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J Clin Invest. 1958;37(2):294-305. https://doi.org/10.1172/JCI103608.

Research Article

THE EFFECT OF ABRUPT CHANGES IN PLASMA CALCIUM CONCENTRATIONS ON RENAL FUNCTION AND ELECTROLYTE EXCRETION IN MAN AND MONKEY [1,2]

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(Submitted for publication June 25, 1957; accepted September 26, 1957)

It is well known that patients with hypercalcemia of diverse etiologies may exhibit marked polyuria (1–5). The increased rate of urine formation is often associated with considerable losses of urinary solute and sometimes results in severe depletion of extracellular salt and water stores (6). This urinary wastage has been attributed to slowly developing pathological changes in the renal tubules produced by prolonged hypercalciuria and nephrocalcinosis. It is possible, however, that the renal response may in part be conditioned by a direct and immediate physiological effect of the hypercalcemia and/or hypercalciuria. The studies of Wolf and Ball in which calcium infusions in the dog provoked a prompt increase in the rate of sodium excretion (7) suggest that such is the case. To test this hypothesis further, experiments were devised in man and monkey to evaluate the immediate effects of changing filtered calcium loads upon discrete renal functions and upon the rate of excretion of electrolytes.

MATERIALS AND METHODS

An increase in the filtered load of calcium was achieved by a sustained calcium infusion or by the single intravenous injection of calcium in the form of gluconate or lactate. In monkey and man the infusions were administered in the form of calcium gluconate or lactate at the rate of 0.07 mg. of calcium per minute per Kg. for a period of 60 to 90 minutes. The calcium salts were dissolved in hypotonic saline solutions (0.45 per cent). The infusion was administered at a constant rate of 1 ml. per minute in man and 0.1 ml. per minute in monkey and contained proper quantities of inulin and PAH for the measurement of renal clearances. Comparable solutions free of calcium were administered at the same rate before and after the calcium infusion. Three to four 20 minute control periods were obtained prior to the calcium infusion, during which inulin and PAH clearances and the control rates of sodium, chloride, potassium, calcium, phosphorus and ammonium (pH and bicarbonate in some experiments) excretion were determined. Similar measurements were made in four 20 minute periods during the calcium infusion, and for two to three comparable periods after the calcium infusion was discontinued. Standard catheter and air flush techniques were used for bladder emptying and clearance determinations. During the control period at least two and generally three heparinized blood samples were obtained for the determination of plasma calcium, phosphorus, sodium, potassium, chloride, bicarbonate, inulin and PAH concentrations. Similar measurements were repeated at 15 minute intervals during the calcium infusion and after its discontinuation. The calcium infusion studies were performed in five resting normal adults in a fasting state and in three normal fasting cynomolgus monkeys. Similar measurements were made in man before and after a single intravenous injection of 10 ml., 20 ml., and 40 ml. of 10 per cent calcium gluconate solution, respectively. These single injection experiments were performed in seven normal fasting male subjects.

After the typical response to a standard rapid injection of 20 ml. of calcium gluconate was evaluated, similar loads were administered to eight patients in whom the urine had been either alkalinized or acidified with appropriate prior therapy. In the latter subjects sodium bicarbonate or ammonium chloride solutions of 150 mEq. per liter were administered at the rate of 2 ml. per minute for 90 minutes before and for a similar period after the injection of the calcium load. In these subjects, measurements similar to those mentioned above were made during the acidifying or alkalinizing infusion both before and after the administration of the calcium load.

The plasma calcium concentration was reduced in three normal patients by the infusion of a chelating solution. Sodium Versenate® (sodium salt of ethylenediaminetetraacetic acid, Riker Laboratories, Inc.) was infused at the rate of 15 mg. per minute for 40 minutes. Measurements identical to those listed above were repeated before, during and for 90 minutes after the chelate

[1] Supported by grants from the United States Air Force [Contract No. AF 41(657)], the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health (Grant No. A-277), and the National Foundation for Infantile Paralysis.

[2] Presented in abstract form at the Forty-Eighth Annual Meeting of The American Society for Clinical Investigation, May, 1956.

infusion. In addition, free and total (digested) calcium concentration in the urine was measured during and after the Versenate® infusion.

The chemical methods are, for the most part, identical to those previously used and reported from this laboratory (8, 9). In addition, phosphorus was analyzed by the method of Fiske and Subbarow (10) and calcium by the technique of Kramer and Tisdall (11).

RESULTS

Calcium infusions in man (Table I)

The plasma calcium concentration rose promptly during the calcium infusion, remained elevated throughout the infusion and tended to fall toward normal in the postinfusion period (Figure 1, Table I). The plasma phosphorus rose consistently but much more slowly, reaching its highest levels after the discontinuation of the infusion in four of the five subjects (Table I). The peak increases in plasma calcium and phosphorus concentration averaged 6.0 mg. per cent (2.7 to 12.0) and 1.5 mg. per cent (0.9 to 1.9), respectively. No changes were noted in plasma sodium, potassium, chloride, bicarbonate concentrations or in the plasma pH.

The rate of calcium excretion began to increase promptly after the onset of the calcium infusion and reached a maximum toward the end of the infusion period (Figure 1, Table I), with the increment averaging 56 μEq. per minute (44 to 62). Phosphorus excretion also rose after the onset of the calcium infusion. This peak increase averaged 21 μM per minute and tended to occur somewhat later than the maximal increase in the rate of calcium excretion.

The calcium infusions induced a prompt increase in the rate of salt excretion (Figure 1, Table I). This increase was noted in the first infusion period, reached a peak toward the end of the calcium infusion, and persisted to a lesser extent during the postinfusion period. The maximum increase in the rate of sodium excretion averaged 700 μEq. per minute (375 to 1,086 μEq. per minute) or more than four times the control values. The simultaneous peak increase in the rate of chloride excretion averaged 520 μEq. per minute (190 to 870 μEq. per minute) or greater than two times the control values. Coincident with the peak increase in salt excretion, there occurred a moderate increase in the rate of urine flow averaging 3 ml. per minute. The increases in the rate of calcium, salt and water excretion tended to coincide. The rate of potassium excretion did not change consistently during the calcium infusion (Table I), tending to increase in two experiments, fall in two and remain unchanged in one. No consistent changes in the rate of urinary excretion of ammonia, bicarbonate, or in urinary pH were noted during or after the calcium infusions in those experiments in which these indices were measured.

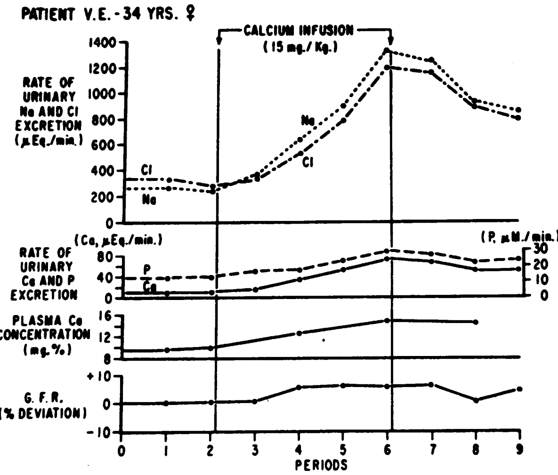

FIG. 1. THE EFFECT OF A CALCIUM INFUSION ON RENAL FUNCTION, ELECTROLYTE EXCRETION, CALCIUM AND PHOSPHORUS PLASMA CONCENTRATIONS IN MAN

Inulin clearance measurements showed no detectable changes in three of the human subjects and a small increase in the two remaining subjects (Table I—S. E. and V. E.). PAH clearances showed an increase in four of the five subjects (Table I).

Calcium infusions in monkey (Table II)

The data obtained from calcium infusions in three monkeys were similar to those obtained in man (Figure 2, Table II). The changes in plasma calcium and phosphorus concentrations corresponded to those seen in man with the rise in phosphorus tending to occur more slowly and reaching its peak later. The maximum increases in calcium and phosphorus concentrations averaged 2.6 and 0.9 mg. per cent, respectively. The peak increase in the rate of calcium excretion averaged 14 μEq. per minute and tended to coincide

TABLE I

The effects of calcium infusion on renal function and electrolyte excretion in man

		Clearances		Urine electrolyte excretion						Plasma concentration	
Subject	Periods	Inulin *ml./min.*	PAH *ml./min.*	Sodium *μEq./min.*	Chloride *μEq./min.*	Potassium *μEq./min.*	Calcium *μEq./min.*	Phosphorus *μM/min.*	Urine volume *ml./min.*	Calcium *mg. %*	Phosphorus *mg. %*
R. R.	Control*	103	553	293	300	76	3.3	12.1	3.2	9.4	3.3
	Calcium gluconate infusion	114	688	434	387	82	8.2	20.1	6.9	12.6	4.1
		109	654	609	449	34	36.7	21.3	3.9		
		100	650	666	490	34	47.1	23.0	1.2	13.7	
	After calcium infusion	103	592	582	471	28	44.8	28.9	1.3	13.4	4.8
S. E.	Control*	74	412	217	149	53	4.3	2.3	1.4	9.3	2.1
	Calcium gluconate infusion	81	470	357	316	73	14.8	5.6	4.5	21.4	2.3
		93	546	1,211	848	92	62.3	13.4	5.0	16.4	
	After calcium infusion	82	437	803	534	102	47.6	10.1	3.3	15.0	3.7
		71	428	617	425	74	31.6	7.0	2.9		
V. E.†	Control*	95	321	284	332	78	6.2	11.7	1.8	9.3	3.7
	Calcium gluconate infusion	96	364	387	370	62	12.6	15.5	1.8	12.2	4.3
		108	413	675	582	47	31.9	17.6	3.2		
		108	410	934	822	49	48.4	21.8	4.6	14.6	4.7
		108	487	1,370	1,240	64	70.2	27.0	8.5		
	After calcium infusion	109	448	1,291	1,198	67	67.5	25.6	7.1		
		97	405	950	923	50	47.5	20.6	4.5	14.0	5.2
		106	433	875	814	68	45.5	21.3	4.6		
R. M.	Control*	126	590	130	228	140	10.4	4.9	5.7	9.2	2.6
	Calcium gluconate infusion	128	624	263	415	130	22.8	4.5	5.4	10.0	2.6
		122	608	536	473	116	40.4	8.4	4.0	12.4	
		123	640	731	612	121	71.7	13.7	5.0	15.0	3.2
	After calcium infusion	127	610	578	477	103	67.5	14.5	2.8		3.5
N. L.	Control*	121	632	239	229	98	18.1	0.9	2.7	9.9	2.1
	Calcium gluconate infusion	127	676	414	388	127	36.8	1.6	9.4	11.2	2.2
		125	608	705	641	97	65.2	5.2	6.9		
		124	555	761	691	77	74.7	9.0	5.3	12.6	4.0
	After calcium infusion	123	531	658	590	62	69.8	11.8	4.1	11.2	2.9
		120	670	448	418	50	57.8	11.5	2.3		

* Controls represent the average of three 20 minute periods. Subsequent periods varied between 20 and 25 minutes in length.

† In this patient 0.15 mg. of calcium per Kg. per minute was administered.

with the increases in the rate of sodium and chloride excretion. The maximal increments in the rate of sodium and chloride excretion averaged 22 and 14 μEq. per minute or about six times the control values, respectively. In contrast to man, a consistent increase in the rate of potassium excretion averaging 7 μEq. per minute occurred simultaneously with the maximum rate of salt excretion. No changes in inulin clearance were noted during or after the calcium infusion.

TABLE II

The effects of calcium infusion on renal function and electrolyte excretion in the monkey

Monkey	Periods	Clearances: Inulin ml./min.	Clearances: PAH ml./min.	Electrolyte excretion: Sodium µEq./min.	Electrolyte excretion: Chloride µEq./min.	Electrolyte excretion: Potassium µEq./min.	Electrolyte excretion: Calcium µEq./min.	Electrolyte excretion: Ammonia mg./min.	Plasma concentration: Calcium mg. %	Plasma concentration: Phosphorus mg. %
I	Control*	10.6		0.4	2.4	6.3	6.6		12.6	2.4
	Calcium gluconate infusion	10.0		0.6	3.4	5.0	7.4			
		11.4		2.0	6.5	11.7	13.7		14.0	2.7
		9.1		3.4	10.1	11.8	15.9			
		9.4		1.2	5.6	6.5	16.6		15.6	2.7
		8.6		2.3	8.7	9.4	17.0			
	After calcium infusion	9.7		1.2	4.5	5.1	10.2			
		11.4		0.9	2.7	2.2	13.7		11.8	3.5
		7.5		0.9	2.4	1.5	5.6			
II	Control*	14.8		6.1	12.3	6.3	10.2	7.0	11.4	2.5
	Calcium gluconate infusion	12.7		7.3	13.7	6.5	12.1	6.5	14.2	2.6
		13.7		23.0	37.9	12.2	21.0	9.9		
		13.0		21.0	36.4	9.4	20.3	8.4	15.6	3.5
		12.5		22.6	35.5	8.0	15.5	6.5		
	After calcium infusion	11.4		10.3	22.1	6.5	17.1	5.9		
		11.2		8.0	14.3	5.2	12.8	5.0	11.1	3.2
		10.6		7.2	14.5	4.8	10.1	4.8		
III	Control*	14.5	79.7	1.9	3.4	5.7	5.1	6.1	11.6	4.2
	Calcium gluconate infusion	15.1	86.7	6.0	15.4	6.7	14.7	9.4	12.4	4.6
		15.7	90.7	14.1	37.8	10.2	26.2	14.3		
		13.9	81.3	13.1	34.0	9.0	24.7	9.8	12.6	5.8
		15.0	87.8	22.7	37.0	13.4	29.6	11.2		
	After calcium infusion	14.3	90.3	5.1	28.8	4.1	20.6	4.2		
		14.1	89.1	0.9	7.4	1.6	15.7	8.5	9.4	5.4
		12.6	83.0	1.1	3.3	3.3	7.8	7.9		

* Controls represent the average of three 20 minute periods. Each subsequent period varied between 20 and 25 minutes in length.

Single intravenous administration of calcium in man (Tables III and IV)

The rapid intravenous administration of 10, 20, and 40 ml. of 10 per cent calcium gluconate solution in man likewise produced an increase in the rate of calcium and salt excretion with the precise response proportionate to the quantity injected (Table III). Following the 20 ml. load, the rate of calcium and phosphorus excretion increased an average of 17 µEq. and 13 µM per minute, respectively. Coincidentally, the increment in the rate of sodium and chloride excretion averaged 183 and 148 µEq. per minute, or 200 and 110 per cent greater than the control rates, respectively. A small transient increase in potassium excretion was noted but no changes in urinary pH or bicarbonate concentration were noted. The changes following the injection of a 40 ml. calcium load were qualitatively similar but greater, whereas those following the injection of 10 ml. of calcium gluconate solution were considerably smaller (Table III). No changes in glomerular filtration rate or renal plasma flow were detected in those subjects in which it was measured following the single intravenous calcium injections (Table III—M. V., S. S., and J. M.)

In the experiments in which 20 ml. of calcium gluconate was administered intravenously to subjects being infused with bicarbonate or ammonium chloride, no definite difference in the response to the calcium load was noted from that observed in the unprepared patients (Table IV). The increase in the rate of calcium, sodium, and chloride excretion approximated that observed in patients

TABLE III

The effects of a single calcium gluconate injection on renal function and electrolyte excretion in man

Subject	Periods	Clearances: Inulin	Clearances: PAH	Urine electrolyte excretion: Sodium	Chloride	Potassium	Calcium	Phosphorus	CO_2	Ammonia	Urine: Volume	Urine: pH	Plasma concentration: Calcium	Plasma concentration: Phosphorus
		ml./min.	*ml./min.*	*µEq./min.*	*µEq./min.*	*µEq./min.*	*µEq./min.*	*µM/min.*	*vol. %*	*mg./min.*	*ml./min.*		*mg. %*	*mg. %*
M. V.	Control*	84	449	242	248	70	4.7	10.9		60.0	1.4		9.1	3.3
	10 ml. of calcium gluconate injected													
	After calcium gluconate injection	93	587	351	350	80	7.4	15.4		58.7	4.4		9.0	3.3
		86	427	326	323	47	12.3	13.0		60.3	5.0			
		89	466	365	335	48	14.0	12.3		56.0	4.7		11.2	
		87	468	365	330	49	14.3	12.3		58.5	4.8			
		79	418	316	312	43	13.4	10.6		55.6	3.3		9.6	3.8
		83	435	318	308	46	12.2	11.1		60.0	3.5			

Subject	Periods	Inulin	PAH	Sodium	Chloride	Potassium	Calcium	Phosphorus	CO_2	Ammonia	Volume	pH	Plasma Calcium	Plasma Phosphorus
L. G.	Control*			120	135	29	2.5	13.5	6.0		8.2	5.93		
	20 ml. of calcium gluconate injected													
	After calcium gluconate injection			328	280	43	12.1	39.9	6.3		17.3	6.09	12.6	3.5
				324	285	45	17.4	37.2	6.3		12.4	6.06		
				201	188	34	14.5	32.9	5.5		17.0	6.04	11.8	3.8
				167	165	31	14.4	28.3	5.3		12.5	5.95		
				136	142	28	13.5	23.0	5.3		13.8	5.95	10.8	3.8

Subject	Periods	Inulin	PAH	Sodium	Chloride	Potassium	Calcium	Phosphorus	CO_2	Ammonia	Volume	pH	Plasma Calcium	Plasma Phosphorus
C. J.	Control*			107	165	133	5.2	21.9	15.6		9.8	6.60	10.8	3.9
	20 ml. of calcium gluconate injected													
	After calcium gluconate injection			330	361	218	30.2	32.9	17.1		16.3	6.65		
				239	253	120	24.4	23.3	15.5		6.3	6.49		
				200	215	119	22.1	22.6	16.2		14.8	6.60	11.4	3.7
				117	117	93	15.4	17.0	13.4		13.4	6.52		
				147	134	101	20.1	19.3	12.5		17.5	6.57		
				118	124	77	15.1	15.6	12.5		13.8	6.59	12.2	3.6

Subject	Periods	Inulin	PAH	Sodium	Chloride	Potassium	Calcium	Phosphorus	CO_2	Ammonia	Volume	pH	Plasma Calcium	Plasma Phosphorus
C. J.	Control*			91	140	83	10.0	3.9	12.9		6.5	6.68	10.2	2.6
	20 ml. of calcium gluconate injected													
	After calcium gluconate injection			299	347	157	14.1	7.7	15.3		20.0	6.74		
				300	334	130	34.6	10.8	14.4		21.6	6.70		
				196	219	105	25.6	8.9	12.1		18.3	6.63		
				169	214	122	26.1	8.5	11.5		19.3	6.62		
				85	114	71	16.1	4.6	12.1		11.9	6.64	11.2	2.8
				140	192	122	29.6	8.2	12.1		21.1	6.60		
				106	119	86	21.5	6.5	11.3		14.8	6.54	10.8	3.1

* Controls represent the average of three 20 minute periods. Subsequent periods varied between 20 and 25 minutes in length.

TABLE III—*Continued*

Subject	Periods	Clearances		Urine electrolyte excretion							Urine		Plasma concentration	
		Inulin	PAH	Sodium	Chloride	Potassium	Calcium	Phosphorus	CO_2	Ammonia	Volume	pH	Calcium	Phosphorus
		ml./min.	*ml./min.*	*μEq./min.*	*μEq./min.*	*μEq./min.*	*μEq./min.*	*μM/min.*	*vol. %*	*mg./min.*	*ml./min.*		*mg. %*	*mg. %*
S. A.	Control*			132	146	55	7.5	0.9	26.5		9.6	6.57	11.0	1.8
	20 ml. of calcium gluconate injected													
				220	174	63	10.2	0.9	28.5		17.0	6.60		
	After			225	183	53	15.2	1.0	26.8		17.7	6.55		
	calcium			207	181	52	13.6	1.1	25.6		18.2	6.48	11.2	2.3
	gluconate			185	178	65	11.9	0.9	23.3		17.0	6.32		
	injection			153	160	57	8.9	1.1	23.3		14.8	6.34		
				161	168	56	9.1	1.2	23.3		14.0	6.39		
				183	190	61	11.0	1.7	23.6		14.7	6.46	13.0	2.7
S. S.	Control*	129	542	267	269	128	11.0	14.7		69.4	5.0		9.6	3.6
	40 ml. of calcium gluconate injected													
	After	130	532	517	422	135	28.3	27.1		85.0	9.7		11.0	3.8
	calcium	138	478	667	520	92	47.8	32.9		85.4	11.8		11.0	4.3
	gluconate	118	427	467	398	64	30.4	24.5		61.9	6.3		10.8	4.1
	injection	126	462	422	374	65	28.2	24.1		68.1	7.0		10.2	4.2
J. M.	Control*	125	688	243	240	59	11.5	11.3		81.0	3.7		9.6	3.2
	40 ml. of calcium gluconate injected													
	After	131	794	577	564	93	35.8	16.3		93.9	10.5		12.0	3.5
	calcium	128	686	764	737	83	54.1	24.2		66.5	6.0		10.8	3.7
	gluconate	132		638	592	71	43.4				6.6			
	injection	127	674	397	384	48	39.1	27.0		95.8	10.6		10.4	4.2

whose urine had not been previously acidified or alkalinized. At the time that the calcium load was administered, the urine pH's averaged 6.01, 6.52, and 7.33 in the acidified group, the untreated, and the alkalinized group, respectively. No change in the plasma pH was detected during the acid or the alkaline infusions.

Versenate® infusion in man (Table V)

In the chelate experiments, as the plasma calcium concentration fell, the rate of sodium and chloride excretion likewise decreased (Figure 3, Table V). Plasma calcium concentration began to fall toward the end of the chelating infusion and continued to fall thereafter. Total calcium excretion, free plus chelated (digested), rose promptly after the onset of the infusion but the rate of excretion of free calcium fell toward the end of the Versenate® infusion. Coincidentally, there occurred a fall in the rate of sodium and chloride excretion. These falls in electrolyte excretion averaged 177 and 144 μEq. per minute or 45 and 47 per cent of the control values for sodium and chloride, respectively. Total phosphorus excretion tended to rise slowly after the onset of the Versenate® infusion reaching its highest levels after the cessation of the infusion. No changes in glomerular filtration rate or renal plasma flow were noted throughout these chelate experiments.

DISCUSSION

These data indicate that an increase or decrease in the plasma calcium concentration promptly produces a similar change in the rate of salt excretion

TABLE IV

The effects on electrolyte excretion of a single calcium injection in patients receiving an acid or alkaline infusion

		Urine electrolyte excretion								Plasma concentration	
Subject	Periods	Sodium	Chloride	Potassium	Calcium	Phosphorus	Urine volume	Urine pH	Plasma pH	Calcium	Phosphorus
(Infused with NH_4Cl)		*μEq./min.*	*μEq./min.*	*μEq./min.*	*μEq./min.*	*μM/min.*	*ml./min.*			*mg. %*	*mg. %*
P. L.	Control*	85	118	61	8.4	8.3	4.5	6.45		10.4	1.9
	20 ml. of calcium gluconate injected										
	After calcium gluconate	216	208	60	34.7	16.0	12.6	6.32			
		222	239	46	21.6	19.5	12.7	6.18			
		110	123	24	12.8	10.8	7.5	6.11			
		145	181	33	19.6	14.6	11.5	6.07			
A. A.	Control*	151	156	36	13.5	10.2	0.8	6.21	7.23	10.1	1.4
	20 ml. of calcium gluconate injected										
	After calcium gluconate	231	208	29	14.8	8.0	5.6	6.18	7.32	11.0	1.8
		154	149	11	15.1	6.7	1.2	5.51			
		205	225	14	20.8	7.5	1.2	5.48	7.34	10.6	2.0
		220	246	14	21.6	6.7	1.2	5.47			
R. B.	Control*	27	57	20	6.2	4.7	0.5	5.50	7.36	10.0	
	20 ml. of calcium gluconate injected										
	After calcium gluconate	143	180	38	20.9	6.6	1.3	5.46	7.38	12.7	
		96	117	25	23.7	5.9	0.7	5.02			
		116	168	21	31.1	7.9	0.9	5.09	7.39	11.0	
		159	225	23	28.1	6.7	1.5	5.09			
D. M.	Control*	155	242	123	6.7	4.0	9.7	6.82	7.34	11.1	1.7
	20 ml. of calcium gluconate injected										
	After calcium gluconate	287	335	126	19.8	6.6	7.6	6.70	7.36	13.8	
		246	304	100	17.6	6.6	3.9	6.60			
		213	282	88	15.1	7.9	2.9	6.44	7.36		
		228	337	113	15.1	9.9	5.7	6.32			

* Controls represent the average of three 20 minute periods. Subsequent periods varied between 20 and 25 minutes in length.

TABLE IV—*Continued*

Subject	Periods	Urine electrolyte excretion: Sodium	Chloride	Potassium	Calcium	Phosphorus	Urine volume	Urine pH	Plasma pH	Plasma concentration: Calcium	Phosphorus
(Infused with $NaHCO_3$)		*μEq./min.*	*μEq./min.*	*μEq./min.*	*μEq./min.*	*μM/min.*	*ml./min.*			*mg. %*	*mg. %*
V. V.	Control*	404	189	106	2.8	23.8	6.7	7.74		9.5	2.8
	20 ml. of calcium gluconate injected										
		491	245	70	4.2	25.7	11.8	7.16		10.6	2.9
	After	477	264	38	6.2	21.2	15.5	6.90			
	calcium	447	240	44	7.1	18.9	16.7	6.81		9.9	3.1
	gluconate	396	204	42	7.8	14.3	18.2	7.07			
		384	222	31	9.0	8.0	9.0	7.39			
G. I.	Control*	309	142	176	4.6	23.3	4.9	7.66		10.0	2.4
	20 ml. of calcium gluconate injected										
		473	225	157	15.1	21.0	4.5	7.63		10.4	2.5
	After	430	188	95	19.2	23.1	10.4	7.29			
	calcium	199	72	63	8.7	18.9	10.8	7.12			
	gluconate	205	60	78	8.0	10.2	13.4	7.12			
		266	77	87	10.5	10.3	12.3	7.29			
S. L.	Control*	121	43	181	7.5	36.3	6.7	7.20		10.2	2.2
	20 ml. of calcium gluconate injected										
		319	100	272	27.0	39.3	21.8	7.17		10.3	2.2
	After	214	46	79	20.3	19.6	10.5	7.15			
	calcium	229	50	94	28.7	28.4	14.2	7.00			
	gluconate	160	24	48	20.9	23.9	10.7	7.03			
		199	28	58	23.7	22.1	11.8	7.09			
P. L.	Control*	360	116	198	5.3	8.8	6.6	7.70		9.3	2.1
	20 ml. of calcium gluconate injected										
		565	172	145	23.5	31.8	9.3	7.36			
	After	299	87	53	14.4	26.2	4.3	7.36			
	calcium	188	46	44	9.6	21.3	6.6	7.01			
	gluconate	148	44	69	11.2	25.9	9.7	7.03			
		236	39	64	9.5	23.7	7.3	7.23			

in man and monkey. The mechanism by which this change in the rate of electrolyte excretion occurs is not certain. It is possible that a change in the rate of electrolyte excretion could be explained by a similar change in glomerular filtration rate. Indeed, in two of the five calcium infusion studies in man an increase in filtration rate was observed coincident with the peak increase in salt excretion. However, in the remaining experiments in man and monkey, no measurable changes in filtration rate were apparent. Furthermore, in those experiments where a slight increase in filtration rate did occur, the markedly elevated rate of salt excretion persisted after the filtration rate had returned to control levels (Figure 1, Table I). The changes in salt excretion are compared with the changes in filtration rate in Figure 4, but no consistent relation is apparent. In the chelate infusion experiments the falls in electrolyte excretion were not associated with a measurable fall in filtration rate. These data, therefore, show no consistent trend to suggest that the changes in salt excretion are mediated through changes in glomerular filtration rate. Instead, they imply that a change in plasma calcium concentration and in the rate of calcium excretion effects an immediate and opposite change in the rate of tubular reabsorption of sodium and chloride. Figure 5 suggests that this altered tubular function correlates best with the change in the rate of calcium excretion.

The contention that the salt diuresis is caused by the osmotic load imposed by the calcium does not appear tenable. The salt diuresis produced

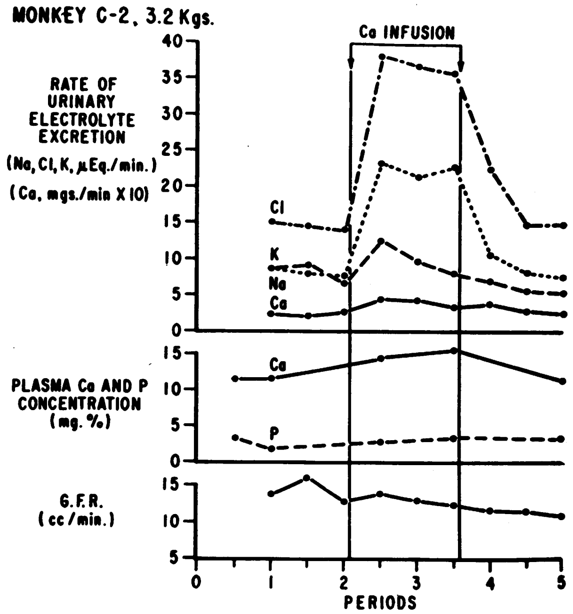

FIG. 2. THE EFFECT OF A CALCIUM INFUSION ON RENAL FUNCTION, ELECTROLYTE EXCRETION, CALCIUM AND PHOSPHORUS PLASMA CONCENTRATIONS IN MONKEY

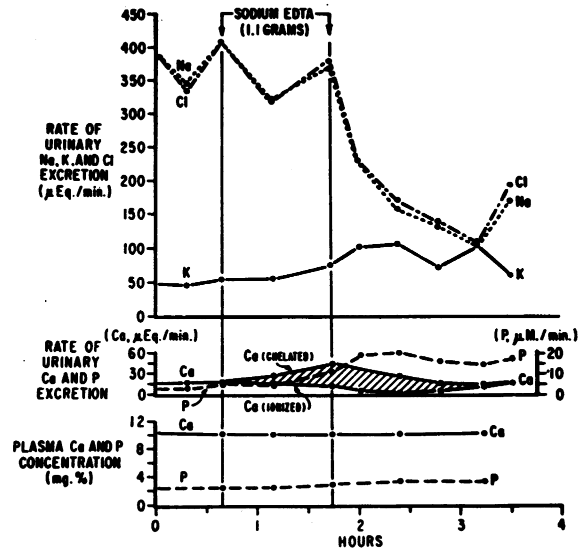

FIG. 3. THE EFFECT OF A CHELATING INFUSION ON PLASMA CALCIUM CONCENTRATION, FREE CALCIUM EXCRETION, RENAL FUNCTION AND ELECTROLYTE EXCRETION IN MAN

by the calcium infusions in man averaged almost twenty times in total solute that due to the calcium *per se*. Similarly, after the chelate infusions, the fall in excretion of salt far exceeded in total solute the coincident decrease in free calcium excretion.

The site in the tubular lumen or in the tubular cells affected by a change in the rate of calcium excretion remains unknown. It has been demonstrated in isolated flounder tubules that changing calcium concentration affects the rate of phenol red transport (12). Of interest is the fact that considerable changes in the urinary pH by acid or alkaline infusions did not appreciably alter the saluresis of a standardized calcium load (20 ml. calcium gluconate intravenously).

The consistent and prompt increase in the rate of phosphorus excretion and the slower rise in plasma phosphorus concentration produced by the administration of calcium deserve some comment. It has been repeatedly demonstrated that a calcium infusion in normal man will reduce the overall rate of phosphorus excretion in the subsequent 24 hour period (13, 14). However, it has also been noted that comparable calcium loads in hypoparathyroid subjects, or in normal subjects in whom the rate of phosphorus excretion is measured during the infusion and shortly thereafter, produce an immediate increase in phosphorus excretion (13–15). This latter observation appears in substantial agreement with those reported here. The apparent discrepancy suggests that the calcium infusion evokes a prompt increase in the rate of phosphorus excretion prior to its slower and opposite effect in reducing the rate of excretion. This latter change has been attributed to the gradual suppression of parathyroid function with a consequent increase in the rate of phosphorus reabsorption by the renal tubules (13, 14).

The cause of the more immediate increase in phosphorus excretion is not established. It is conceivable that the calcium infusion promptly stimulated parathyroid function with a consequent reduction in tubular reabsorption of phosphorus. However, this alternate explanation is not consistent with the large body of evidence which argues that a calcium infusion suppresses parathyroid function (13, 14, 16, 17). It is likely that, in part at least, this increased rate of excretion simply reflects the rising plasma phosphorus concentrations produced by the administration of calcium. However, the change in excretory rate seems more impressive and appears to precede the slower rise in plasma phosphorus concentration. It is tempting to attribute this phosphate diuresis in large part to the immediate alteration in tubular function effected by the calcium administration. In this view, the reduced capacity for the reabsorption of sodium chloride and phosphorus may

TABLE V

The effects of a chelating infusion on renal function and electrolyte excretion in man

Subject	Periods	Clearances		Urine electrolyte excretion						Urine volume	Plasma concentration	
		Inulin	PAH	Sodium	Chloride	Potassium	Calcium: Free	Calcium: Digested	Phosphorus		Calcium	Phosphorus
		ml./min.	*ml./min.*	*µEq./min.*	*µEq./min.*	*µEq./min.*	*µEq./min.*		*µM/min.*	*ml./min.*	*mg. %*	*mg. %*
S. C.	Control*	124	555	346	353	127	7.2	7.2	4.1	5.3	9.2	2.9
	EDTA (76 ml.) infusion	134	670	335	331	131	6.6	31.5	5.2	7.2	9.1	3.4
		124	576	298	258	144	5.3	60.6	8.9	4.9	8.6	3.5
	After EDTA infusion	135	473	219	225	140	2.4	58.6	11.8	6.9	8.8	3.3
		114	466	185	191	116	0.6	43.0	14.5	5.1		
W. R.	Control*	169	649	372	380	136	15.1	15.1	37.3	8.5	10.7	5.1
	EDTA (60 ml.) infusion	156	677	339	331	124	15.3	21.4	42.2	9.1	10.4	4.9
		161	667	292	258	118	14.5	22.8	49.3	9.3	9.8	4.9
	After EDTA infusion	158	610	273	233	112	10.9	22.4	48.5	7.8	9.8	4.7
		152	596	247	228	93	8.2	23.0	37.1	5.6		
		170	605	253	228	84	8.5	15.9	48.3	3.3	10.6	4.7
D. B.	Control*	126	825	379	343	49	16.6	16.6	3.8	3.9	10.9	2.4
	EDTA (110 ml.) infusion	128	802	321	319	55	15.1	22.2	4.1	2.6	10.0	2.4
		142	900	369	382	75	12.0	44.7	10.7	2.8	10.0	2.7
	After EDTA infusion	136	898	231	231	102	5.2	36.4	18.6	8.0	10.2	3.2
		122	879	157	162	106	2.9	26.5	20.3	12.1		
		122	740	133	139	71	5.0	15.7	16.0	3.4		

* Controls represent the average of three 20 minute periods. Subsequent periods varied between 20 and 25 minutes in length.

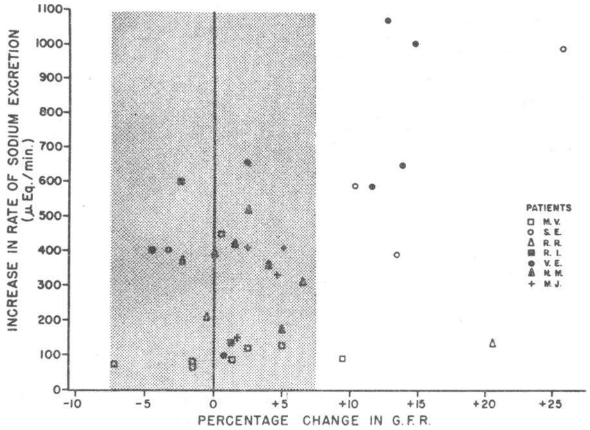

FIG. 4. CHANGES IN SODIUM EXCRETION PLOTTED AGAINST CHANGES IN GLOMERULAR FILTRATION RATE

Shaded areas represent changes of ± 7.5 per cent in filtration rate—changes which are within the experimental error.

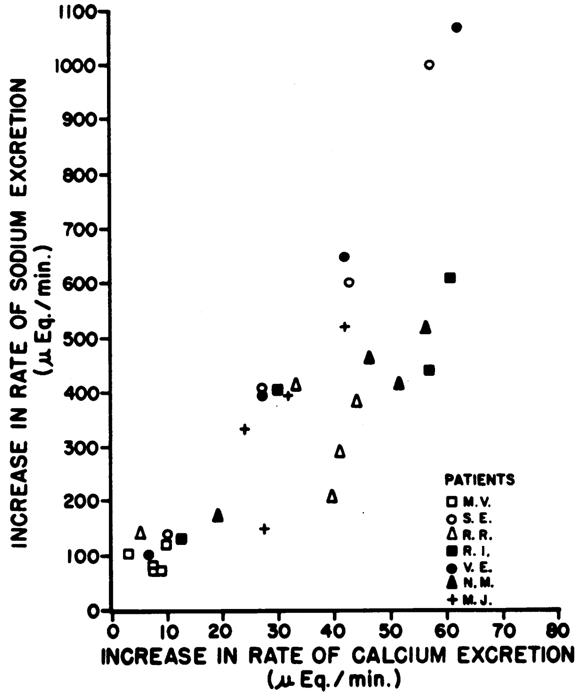

FIG. 5. CHANGES IN SODIUM EXCRETION IN THE INFUSION STUDIES IN MAN PLOTTED AGAINST CHANGES IN THE RATE OF EXCRETION OF CALCIUM

all represent the direct effect of a sudden increase in filtered calcium load.

The slow rise in plasma phosphorus concentration noted toward the end of the calcium infusion and thereafter agrees with similar observations reported by others (17, 18). This finding has been attributed to the rapid release of phosphorus from some source such as bone or tissue cells. These data are in accord with such a hypothesis but do not help to delineate the site from which the phosphorus stores were transferred nor the mechanism by which hypercalcemia induces such a transfer.

The slight tendency towards an increase in phosphorus excretion toward the end and after the chelating infusion may best be explained by an increased secretion of parathyroid hormone. An increased rate of hormone secretion would be expected to result from a falling plasma calcium level (19, 20) induced by the increased urinary loss of calcium in the chelated form.

The difference between the consistent increase in potassium excretion in the monkey and the inconsistent changes in man after a comparable calcium load may reflect the basic dietary habits of both species. The monkey maintained on a predominantly fruit diet responds like any subject on a sodium free regimen. If an anion load is imposed by a calcium induced chloruresis, potassium is excreted because less sodium is available (21). An alternate hypothesis to explain this difference would place the calcium effect directly on sodium reabsorption at a site proximal to the potassium secreting segment.

Whether the salt diuresis induced by hypercalcemia might ultimately prove of therapeutic value in the edematous subject remains to be seen. As a separate form of therapy or combined with other known diuretic agents, such calcium loads might prove therapeutically feasible.

SUMMARY

1. Calcium infusions in man and monkey at the rate of 0.1 mg. calcium per minute per kilogram produce a prompt increase in the rate of sodium, chloride, and water excretion.

2. Single intravenous administration of 10, 20, and 40 ml. of 10 per cent calcium gluconate solution in man produces a comparable increase in the rate of salt and water excretion in proportion to the dose administered.

3. The calcium infusions or single intravenous injections evoke a prompt increase in the rate of phosphorus excretion.

4. The effects of a single intravenous injection of calcium are not appreciably modified by the prior acidification or alkalinization of the urine.

5. A reduction in the plasma calcium concentration by the administration of a chelating agent causes a fall in the rate of salt excretion.

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