] *Abbreviations used in this paper:* CTZ, chlorothiazide; PTH, parathyroid hormone; SCA^{+2}, ionized serum calcium concentration; TSCA, total serum calcium concentration.

[2] Merck, Sharp, and Dohme, West Point, Pa.

[3] Eli Lilly & Co., Indianapolis, Ind.

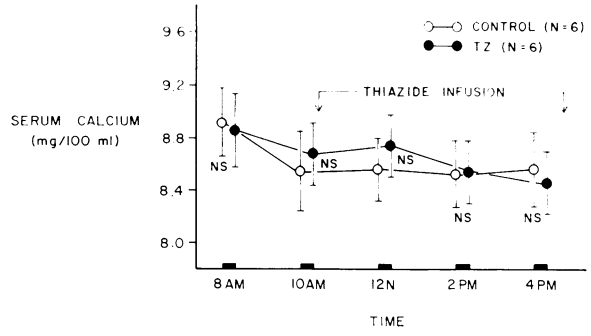

FIGURE 4 The acute effect of CTZ on TSCA in hypoparathyroid patients.

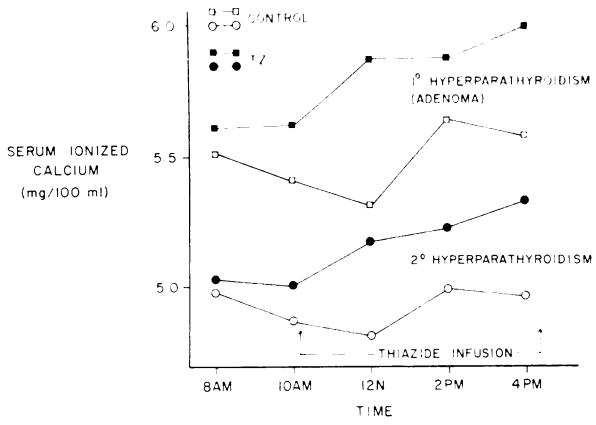

FIGURE 5 The acute effect of CTZ on SCA^{+2} in two patients with hyperparathyroidism.

vacutainers (Becton, Dickinson, and Co., Rutherford, N.J.), every 2 h, at 8:00 a.m., 10:00 a.m., 12 noon, 2:00 p.m., and 4:00 p.m. The 8:00 a.m. specimen was obtained after breakfast whereas the 12 noon specimen was withdrawn before lunch.

All serum samples were assayed for creatinine, calcium, phosphorus, magnesium, sodium, and potassium by methods reported previously from this laboratory (12). Serum pH was measured in all serum specimens by a Corning Blood pH meter (Corning Glass Works, Orange, Calif.). Serum ionized calcium (SCA^{+2}) was determined with the model 801 "Ionalyzer" (Orion Research Inc., Cambridge, Mass.). The system that we used consisted of a digital expanded-scale pH/mV meter, a Calomel reference electrode, a calcium exchange electrode, and a gear driven syringe pump. The only refinement was additional metal shielding (de-

TABLE I

The Effects of CTZ, PTH, and Combined CTZ with PTH Infusions on Urinary Excretion of Calcium ($U_{Ca}V$) and Magnesium ($U_{Mg}V$) in Six Normal Subjects

Time		8–9(a.m.)	9–10(a.m.)	10–11(a.m.)	11–12(a.m.)	12–1(p.m.)	1–2(p.m.)	2–3(p.m.)	3–4(p.m.)
$U_{Ca}V$, *μg/min*									
Control	Mean	142	204	218	172	150	195	194	197
	SE	68	103	57	40	35	52	59	49
CTZ	Mean	119	178	246	266	254	301	281	342
	SE	42	59	64	60	53	68	62	72
	*P**	NS	NS	<0.05	<0.005	<0.01	<0.005	<0.005	<0.005
PTH	Mean	200	248	191	95	83	116	113	157
	SE	69	100	43	27	17	25	27	46
	*P**	NS	NS	NS	<0.01	<0.01	<0.01	<0.0125	<0.025
PTH + CTZ	Mean	134	186	202	193	134	177	195	195
	SE	47	55	41	40	30	30	43	35
	P‡	NS	NS	NS	<0.001	<0.01	<0.005	<0.005	<0.0025
$U_{Mg}V$, *μg/min*									
Control	Mean	66	82	75	70	70	77	74	88
	SE	15	23	15	13	10	13	13	12
CTZ	Mean	60	79	98	125	103	112	112	127
	SE	13	14	13	13	13	17	18	26
	*P**	NS	NS	<0.01	<0.005	<0.005	<0.005	<0.05	<0.025
PTH	Mean	55	71	70	42	35	36	40	52
	SE	13	14	15	7	7	6	7	10
	*P**	NS	NS	NS	<0.025	<0.01	<0.005	<0.005	<0.005
PTH + CTZ	Mean	67	69	60	67	50	73	89	94
	SE	32	21	16	14	10	13	17	14
	P‡	NS	NS	NS	<0.01	<0.01	<0.0025	<0.005	<0.005

* Compared with control infusion.

‡ Compared with PTH infusion only.

TABLE II

The Effects of CTZ, PTH, and Combined CTZ with PTH Infusions on Urinary Excretion of Phosphorus (U_pV) and Sodium ($U_{Na}V$) in Six Normal Subjects

Time		8–9 (a.m.)	9–10 (a.m.)	10–11 (a.m.)	11–12 (a.m.)	12–1 (p.m.)	1–2 (p.m.)	2–3 (p.m.)	3–4 (p.m.)
U_pV, *μg/min*									
Control	Mean	473	375	352	366	468	571	626	827
	SE	81	79	71	74	115	151	140	124
CTZ	Mean	510	452	596	611	731	1,052	1,010	1,321
	SE	118	92	108	132	152	230	190	241
	P*	NS	NS	<0.05	<0.01	<0.005	<0.005	<0.05	<0.025
PTH	Mean	594	980	1,075	1,120	1,227	1,330	1,240	1,618
	SE	102	132	155	180	210	191	141	180
	*P**	NS	<0.005	<0.005	<0.005	<0.0125	<0.001	<0.005	<0.005
PTH + CTZ	Mean	563	896	1,188	1,266	1,356	1,736	1,716	1,762
	SE	103	134	250	150	265	290	311	260
	P‡	NS	NS	NS	NS	<0.01	<0.025	<0.05	NS
$U_{Na}V$, *μeq/min*									
Control	Mean	1,027	1,091	1,252	940	894	1,081	1,070	1,140
	SE	172	269	304	210	183	193	198	204
CTZ	Mean	697	998	3,203	4,490	4,290	5,400	4,800	6,600
	SE	180	210	770	710	470	700	461	940
	*P**	NS	NS	<0.025	<0.005	<0.001	<0.001	<0.001	<0.001
PTH	Mean	601	1,310	1,945	1,986	1,425	1,899	2,186	2,505
	SE	180	241	263	200	163	251	270	381
	*P**	NS	NS	<0.01	<0.005	<0.01	<0.001	<0.001	<0.005
PTH + CTZ	Mean	483	1,290	6,550	7,372	6,060	8,023	8,317	8,420
	SE	160	241	390	980	1,081	1,293	1,116	790
	P‡	NS	NS	<0.005	<0.0025	<0.005	<0.005	<0.001	<0.001

* Compared with control infusion.

‡ Compared with PTH infusion only.

signed locally) around the electrodes to prevent electrostatic interference (13). Concentration of SCA^{+2} of 44 normal subjects ranged from 4.1 to 5.0 mg/100 ml (mean 4.55, SD of 0.21 mg/100 ml). Evaluation of the method by determining its replicability elicited a SD of 0.024 mg/100 ml. Total serum protein concentration was measured with a refractometer (American Optical Company, Instrument Div., Buffalo, N. Y.). Serum albumin was measured with the Monitor Kit Method, American Monitor Corp., Indianapolis, Ind.) (14).

All urine specimens were assayed for calcium, magnesium, phosphorus, sodium, and creatinine. All results were evaluated by comparing the experimental values with the corresponding values of the control infusions, each patient serving as his own control, with a paired student's *t* test.

RESULTS

CTZ infusion. The administration of CTZ did not significantly alter serum pH, total protein, albumin, phosphorus, magnesium, sodium, potassium, and creatinine concentrations in all patients. In group 1 there was no significant difference between the corresponding SCA^{+2} during the control and the CTZ infusion, with the exception of the values obtained 2 h after the beginning of the CTZ infusion at 12:00 noon. The experimental value was significantly higher than the corresponding control ($P < 0.025$) as well as the preinfusion value, $P < 0.05$ (Fig. 1). Thus the transient increment in SCA^{+2} did not only represent a relative change due to a decrease in the control values, but also an absolute increase in relation to the preinfusion values. Measurement of total serum calcium concentration (TSCA) showed a transient increase in serum concentration at 12:00 noon only in relation to the corresponding control infusion values (Fig. 2). In patients with hypoparathyroidism treated with vitamin D (Group 2), no difference could be noticed between the SCA^{+2} and TSCA during the control and the CTZ infusions (Fig. 3 and 4). The two patients with hyperparathyroidism (group 3) showed a sustained elevation in SCA^{+2} during CTZ infusion above the values recorded during the control infusion (Fig. 5).

Urinary excretion rates of calcium, magnesium, phosphorus, and sodium during CTZ infusions were significantly higher than the corresponding values during the control infusions and higher than the preinfusion values in both groups 1 and 2 (Tables I, II, III and IV).

TABLE III

The Effects of CTZ, PTH, and Combined CTZ with PTH Infusions on Urinary Excretion of Calcium ($U_{Ca}V$) and Magnesium ($U_{Mg}V$) in Six Hypoparathyroid Patients

Time.....		8-9(a.m.)	9-10(a.m.)	10-11(a.m.)	11-12(a.m.)	12-1(p.m.)	1-2(p.m.)	2-3(p.m.)	3-4(p.m.)
$U_{Ca}V$, *μg/min*									
Control	Mean	116	152	170	203	168	155	154	181
	SE	8	43	39	58	23	22	49	45
CTZ	Mean	144	169	341	333	311	350	310	302
	SE	45	59	35	81	86	96	88	85
	*P**	NS	NS	<0.001	<0.0125	<0.05	<0.01	<0.0025	<0.025
PTH	Mean	144	171	162	120	120	100	109	124
	SE	46	58	36	21	30	27	27	22
	*P**	NS	NS	NS	<0.005	<0.005	<0.01	<0.01	<0.005
PTH + CTZ	Mean	202	152	252	226	231	256	218	227
	SE	62	42	35	36	45	36	37	41
	P‡	NS	NS	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01
$U_{Mg}V$, *μg/min*									
Control	Mean	33	40	41	41	42	44	36	48
	SE	4	10	7	14	4	4	7	5
CTZ	Mean	38	38	70	66	64	76	73	76
	SE	14	10	8	11	10	18	16	15
	*P**	NS	NS	<0.0025	<0.01	<0.025	<0.025	<0.01	<0.025
PTH	Mean	36	38	37	27	25	27	28	32
	SE	7	9	6	5	5	6	6	5
	*P**	NS	NS	NS	<0.005	<0.001	<0.005	<0.025	<0.005
PTH + CTZ	Mean	43	37	45	48	42	54	53	59
	SE	13	6	6	6	5	3	9	8
	P‡	NS	NS	<0.025	<0.01	<0.025	<0.01	<0.025	<0.01

* Compared with control infusion.

‡ Compared with PTH infusion only.

There were no significant changes in creatinine clearance rates. The urinary excretion rates of all ions in group 3 during CTZ infusion showed similar changes but they were not statistically significant.

Intravenous administration of CTZ during continuous infusion of parathyroid hormone (PTH). The i.v. administration of CTZ during continuous PTH infusion was associated with a significant increase in serum calcium concentrations above the corresponding values recorded during PTH infusion alone. A sustained increase in the SCA^{+2} and TSCA was exhibited by both the normoparathyroid and hypoparathyroid patients (Fig. 6 and 7). In the normoparathyroid patients the maximal increase in SCA^{+2} was noticed at periods during which CTZ had no effect on serum calcium. The most striking hypercalcemic response was observed in group 1 in which the mean concentration of ionized calcium exceeded the upper normal value of 5 mg/100 ml.

During PTH infusions urinary excretion rates of calcium and magnesium were significantly lower and those of phosphorus and sodium were significantly higher, than the corresponding excretion rates during control infusions, both in the normoparathyroid and the hypoparathyroid individuals (Tables I and III). There were no significant differences between creatinine clearance rates. There were no significant changes in serum pH, total protein, albumin, phosphorus, magnesium, sodium, and potassium during PTH infusion.

The i.v. administration of CTZ blunted or abolished both the hypocalciuric and the hypomagnesiuric actions of PTH but enhanced its natriuretic and the phosphaturic actions, both in the normoparathyroid and the hypoparathyroid individuals (Tables I, II, III, and IV).

DISCUSSION

The results of the present study demonstrated an acute increase of serum calcium concentration after i.v. administration of CTZ. This effect was transient in normoparathyroid subjects, absent in hypoparathyroid patients, and sustained in hyperparathyroid patients or in others receiving constant infusion of PTH. The dif-

TABLE IV

The Effects of CTZ, PTH, and Combined CTZ and PTH Infusions on Urinary Excretion of Phosphorus (U_pV) and Sodium ($U_{Na}V$) in Six Hypoparathyroid Patients

Time		8–9(a.m.)	9–10(a.m.)	10–11(a.m.)	11–12(a.m.)	12–1(p.m.)	1–2(p.m.)	2–3(p.m.)	3–4(p.m.)
U_pV, *μg/min*									
Control	Mean	358	446	217	220	370	561	532	540
	SE	47	116	45	45	52	110	131	72
CTZ	Mean	215	396	438	434	826	933	965	582
	SE	52	117	68	100	190	170	160	190
	*P**	NS	NS	<0.025	<0.05	<0.05	<0.05	<0.05	NS
PTH	Mean	616	1,083	1,021	942	966	1,274	1,140	1,162
	SE	112	275	150	144	129	240	1,100	62
	*P**	0.05	0.01	0.001	0.001	0.001	0.001	0.0025	0.001
PTH + CTZ	Mean	590	812	1,276	1,400	1,510	1,820	1,650	1,558
	SE	136	290	270	161	159	157	122	140
	P‡	NS	NS	<0.01	<0.01	<0.0025	<0.005	<0.005	<0.0125
$U_{Na}V$, *μeq/min*									
Control	Mean	268	320	500	697	807	809	1,091	794
	SE	150	75	99	203	244	154	450	191
CTZ	Mean	268	378	2,431	3,881	3,775	4,391	4,137	4,352
	SE	50	130	582	641	740	780	885	871
	*P**	NS	NS	<0.005	<0.0025	<0.01	<0.0025	<0.01	<0.01
PTH	Mean	682	762	1,135	1,312	1,465	1,605	1,712	1,545
	SE	181	340	312	270	401	280	213	72
	*P**	<0.001	<0.005	<0.01	<0.001	<0.005	<0.005	<0.005	<0.001
PTH + CTZ	Mean	1,090	926	3,440	5,410	6,381	6,676	7,008	6,274
	SE	450	484	1,351	1,250	1,298	1,089	1,973	1,055
	P‡	NS	NS	<0.005	<0.01	<0.005	<0.001	<0.025	<0.0025

* Compared with control infusion only.
‡ Compared with PTH infusion only.

ference between the normoparathyroid and hypoparathyroid individuals in their response to CTZ infusion is not well understood. Obviously the presence of parathyroid activity might be one of the factors upon which the transient increase in serum calcium was dependent. Such a dependence could either involve stimulation of PTH secretion (15) or potentiation of its peripheral action by CTZ (3). Both possibilities were considered in previous studies (3–5).

The short duration of the thiazide-induced increase in serum calcium concentration in the normoparathyroid subjects suggested a possible feedback control of serum calcium based on suppression of PTH secretion as a result of a rise in serum calcium concentrations. Such a feedback mechanism could account for the return of serum calcium to normal after a short increase, irrespective of whether CTZ stimulated secre-

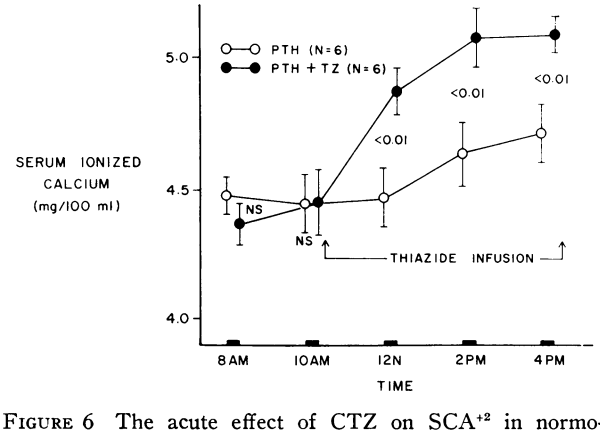

FIGURE 6 The acute effect of CTZ on SCA^{+2} in normoparathyroid subjects undergoing PTH infusion.

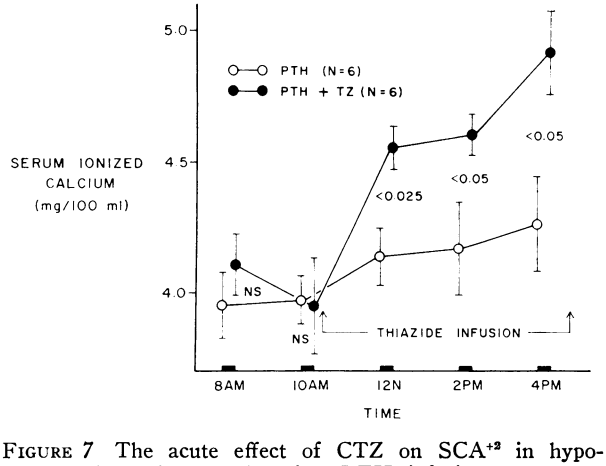

FIGURE 7 The acute effect of CTZ on SCA^{+2} in hypoparathyroid patients undergoing PTH infusion.

tion of endogenous PTH or acted by enhancing the peripheral effect of the hormone. To further explore these two possibilities, serum PTH level was maintained constantly high by a continuous infusion of parathyroid extract. Theoretically, this experimental maneuver was expected to disrupt the feedback mechanism and its inhibitory effect on thiazide-induced hypercalcemia. The sustained increase in serum calcium concentration, which occurred when CTZ infusion was added to PTH infusion, indicated that in the presence of an unsuppressible source of PTH, CTZ was capable of inducing a continuous increase in serum calcium concentration. Additional evidence supporting this possibility was obtained from the observation made in two patients with hyperparathyroidism and presumably with poorly suppressible secretion of PTH. In both patients i.v. administration of CTZ was associated with a sustained increase in serum calcium similarly to that observed in normal subjects receiving constant infusion of exogenous PTH. These findings were consistent with a potentiation of the peripheral action of PTH by CTZ. The alternative possibility that stimulation of endogenous hormone secretion could contribute to the observed increase in serum calcium concentrations seemed unlikely in the presence of already very high circulating levels of PTH during the infusion of the extract. However, this could not be excluded with absolute certainty in the presence of an intact endogenous source of PTH. To gain further information to answer the above questions, the same studies were performed in hypoparathyroid patients who presumably were devoid of parathyroid activity.

The observed sustained increase in serum calcium in the hypoparathyroid patients with i.v. CTZ during continuous PTH infusion lent strong support to the peripheral action of CTZ as the primary cause of the rise in serum calcium. Thus we could conclude that the acute hypercalcemic effect of CTZ was dependent on the presence of circulating PTH but did not require the presence of parathyroid tissue, and that it effected an increase in serum calcium by enhancing the peripheral action of PTH.

The hypercalcemic action of PTH is a result of its skeletal mobilization of calcium and increased gastrointestinal absorption of calcium (16–19). The results of our study confirmed the previously reported hypocalciuric effect of PTH in hypoparathyroid patients (17) and demonstrated it also in normal subjects. By contrast to the occurrence of hypocalciuria after chronic administration of thiazide diuretics (20, 21) in the present study the acute administration of CTZ caused a pronounced calciuresis both in the normoparathyroid and hypoparathyroid individuals. Similar response to i.v. CTZ was also reported by other investigators (22, 23). Furthermore, in the present study the thiazide diuretics blunted substantially the hypocalciuric effect of exogenous PTH. Thus the renal actions of CTZ which tended to reduce serum calcium concentration obviously could not account for the observed rise in serum calcium and in fact could play a role in blunting the hypercalcemic action of thiazides in the normal subjects.

Although PTH has been shown to effect an increase in the gastrointestinal absorption of calcium, and theoretically CTZ could act by enhancing this effect, the present data did not provide sufficient evidence either to support or to exclude this possibility. The onset of PTH's actions on the bowel is delayed and was reported to start 5 or more h after the administration of the hormone (19). Long-term thiazide therapy failed to alter gastrointestinal absorption of calcium in patients with recurrent renal calculi (24), whereas the acute effect is unknown.

CTZ infusion caused a phosphaturia both in normoparathyroid and in hypoparathyroid individuals in the presence and in the absence of PTH. A drop in serum phosphorus could induce a reciprocal increase in serum calcium. However, the fact that no changes were noticed in serum phosphorus concentration makes this possibility unlikely.

In view of these considerations, and the rapidity of the hypercalcemic response, it is most likely that the increase in TSCA and SCA^{+2} in our patients was primarily due to a thiazide-induced enhancement of PTH action on the bone. We were unable to demonstrate a hypercalcemic effect in hypoparathyroid patients treated with large doses of vitamin D, which has been reported by other investigators during chronic administration of thiazide diuretics (3, 5). However, it has to be emphasized that the results of our study are limited to the acute actions of CTZ and may not bear on the effects of chronic administration of thiazide diuretics. Furthermore, the occurrence of hypercalciuria during the acute administration of CTZ might have blunted a possible hypercalcemic action of thiazides in the hypoparathyroid patients.

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