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## Renal Excretion of Phosphate, Calcium and Sodium During and After a Prolonged Thyrocalcitonin Infusion in Man (33803)

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Various experiments suggested that thyrocalcitonin acts on the kidney, and that its action is therefore not limited to bone. However, results are different according to the various species studied. In the rat, the renal excretion of phosphate increases (1, 3–5) or remains unchanged (6), whereas the renal excretion of calcium decreases (1, 5, 6). A rise in sodium excretion has also been noted (5). In the dog, the excretion rates of these electrolytes are not modified (7). Nevertheless, when a large dose is infused into the renal artery of a dog, there is a rise in phosphate excretion (8). A similar effect has been described in the pig (8). In man, we have previously shown that thyrocalcitonin brings about an increase in the excretion rates of phosphate and calcium (9), sodium and chloride (10). The purpose of the present study was to investigate the duration of these changes during and after a prolonged infusion of thyrocalcitonin in man and to compare the results with those previously obtained in laboratory animals by other workers.

*Subjects and Methods.* Six male subjects were studied: there were four normal, one hyperparathyroid in whom the presence of an adenoma was later surgically confirmed, and one hypoparathyroid whose disease was primary. A diet containing 300 mg of calcium and 1,000 mg of phosphate was given on the day of the experiment and on the 3 days preceding it. Control values for plasma calcium, plasma phosphate and inulin clearance

TABLE I. Plasma Concentrations of Calcium and Phosphate, Inulin Clearances Immediately before the Study.

| | Plasma calcium (meq/liter) | Plasma phosphorus (mmoles/liter) | Inulin clearance (ml/min) |
|---|---|---|---|
| Normal subject 1 | 4.30 | 0.71 | 111 |
| 2 | 5.0 | 0.60 | 122 |
| 3 | 5.3 | 0.78 | 124 |
| 4 | 5.3 | 0.77 | 100 |
| Hypoparathyroidism | 3.70 | 1.57 | 116 |
| Hyperparathyroidism | 5.50 | 0.33 | 108 |

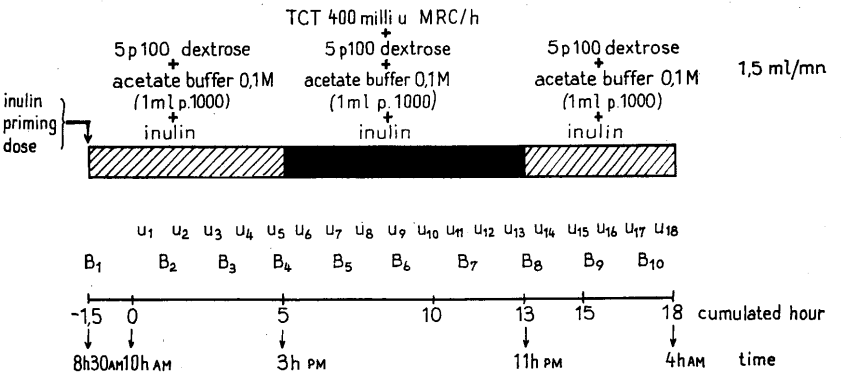


FIG. 1. Experimental procedure.

are given in Table I. The thyrocalcitonin used was extracted from the thyroid gland of the pig (2), and had a specific activity of 200 MRC m.u./mg.

The pattern of the experiment is illustrated in Fig. 1. 3200 MRC m.u. of thyrocalcitonin dissolved in 0.1 *M* acetate buffer at pH 4.6 were infused intravenously over 8 hr in 5% dextrose given at 1.5 ml/min. A control infusion of 5% dextrose which contained the

TABLE II. Sodium, Chloride, Calcium, and Phosphate Excretion.[a]

| | | Sodium ($\mu$eq/min) | Chloride ($\mu$eq/min) | Calcium ($\mu$eq/min) | Phosphate ($\mu$moles/min) |
|---|---|---|---|---|---|
| Normal subject 1 | 1. | 37.43 ± 2.25 | 53.06 ± 4.98 | 3.26 ± 0.36 | 11.05 ± 0.94 |
| | 2. | 135.53 ± 22.15 | 80.76 ± 15.33 | 7.66 ± 1.43 | 23.90 ± 4.10 |
| | 3. | 58.25 ± 13.72 | 24.58 ± 5.66 | 4.18 ± 0.95 | 29.72 ± 2.16 |
| | 4. | 11.97 ± 5.20 | 8.76 ± 1.70 | 2.52 ± 0.42 | 23.68 ± 1.83 |
| 2 | 1. | 133.85 ± 15.05 | 117.02 ± 4.98 | 7.15 ± 0.93 | 8.70 ± 0.55 |
| | 2. | 317.88 ± 15.17 | 224.13 ± 16.02 | 13.60 ± 0.95 | 17.41 ± 1.71 |
| | 3. | 190.93 ± 10.15 | 132.60 ± 7.91 | 9.74 ± 1.79 | 22.13 ± 0.55 |
| | 4. | 69.70 ± 19.45 | 58.06 ± 8.68 | 4.09 ± 0.88 | 15.80 ± 1.49 |
| 3 | 1. | 47.32 ± 2.82 | 15.51 ± 3.13 | 3.14 ± 0.34 | 10.43 ± 2.05 |
| | 2. | 154.08 ± 20.74 | 71.14 ± 11.20 | 4.24 ± 0.44 | 18.83 ± 3.45 |
| | 3. | 138.31 ± 13.82 | 63.45 ± 9.33 | 3.04 ± 0.64 | 30.40 ± 3.58 |
| | 4. | 67.59 ± 7.94 | 31.86 ± 6.31 | 2.42 ± 0.32 | 31.08 ± 2.56 |
| 4 | 1. | 49.93 ± 3.38 | 57.43 ± 4.37 | 5.96 ± 0.96 | 8.05 ± 2.15 |
| | 2. | 126.34 ± 5.52 | 77.36 ± 1.88 | 7.18 ± 1.16 | 19.06 ± 3.52 |
| | 3. | 77.02 ± 5.68 | 53.91 ± 6.89 | 5.02 ± 1.12 | 20.08 ± 1.27 |
| | 4. | 16.79 ± 6.57 | 26.05 ± 2.72 | 2.78 ± 0.44 | 13.41 ± 1.15 |
| Hypoparathyroidism | 1. | 308.22 ± 10.56 | 235.39 ± 7.07 | 3.28 ± 0.34 | 11.95 ± 3.56 |
| | 2. | 519.61 ± 20.80 | 357.65 ± 9.73 | 5.24 ± 0.15 | 32.28 ± 0.38 |
| | 3. | 399.71 ± 63.55 | 329.03 ± 45.13 | 3.95 ± 1.04 | 31.21 ± 4.08 |
| | 4. | 37.28 ± 8.57 | 72.12 ± 6.66 | 0.48 ± 0.32 | 10.05 ± 2.29 |
| Hyperparathyroidism | 1. | 155.04 ± 27.16 | 149.21 ± 23.28 | 11.78 ± 0.90 | 14.67 ± 2.41 |
| | 2. | 200.78 ± 7.28 | 151.53 ± 9.59 | 18.37 ± 2.45 | 21.72 ± 1.47 |
| | 3. | 109.54 ± 15.11 | 92.77 ± 7.21 | 9.52 ± 0.85 | 15.76 ± 1.27 |
| | 4. | 22.92 ± 11.07 | 37.14 ± 5.75 | 8.73 ± 1.94 | 9.51 ± 0.86 |

[a] The results are given as mean ± standard error of the mean. Period 1 represents results obtained before thyrocalcitonin infusion, Period 2 during the first 4 hr of the infusion, Period 3 during the last 4 hr of the infusion, Period 4 after the end of the infusion.

same amount of acetate buffer was given at the same rate during the 7 hr preceeding and the 5 hr following the administration of thyrocalcitonin. The timing shown in Fig. 1 was used in all the experiments so as to be able to interpret the results as a function of the circadian rhythm. A priming dose of inulin, 30 mg/kg was given at the beginning of the experiment. The concentration of inulin in the solution infused was sufficient to maintain a constant plasma level of 15 mg/100 ml. One-hr urine collections with an uretral catheter was made, the bladder being totally emptied by an injection of air. A venous blood sample was taken every 2 hr. The following estimations were carried out on all urine and plasma samples: sodium and potassium by emission flame photometry, calcium and magnesium by absorption flame photometry, chloride by potentiometry, phosphate and creatinine by the usual methods for AutoAnalyzer Technicon, and inulin by the method of Galli and Jeanmaire (11).

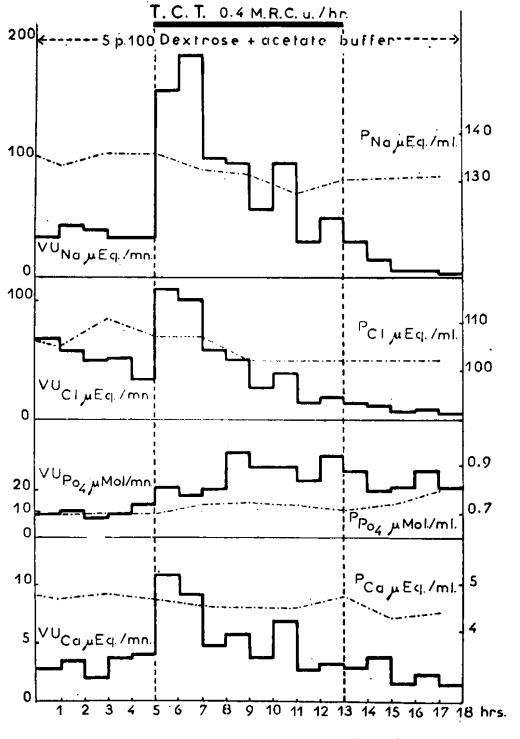


FIG. 2. Plasma concentrations and urinary excretion rates of phosphate, calcium, sodium, and chloride in normal subject 1.

*Results.* The results in the four normal subjects are summarized in Table II. An individual experiment is illustrated in Fig. 2.

*During the infusion of thyrocalcitonin*: (i) In the four normals and the hypoparathyroid subject, the rate of phosphate excretion increased as soon as the infusion of thyrocalcitonin was started, and remained high throughout the infusion. In the hyperparathyroid subject, the infusion of thyrocalcitonin did not produce any interpretable change in phosphate excretion. The plasma levels of phosphate in the six subjects were only slightly modified by the infusion of thyrocalcitonin. The percentage tubular reabsorption of phosphate [1— (phosphate clearance/inulin clearance)] diminished with the rise in phosphate excretion. (ii) The infusion of thyrocalcitonin increased the rate of calcium excretion in the six subjects. This increase lasted only for the first 3–6 hr of the 8-hr infusion. The mean fall in plasma calcium during the infusion was 0.625 meq/liter in the hyperparathyroid subject and 0.45, 0.45, 0.32, and 0.40 meq/liter in the four normal subjects. The level of the plasma clacium in the hypoparathyroid subject did not change. (iii) The rate of sodium and chloride excretion rose during the first 4–7 hr of the thyrocalcitonin infusion. The excretion rates then started to fall but remained above control values. The excess sodium excretion during the 8-hr infusion was 59.2, 30.0, 54.4, and 25.1 meq for the 4 normal subjects, 30.0 and 72.7 meq for the hyperparathyroid and hypoparathyroid subjects, respectively. There was a fall in plasma sodium and plasma chloride in the four normal subjects, and no significant change in the hypoparathyroid and hyperparathyroid subjects. (iv) The plasma levels and urinary excretion rate of potassium and magnesium did not change consistently. The inulin clearance remained constant except in one patient in whom it increased.

*After the infusion of thyrocalcitonin*: (i) After the infusion of thyrocalcitonin the phosphate excretion in the four normal subjects decreased progressively but remained above control values for up to 5 hr. In the hypoparathyroid patient the phosphate excre-

tion returned to the control value as soon as the infusion was stopped. (ii) In the four normals and the hypoparathyroid patient the calcium excretion reached values below the control level. This phenomenon was not as clear in the hyperparathyroid patient. (iii) In all but one of the subjects the sodium and chloride excretion rates reached very low values which were below control levels. When compared to control periods the amounts of sodium retained during the 5 hr following the infusion of thyrocalcitonin were 19.2, 7.5, and 7.1 meq in 3 of the 4 normal subjects, 20.9 and 81.3 meq in the hyper-and hypoparathyroid patients, respectively.

*Discussion. 1. Phosphate.* The present work demonstrates that the effect of thyrocalcitonin on phosphate excretion is more marked in man than in rats. Furthermore, the rise in phosphate excretion persists throughout the infusion period and up to 5 hr afterwards. The change produced by the thyrocalcitonin infusion was observed between 3 and 11 p.m. Therefore it cannot be explained by the circadian rhythm since it has been previously demonstrated that the phosphate excretion rises during the day and decreases after 6 p.m. (12). In the present work, the action of thyrocalcitonin on phosphate excretion could be shown although the amount infused per hour was five times lower than in our previous study. Moreover, the route of introduction and the low dose administered make it probable that the concentration of thyrocalcitonin in the renal artery of the present subjects was much lower than that obtained in dog and pig by Russel and Fleisch (8). The hypothesis put forward by Rasmussen *et al.* (5) in which hyperphosphaturia is related to hypocalcemia appears unlikely since in the present study the changes in plasma calcium were very slight. Furthermore, in the hypoparathyroid patient, there was a rise in phosphate excretion although there was no detectable change in plasma calcium.

Similarly, the present work in which only 5% dextrose was infused does not support the conclusions of Pechet *et al.* (6) who suggested that the renal action of thyrocalcitonin was dependent upon the concentration ratio of calcium and magnesium in the solution infused. The difference observed between the prolonged rise in phosphate excretion in man and the transitory rise in phosphate excretion in the rat may be explained by differences in bone metabolism. In the rat, thyrocalcitonin produces a marked inhibition of bone metabolism, leading to marked hypophosphatemia. The filtered load of phosphate is therefore reduced, and this may blunt a diminished tubular reabsorption due to thyrocalcitonin. Conversely in man, the action of thyrocalcitonin on bone is less marked so that the plasma phosphate remains constant. The filtered load of phosphate also remains constant, so that the diminished reabsorption of phosphate due to thyrocalcitonin increases the phosphate excretion. The absence of any interpretable change of phosphate excretion in the hyperparathyroid subject differs from our previous results. It is however in agreement with the work of one of us (13) in which rats were submitted to simultaneous injections of thyrocalcitonin and parathormone. The rapid return to control values of the phosphate excretion in the hypoparathyroid subject may be related to the absence of circulating parathormone. In this hypothesis, the increase in phosphate excretion observed in the normal subjects after the end of the perfusion of thyrocalcitonin, may be due to parathormone secretion induced by hypocalcemia. The duration of action of thyrocalcitonin would therefore be limited to the period during which it is infused.

*2. Calcium.* The action of thyrocalcitonin on the urinary calcium excretion is definite though not as marked as its action on phosphate excretion. Here again, the discrepancy between the increased calcium excretion in man and the decreased calcium excretion in rat, may be explained by the differences in bone metabolism producing marked hypocalcemia in rat but not in man. One may therefore postulate that the hypocalcemia produced in the rat by thyrocalcitonin reduces the filtered load of calcium and masks a possible diminution of the tubular reabsorption of calcium.

*3. Sodium and chloride.* The marked natriuretic and chloruretic effect of thyrocalcitonin lasts 4–7 hrs. Although the rate of sodium and chloride excretion started to decrease before the end of the infusion it remained above control values. The considerable reduction in sodium excretion at the end of the infusion suggests that thyrocalcitonin induces a depletion of sodium and chloride later compensated by an increase in tubular reabsorption of sodium. This phenomenon is observed independently of the control level of sodium excretion, which varies from 2.2 to 18.5 meq/hr. It is not possible to relate the rise in sodium excretion to a depression of tubular reabsorption, since a small change in GFR, not measurable with the present techniques, cannot be excluded.

*Summary.* The effect of a prolonged infusion of thyrocalcitonin on the plasma levels and urinary excretion rates of phosphate, calcium, sodium, and chloride, have been studied in man: 4 normals, 1 hyperparathyroid, and 1 hypoparathyroid. There was during the infusion and the 5 hr following it a marked rise in the excretion rate of phosphate in all the subjects except in the hyperparathyroid. There was no change in plasma phosphate. The excretion rates of sodium, calcium, and chloride, increased in all the subjects during the first 4–7 hr of the infusion. They began to fall before the end of the infusion and reached very low values afterwards. The increased excretion of phosphate occurred without any important fall of plasma calcium or plasma phosphate and in spite of the fact that the solution infused did not contain any electrolyte. The rise in both phosphate and calcium excretion is explained by a diminished tubular reabsorption. The increased excretion of sodium and chloride is marked and prolonged. It is not possible to determine whether it is due to a diminished tubular reabsorption or to a small nonmeasurable increase in the filtered load.

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