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## Renal Effects of Calcitonin

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**Summary:** Porcine calcitonin in a slow-release gelatin vehicle was given by intramuscular injection to 10 patients—four with primary hyperparathyroidism, four with Paget's disease, and two with carcinoma of the breast and hypercalcaemia. All cases showed a fall in serum calcium with an immediate rise in urine calcium. All except three patients with primary hyperparathyroidism showed a fall in serum phosphorus, but an immediate rise in urine phosphorus occurred in all cases. Urine hydroxyproline output fell in three patients with severe Paget's disease. Urine sodium rose in all cases, but the effects on potassium, magnesium, water, and pH were not appreciably different from results obtained in four control subjects who were given the gelatin vehicle alone.

The data suggest that calcitonin caused a decrease in the tubular resorption of calcium and phosphorus. The hypocalcaemic effect appeared to be due to a decrease in bone resorption in the patients with Paget's disease but in the remaining cases could be accounted for in part or entirely by the rise in urine calcium.

### Introduction

Observation in rats has established that calcitonin lowers serum calcium by inhibition of bone resorption (Milhaud *et al.*, 1965; Robinson *et al.*, 1967; Wallach *et al.*, 1967), and this effect has also been demonstrated in tissue culture (Friedman and Raisz, 1965; Aliapoulis *et al.*, 1966; Nisbet and Nordin, 1968). Cooper *et al.* (1967) and Copp and Kuczerpa (1968)

showed that the hypocalcaemic action is greatest in young animals with a rapid bone turnover. The effect of calcitonin on urinary hydroxyproline in Paget's disease in man (Bijvoet *et al.*, 1968) has confirmed the inhibitory action of calcitonin on bone resorption when the resorption rate is high.

Some workers have also shown that calcitonin has a phosphaturic action on the kidney (Kenny and Heiskell, 1965; Milhaud *et al.*, 1966; Robinson *et al.*, 1966), and others have noted that it also tends to increase the calcium output in the urine (Ardaillou *et al.*, 1967; Singer *et al.*, 1968). The present paper reports the results of acute calcitonin studies in 10 patients where particular attention was paid to the renal action of the hormone.

### Patients and Methods

The 10 patients comprised four with primary hyperparathyroidism without evidence of bone disease (one man and three women), four with Paget's disease (three men and one woman), and two with hypercalcaemia associated with carcinoma of the breast and bone secondaries. The relevant initial data are shown in Table I. It will be noted that six of the cases had hypercalcaemia. One patient (Case 1) had very mild Paget's disease, only one vertebra being involved.

After an overnight fast the subjects were given 1 litre of

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TABLE I.—Clinical Data and Initial Serum and Urine Values

Case No.	Age and Sex	Weight (Kg.)	Diagnosis	Serum			Urine				
				Alkaline Phosphatase (K.A. units/100 ml.)	Calcium (mg/100 ml.)	Phosphorus (mg/100 ml.)	Creatinine Clearance (ml./min.)	CaE (mg./100 ml. G.F.)	PE (mg./100 ml. G.F.)	Sodium (mEq/100 ml. G.F.)	Hydroxyproline (µg/min.)
Normal range				2-12	9.0-10.6	2.5-4.5	80-120	0.03-0.15	*	0.043-0.236	5-25
1	53 M	65	Paget's disease	14	9.70	3.35	103	0.12	0.19	0.007	11
2	59 M	91	"	260	9.05	3.15	86	0.03	0.33	0.043	335
3	59 M	62	"	188	9.95	3.65	104	0.05	0.34	0.120	88
4	62 F	60	"	160	9.65	3.65	93	0.08	0.43	0.148	173
5	55 M	53	Hyperparathyroidism	8	11.45	2.50	75	0.26	0.64	0.083	22
6	67 F	61	"	8	11.60	2.30	56	0.23	0.62	0.097	17
7	47 F	85	"	10	12.85	1.50	100	0.23	1.25	0.099	15
8	54 F	62	"	14	13.20	2.15	78	0.45	0.85	0.076	20
9	61 F	54	Carcinoma of breast	24	12.40	3.65	41	0.36	0.59	0.043	17
10	49 F	68	"	49	16.20	4.80	18	1.18	2.39	0.348	21

\* Determined by serum phosphorus

water to drink to ensure adequate bladder-emptying and then 200 ml. of water per hour. No food was taken throughout the test. Urine was collected hourly for eight hours and a blood sample withdrawn at the mid-point of each collection. At the end of the second hour porcine calcitonin (10 M.R.C. units/mg.) was injected intramuscularly in a dose of 4 units/kg. body weight in a slow-release gelatin vehicle containing 120 mg. of hydroxyproline. Four normal subjects were given the gelatin vehicle without calcitonin and urine was collected under the same conditions to observe its effect on urine hydroxyproline and mineral excretion.

The Auto-Analyzer was used to estimate the phosphorus (N-4a), creatinine (N-11a), and calcium (Knowles, 1968) in serum and urine. Urine hydroxyproline was also measured on the Auto-Analyzer after acid hydrolysis based on the method of Grant (1964). Sodium, potassium, and magnesium were measured by flame absorption spectrophotometry (Dawson *et al.*, 1968) and pH was measured with an E.I.L. pH meter. Calcium, phosphorus, and sodium excretion are expressed as units/100 ml. of glomerular filtrate as described by Peacock *et al.* (1968). This is calculated by dividing the urine concentration of the element concerned by the urine creatinine concentration and multiplying by the plasma creatinine. Urine hydroxyproline output is expressed in  $\mu\text{g./minute}$ . Calcium, phosphorus, and hydroxyproline excretion after calcitonin is expressed as the absolute change from the mean of the two control values.

**Results**

Serum calcium fell in all cases, least in the patients with primary hyperparathyroidism and most in one of the patients

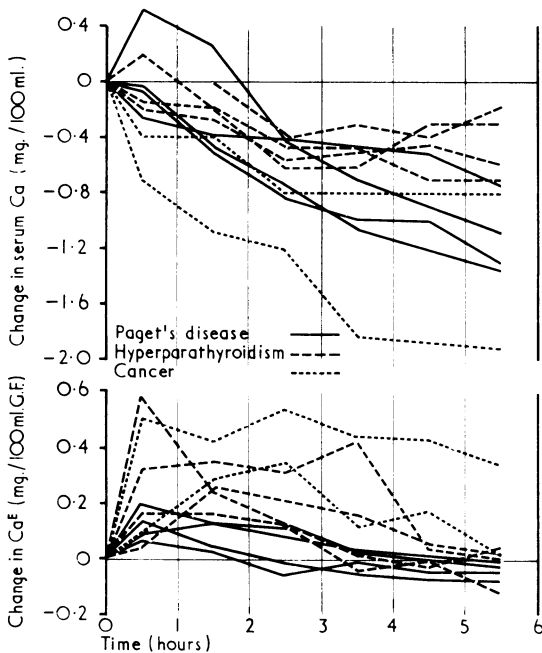


FIG. 1.—Effect of calcitonin (4 units/kg. intramuscularly) on serum calcium (top) and urine calcium (below) in 10 patients. All results are expressed as changes from basal values.

with malignant hypercalcaemia. The fall in serum calcium was associated with an immediate rise in urine calcium in all cases, but this was least pronounced in patients with Paget's disease. In all but one case the urine calcium had returned to the baseline by the sixth hour (Fig. 1).

Serum phosphorus fell in the patients with Paget's disease and cancer but not in three of the four with primary hyperparathyroidism. Urine phosphorus excretion increased in all cases, the patients with Paget's disease as a group showing the

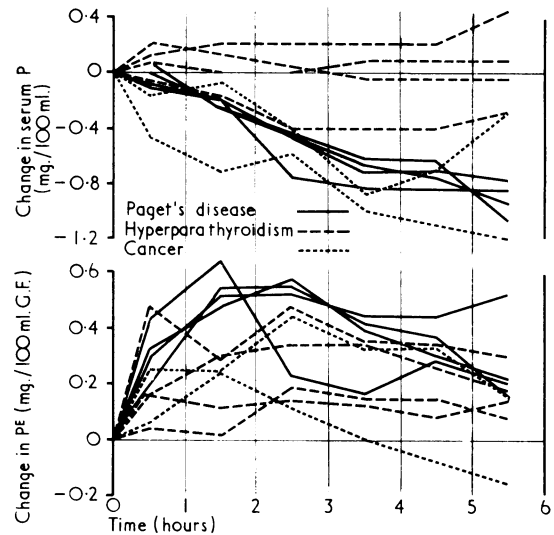


FIG. 2.—Effect of calcitonin on serum and urine phosphorus.

greatest rise (Fig. 2). No consistent change occurred in either serum or urine magnesium after calcitonin, but there was a definite rise in urine sodium (Table II). Small rises were also

TABLE II.—Mean Urine Sodium (mEq/100 ml. of Glomerular Filtrate) and Standard Error for all Patients Before and After Calcitonin

	Basal	Time (Hours)					
		1	2	3	4	5	6
Mean urine sodium	0.120	0.361*	0.307*	0.262*	0.230	0.183	0.167
Standard error	0.031	0.077	0.056	0.049	0.061	0.052	0.054

\* Significantly different from baseline.

found in urine potassium, volume, and pH, but they were no greater than in the control subjects and were not regarded as significant. Urine hydroxyproline fell appreciably in the three patients with severe Paget's disease, in whom the initial excretion was high. In the remainder the basal excretion of hydroxyproline was normal (11–23  $\mu\text{g./minute}$ ) and did not change to any extent after calcitonin (Fig. 3); nor did it change in the four control subjects despite the large amount of gelatin in the vehicle.

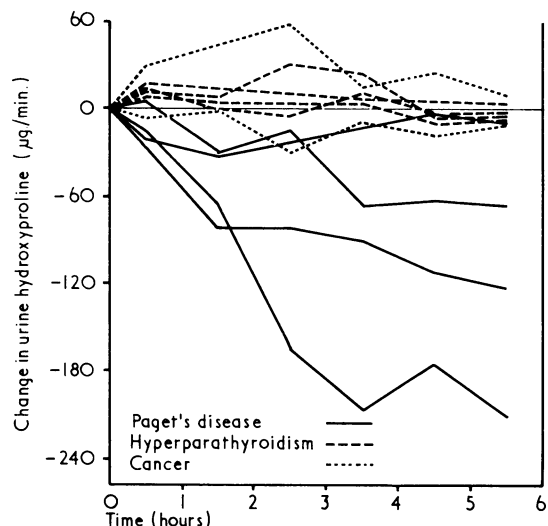


FIG. 3.—Effect of calcitonin on urine hydroxyproline.

### Discussion

Our results suggest that porcine calcitonin reduces tubular reabsorption of calcium and phosphorus in man and that these effects contribute appreciably to the hypocalcaemic and hypophosphataemic actions of the hormone except when bone turnover is very high (as in severe Paget's disease) and inhibition of bone resorption predominates. This is illustrated in Figs. 4 and 5, which show the relation between the total increase in calcium and phosphorus excretion (over the amount predicted from the basal data) and the changes in the serum levels at six hours.

In patients with severe Paget's disease there was no net rise in urine calcium and the entire fall in serum calcium must be attributed to inhibition of bone resorption (Fig. 4). In the

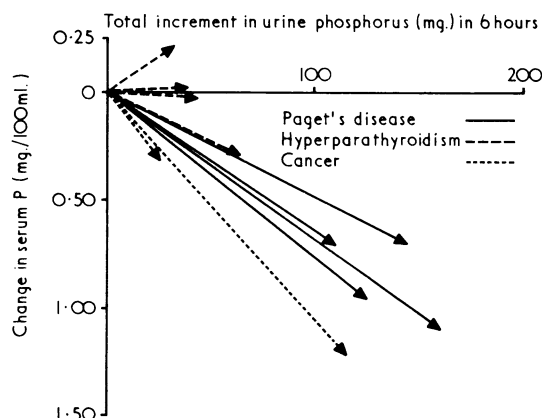


FIG. 4.—Relation between total increment in urine calcium and final fall in serum calcium over the six-hour period following calcitonin.

remainder the serum and urine calcium changes are inversely related. The extent to which the rise in urine calcium can account for the fall in serum level depends on the size of the calcium pool, but even if this is greater than the amount circulating in the plasma and extracellular fluid the urinary calcium clearly contributes substantially to the hypocalcaemia. The corresponding phosphorus data (Fig. 5) show that in the

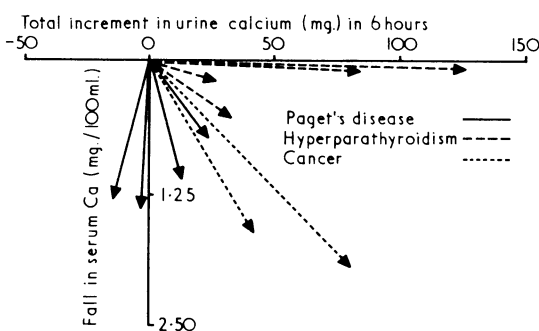


FIG. 5.—Relation between total increment in urine phosphorus and final fall in serum phosphorus over the six-hour period following calcitonin.

three hyperparathyroid patients whose plasma phosphorus did not fall there was little change in urine phosphorus. In the remaining cases the phosphaturia was sufficient to account for the hypophosphataemia if the phosphorus "pool" was confined to the plasma and extracellular fluid—that is, was distributed in a volume of about 15 l. Even in the patients with Paget's disease, in whom the fall in serum calcium was wholly attributable to inhibition of bone resorption, the hypophosphataemia could be entirely accounted for by phosphaturia, suggesting the strange possibility that calcitonin may inhibit calcium but not phosphorus outflow from bone.

It is interesting that calcitonin acts in some ways antago-

nistically and in others similarly to parathyroid hormone. Thus its inhibition of tubular reabsorption of calcium is opposite to the effect of parathyroid hormone (Kleeman *et al.*, 1961), but its phosphaturic effect is similar to that of parathyroid hormone. Its action on sodium output is similar to that of parathyroid hormone (Nordin, 1960), but, unlike parathyroid hormone, calcitonin does not affect urine pH. Parathyroid hormone increases tubular reabsorption of magnesium (Macintyre *et al.*, 1963), but calcitonin appears to have little or no effect on it. Though Clark and Kenny (1969) failed to show any increase in either urine calcium or sodium using calcitonin infusions in dogs, our findings agree well with those of Ardaillou *et al.* (1967) and Bijvoet *et al.* (1968) in man.

Our results provide another example of the critical role of the kidney in serum calcium homeostasis which we have emphasized elsewhere (Peacock *et al.*, 1969). In our opinion bone resorption makes little if any contribution to the normal maintenance of serum calcium in adults, which is determined by the relation between the rate of calcium absorption and the renal threshold for calcium. The latter is largely determined by parathyroid hormone activity, but also it seems by calcitonin. Needless to say, in pathological circumstances, when calcium intake or absorption is low, bone resorption by parathyroid hormone must be invoked to maintain the serum calcium, but in ordinary circumstances and within very wide limits of calcium intake and absorption it is the kidneys, influenced by these hormones, that determines the serum calcium concentration at which the absorbed and the excreted calcium come into equilibrium. This being the case, and since bone turnover in adults is relatively low (Burkinshaw *et al.*, 1969), one would not expect calcitonin to lower serum calcium in adults by an action on the bone. When bone turnover is high, however, as in Paget's disease, the action of calcitonin on the bone becomes very significant and produces a fall in filtered load of calcium which offsets any action it may be having on the renal tubular reabsorption of calcium.

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