Homeostasis and Action of Parathyroid Hormone in Normal Man and Patients with Mild Renal Failure

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Summary

Patients with mild renal failure have elevated blood levels of PTH, and acute hypocalcaemia in these patients produced a greater increment in blood PTH than in normal subjects. There was also a delay in the recovery from hypocalcaemia in patients with mild renal failure as compared to normal subjects. The data are consistent with the presence of skeletal resistance to the calcaemic action of endogenous PTH in patients with mild renal failure. This abnormality is probably responsible for the hypocalcaemia of patients with renal failure and to the state of secondary hyperparathyroidism in such patients.

Introduction

We have shown previously that patients with acute and chronic renal failure display skeletal resistance to the calcaemic action of parathyroid hormone (Massry et al, 1973; Massry et al, 1974). However, this abnormality was demonstrated in studies utilizing the infusion of parathyroid extract (PTE), and there are no data showing impaired calcaemic response to an acute rise in blood levels of endogenous parathyroid hormone in patients with renal failure. Also data on changes in blood levels of PTH following acute hypocalcaemia in patients with renal failure are limited.

METHODS

Acute hypocalcaemia was induced by the infusion of 75 mg/kg body weight of
ethylenediamine-tetra-acetate (EDTA) in 11 normal volunteers (creatinine clearance of 100–150 ml/min/1.73 m²) and 13 patients with mild to moderate renal failure (creatinine clearance: 34–93 ml/min/1.73 m² with a mean of 65 ± 5 SE ml/min). EDTA was infused with 500 ml of 0.28 M dextrose in water between the hours of 08.00–10.00. Blood samples are collected at 30-min intervals during the EDTA infusion, hourly for four hours and at 8, 12, 24 and 28 hr after the initiation of the infusion. Total non-chelated serum calcium was measured by an autoanalyzer micromethod employing plasmacornith B (Wills and Gray, 1964). Total calcium in blood and urine was determined by atomic absorption spectrophotometry. Urinary cyclic AMP was assayed by the method of Gilman (1970). Blood levels of immunoreactive parathyroid hormone (iPTH) was estimated by the method of Serge et al (1972) using 125I BPTH, antiserum GP-1 (kindly supplied by Dr J T Potts, Jr) and purified bovine PTH as a standard.

RESULTS

Before EDTA infusion, the mean value for non-chelated serum calcium in normal subjects (9.6 ± 0.12 mg/dl) was not different from that in patients with renal failure (9.5 ± 0.17 mg/dl). Upon completion of EDTA infusion, the mean serum calcium concentration was 6.4 ± 0.14 mg/dl in normal subjects and 5.8 ± 0.08 mg/dl in those with renal failure. In the normal subjects, the mean level of non-chelated serum calcium increased to 9.5 ± 0.16 by 22 hr after EDTA infusion. In patients with renal failure, however, the levels of serum calcium at 22 and 26 hr after the infusion of EDTA were 8.4 ± 0.22 and 8.4 ± 0.17 mg/dl, respectively; both values are significantly lower than the pre-infusion levels (p < 0.02). This delay in the recovery in serum calcium occurred despite a marked increment in the blood level of endogenous PTH. A representative study in a patient with mild renal failure (creatinine clearance: 84 ml/min/1.73 m²) is shown in Figure 1.

The basal blood levels of iPTH were evaluated in patients with mild renal failure, even in those with creatinine clearance between 80–90 ml/min/1.73 m². With hypocalcaemia, the blood levels of iPTH increased rapidly from less than 0.15 to 0.42 ± 0.02 ng/ml and from 0.36 ± 0.04 to 1.01 ± 0.13 ng/ml in normal subjects and patients with mild renal failure, respectively. At all levels of serum calcium, the levels of iPTH were higher in patients with renal function impairment than in normal subjects. The blood levels of iPTH before and during EDTA infusion for both groups of subjects are shown in Figure 2.

During the infusion of EDTA, urinary cyclic AMP increased in both the normal subjects and the patients with renal failure. The increment, however, was greater in the latter group.

DISCUSSION

The results of the present study show that the levels of iPTH are elevated in
Figure 1. A representative study depicting the effects of EDTA infusion on the blood levels of iPTH and calcium in patients with mild renal failure (creatinine clearance: 84 ml/min/1.73 m²).

Figure 2. Blood levels of iPTH in normal subjects and patients with renal failure before and during the infusion of EDTA.
patients with mild renal failure and endogenous creatinine clearance as high as 93 ml/min/1.73 m². These observations are consistent with observations by Reiss et al (1968). The data also demonstrates an exaggerated secretion of PTH in response to acute hypocalcaemia in patients with renal failure. This phenomenon is probably related to the larger size of the parathyroid glands in these patients (Massry et al, 1969; Parfitt, 1969). A similar finding was reported in patients with parathyroid adenoma when calcium was lowered by EDTA infusion (Murray et al, 1972).

Patients with renal failure, as compared with normal subjects, displayed a delay in the recovery from acute hypocalcaemia despite higher serum concentration of iPTH in the former groups throughout the period of the study. This phenomenon may reflect impaired skeletal response to the calcaemic action of an elevation in endogenous levels of PTH. It might be argued that the increments in levels of iPTH observed in the patients do not reflect elevation in biologically active hormones. This seems remote, since the levels of urinary cyclic AMP increased significantly with elevations of iPTH, reflecting biological activity of the hormone on the kidney.

Since urinary excretion of calcium in the normal subjects was not different from that observed in the patients, one can exclude the possibility that the sustained hypocalcaemia in the patients was due to a greater loss of calcium in the urine.

The continued chelation of additional calcium by the retained EDTA in patients with renal failure might prevent the return of serum calcium to control levels. However, it is known that EDTA will combine immediately and completely with calcium to form an inert complex, calcium EDTA. Although this complex may persist in the circulation for a longer period in patients with renal failure than in normal subjects, this cannot cause further change in the blood levels of non-chelated calcium.

Finally, a difference in intestinal absorption of calcium between the normal subjects and the patients could account for the difference in the behaviour of serum calcium. Studies reported from our laboratory (Coburn et al, 1973) have demonstrated that intestinal calcium absorption in patients with a serum creatinine of 2.5 mg/dl or less is not different from that in normal subjects. In nine of ten patients of the present study, serum creatinine was less than 2.0 mg/dl.

The data of the present study are consistent with the concept that skeletal resistance to the calcaemic action to endogenous PTH exists in patients with mild renal failure. This abnormality is probably responsible for the hypocalcaemia of renal failure and the state of secondary hyperparathyroidism in these patients.

References

Open Discussion

O BETTER (Israel) There is one simple observation that tends to confirm the concept of very early hyperparathyroidism and that is that hypophosphataemia occurs early in renal failure, in the absence of binding agents.

MASSRY I never intended or attempted to say that phosphate is not important. I am sure that phosphate contributes to the hypocalcaemia of renal failure.

E SLATAPOLSKY (Chicago) I am glad to hear from Dr. Massry that phosphate is important. I would like to add a comment. Your concept is confirmed by histology done by Dr. Phillippe Bordier in Paris. Dr. Bordier has bone biopsies in patients with primary and secondary hyperparathyroidism. He also had serum PTH levels measured by Dr. Arnaud, and they found that at any level of serum PTH, patients with secondary hyperparathyroidism had more osteoblasts. In other words there is an excess of cells removing calcium from bone. Since these patients do have hypocalcaemia it seems as though the skeletons were resistant to the increased action of PTH. Maybe this is related to the lack of 1,25 DHCC.

M POKROY (South Africa) May I ask what is the renal clearance of PTH?

Whether in fact the patients may have had elevated serum PTH as a consequence of a reduced renal clearance. This has been shown in other human studies.

D G OREOPOULOS (Canada) A factor that can produce resistance to the action of parathyroid hormone is fluoride. Were your patients drinking fluoridated water?

MASSRY No, in Los Angeles the water is not yet fluoridated.

C R KLEEMAN (Israel) The failure of calcium to return to normal as rapidly in the renal failure patients indicates a resistance to circulating hormone. But has anyone tried to produce mild primary hyperparathyroidism by administering PTH for several days, and then produced EDTA hypocalcaemia? I have never seen such a study in primary hyperparathyroidism.

MASSRY There are no such studies at the moment, but we've found that when
one does subtotal parathyroidectomy in renal failure and measures the hormone, it is reduced from high to normal, but the response to PTE infusion is not different, suggesting that perhaps excess hormone is not important. Secondly, dogs subjected to acute thyroparathyroidectomy and then made uraemic become resistant to PTH within a day.