EFFECT OF OPERATION ON THE KIDNEY FUNCTION AND ON THE BEHAVIOUR OF A TRACER DOSE OF $^{85}$Sr IN TWO PATIENTS WITH HYPERPARATHYROIDISM AND SEVERE HYPERCALCAEMIA

By

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ABSTRACT

Two cases of severe hypercalcaemia due to parathyroid adenoma are reported. In one of the patients an acute hypercalcaemic crisis occurred with a breakdown of renal function and rapidly progressive signs of myocardial damage. An emergency operation was performed from which the patient made a successful recovery. The effects of hypercalcaemia on the kidney function in this patient are reported in detail. In both cases an unexpected difference in the alteration of the serum and urinary concentrations of $^{85}$Sr and stable calcium was observed after operation. The possible significance of this finding is discussed.

As compared with the various clinical syndromes manifested by primary chronic hyperparathyroidism, acute hypercalcaemic crisis presents a rare and less widely-recognized picture. Recently Chodack et al. (1965) estimated the total number of cases published to date at 67.

All the cases presented the same clinical picture: rapidly progressive muscular weakness, anorexia, nausea, vomiting, constipation, non-specific abdominal pain, thirst, polyuria, as well as disturbances in behaviour and in the state of consciousness progressing to coma in association with progressive uraemia and a sharp rise in the levels of calcium and phosphorus in the serum.

The mortality in 36 patients who were operated on was 19.4%; in the remaining 31 patients no surgery was undertaken and all but one died.
Hence early diagnosis is very important, since operation can be life-saving. Sometimes the patient deteriorates so rapidly, that acute surgical intervention becomes imperative if life is to be saved, as was the case with one of our patients. In this patient we studied both kidney function and calcium metabolism, the latter i.a. by means of a tracer dose of $^{85}$Sr. Similar investigations were carried out on a recently observed case of subacute hyperparathyroidism with severe bone involvement; in the latter patient only the $^{85}$Sr-data will be discussed in detail.

**CASE REPORTS**

**Case 1**

A 49-year-old woman was admitted on 9-8-1961 to the surgical department because of a very painful varicose ulcer on the medial side of the left lower leg. During her stay in hospital it was noted that she had a poor appetite and complained of nausea. After a few weeks she started to vomit. Sedatives, anti-emetics and parenteral administration of saline and Ringer-glucose solution resulted in little improvement. The serum electrolytes determined on October 6th gave the following results: Na, K and serum CO$_2$ were found to be normal, but the calcium was 18.6 mg/100 ml and the urea slightly increased (69 mg/100 ml). A more detailed questioning now revealed that for the past few months the patient had felt weak and tired; she had been depressed, nauseated, and a moderate degree of polydipsia and polyuria had developed. On physical examination the patient was an obese, apathetic, somnolent, obviously ill woman. However, there were no signs of dehydration. Behind the sternocleidomastoid muscle a plum-sized tumour was palpable. Varices were present on both legs, the skin being pigmented and the left lower leg ulcerated. The blood pressure was 160/100. Further physical examination revealed nothing abnormal.

**Laboratory data**

Urinalysis disclosed a specific gravity ranging from 1005 to 1008; the urine contained a trace of protein and a few white blood cells in the sediment.

Hb. 12.9 mg/100 ml, 3 860 000 erythrocytes, white blood count 11 500; blood smear normal.

The serum concentrations of urea, creatinine and electrolytes are given in Fig. 1 and Fig. 2.

- Serum Cl 100 mval/l, serum CO$_2$ 25.7 mval/l, albumin 3.3 g/100 ml, globulin 3.0 g/100 ml.

X-ray studies of chest and skeleton were negative. The lamina dura appeared intact, although interpretation was made somewhat difficult owing to a severe degree of paradentosis. Because of the clinical findings and the very high value of the serum calcium, a diagnosis of hyperparathyroidism was made.

In spite of intravenous administration of saline and potassium her condition rapidly deteriorated. She became increasingly drowsy and disoriented, and at times was completely confused. The blood pressure rose to 210/115. Serum calcium, phosphorus, urea and creatinine increased, whereas potassium decreased; the serum CO$_2$ fell to 15 mval/l.
Case I. Concentrations of serum electrolytes and urinary excretions per 24 hours.

The electrocardiogram showed progressively increasing changes in the ST-segments and the T-waves, typical of hypercalcaemia (Bradlow & Segal 1956).

On October 12th, a surgical exploration of the neck was performed. Behind the left sternocleidomastoid muscle, a brownish tumour was found that was separate from the thyroid gland. Its weight was 15.5 g, and on histological examination the tumour was shown to be a parathyroid adenoma.

Postoperatively the patient improved rather slowly; nausea, vomiting, depression and mental confusion disappeared gradually. By October 23rd the electrocardiogram was completely normal. An intravenous pyelogram performed on November 7th did not show any abnormality. The patient was discharged 5 weeks after operation in a satisfactory clinical condition. At present, more than three years after the initial admission, she is active and alert, the blood pressure is 190/115, the endogenous creatinine clearance 70 ml/min and the specific gravity of a 24-hour urine specimen 1014.
Case I

Upper part: concentrations of urea and creatinine in serum.
Lower part: urine volume per 24 hours.

Case II

A 61-year-old woman was admitted suffering from tumours of the bone with multiple spontaneous fractures of both arms and legs. Before admission she had complained of anorexia and constipation for some time. She had lost 3 kg in weight. A small lump was palpated on the left side of the neck.

Laboratory findings were as follows: serum calcium 16.4 mg/100 ml, phosphate 2.6 mg/100 ml, sodium 131 mval/l, potassium 3.1 mval/l, serum Cl 104 mval/l, serum CO₂ 17.3 mval/l, alkaline phosphatase 25 Bessey units, urea 114 mg/100 ml and creatinine 2.1 mg/100 ml. There was no increase in urinary excretion of calcium, which was 250 mg per 24 hours; phosphate excretion 350 mg per 24 hours; striking increase in the hydroxyproline content of the urine, namely 300 mg/24 h. Typical signs of hyperparathyroidism on X-ray examination of the skeleton.

At operation a parathyroid adenoma of 6.2 g was removed.

METHODS

The glomerular filtration rate was estimated by the endogenous creatinine clearance and the ratio of Na, K, Ca and phosphorus clearance to creatinine clearance was calculated.

This ratio \( \frac{C_x}{C_{or}} \) is the fraction of the filtered substance \( (X) \) which is excreted and it is related to the percentage of the filtered substance reabsorbed by the renal tubule \( (\% T. R. X.) \) by the formula

\[
\% T. R. X. = \left[ 1 - \frac{C_x}{C_{or}} \right] \times 100
\]
The exchangeable calcium pool and bone accretion rate were calculated from the plasma disappearance and urinary excretion curves of an intravenously administered dose of 40 μc 85Sr according to the method described by Bauer et al. (1958).

**RESULTS**

**Case I**

Immediately after the operation the serum calcium rose to 24.6 mg/100 ml; subsequently it fell and reached normal values on the 4th postoperative day.

In spite of a rise in serum creatinine and a transient oliguria there was also a fall in serum-P with a typical rise in alkaline phosphatase and reduced output of Ca and P in the urine. Similarly the output of Na and K decreased; the tendency to hypopotassaemia persisted for some time in spite of its lowered excretion and continued intravenous administration (Figs. 1 and 2). The "apparent" reabsorption of potassium (°/o T. R. K.) and the reabsorption of sodium (°/o T. R. Na) were still reduced after several weeks, whereas the °/o T. R. P. and °/o T. R. Ca became normal within ten days (Table 1).

A moderate degree of polyuria with a low specific gravity persisted.

The exchangeable calcium pool and bone accretion rate were not increased before operation. After removal of the parathyroid adenoma the serum disappearance curve showed a sudden change or break six days after administration of 85Sr, when the concentration of 85Sr rose and reached a value 50 °/o higher than on the day of operation (Fig. 3). After this break the curve was somewhat irregular. As the serum calcium fell during this period, the rise in the specific activity (defined as the percentage of the dose of 85Sr per gram serum calcium) was even more pronounced (Fig. 4). The urinary excretion curves showed the same tendency.

**Case II**

Postoperatively the serum calcium became normal within 24 hours and subsequently fell in the following days to 6.8 mg/100 ml in spite of intravenous administration of large amounts of calcium gluconate and AT10 given orally.

Simultaneously the serum phosphate decreased to 1.4 mg/100 ml and the alkaline phosphatase rose to 200 Bessey units. After three weeks of continuous administration of calcium and AT10, serum calcium and phosphate became normal, whereas three months later, the alkaline phosphatase remained at more than 100 Bessey units. The urinary calcium fell to 70 mg/24 h and the hydroxyproline excretion decreased to 30 mg/24 h within two days. The exchangeable calcium pool and the bone accretion rate were markedly increased before the operation. The serum and urinary concentrations of 85Sr are shown in Fig. 5. A break in the concentration curves occurred spontaneously seven days after the administration of a tracer dose of 85Sr; however, a second and
Table 1.
TRNa, »apparent« TRK, TRP and TRCa are the tubular reabsorptions of Na, K, P and Ca expressed as a percentage of the filtered load. (Case 1).

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<th>Date</th>
<th>Endogenous creatinine clearance ml/min</th>
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<th>K clearance ml/min</th>
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Fig. 3.
Case I. Serum concentrations, urinary excretion per 24 hours and retention of $^{85}$Sr in the body, expressed as a percentage of the administered dose, are plotted semi-logarithmically against time. The exchangeable calcium pool (CaE) and bone accretion rate (CaB) are not increased.

more pronounced break was observed immediately after the operation, showing the same pattern as in case I.

DISCUSSION

Hypercalcaemia can produce severe renal impairment. The function of the distal tubules and collecting ducts is particularly impaired, resulting in defective water reabsorption (Cohen et al. 1957; Epstein et al. 1958; Fourman et al. 1960; Gill & Barter 1961), and defective hydrogen-ion excretion due to diminished ammonia-formation, which leads to systemic acidosis (Cohen et al. 1957; Wrong & Davies 1959; Fourman et al. 1960; Epstein 1962) and renal wasting of sodium and potassium (Ferris et al. 1962).

When hypercalcaemia is due to hyperparathyroidism, the disturbances in
renal function are more pronounced and a specific effect of parathormone on the kidney cannot be excluded (Epstein et al. 1959; Epstein 1962).

Our first patient showed marked polyuria, the urine being of low specific gravity; the serum CO₂ had decreased and renal wastage of Na and K occurred, despite low serum concentration of potassium.

The endogenous creatinine clearance fell temporarily to very low values.

As in most cases of hypercalcaemia, morphological changes are chiefly localized in the medulla, the observed decrease in the glomerular filtration rate being probably the result of intratubular obstruction in the lower parts of the nephron.

**Calcium metabolism**

Accurate collection of vomit was not possible in the first patient and hence a calcium balance study could not be performed. However, the high calcium content of the serum and urine indicate a severe degree of bone destruction under the influence of an excess of parathormone. The rapid fall in serum and urinary calcium and phosphorus and the increase in alkaline phosphatase indicate that after operation, a marked change had taken place with a considerable decrease in bone destruction and an increase in bone formation.

It is plausible to attribute the observed break in serum and urine concentration- and specific activity curves (Figs. 3 and 4) to the operation. However, a spontaneous break in the serum specific activity curve after administration of ⁴⁵Ca or ⁸⁵Sr has already been noted by Heany & Whedon (1958) in nonsurgical cases suffering from various kinds of bone disease, and this finding
Case II. Presentation of the data as in Fig. 3. A break occurred spontaneously seven days after administration of $^{85}$Sr, a more distinct rise in the concentration appeared immediately after operation.

has been confirmed by other authors; a similar phenomenon was observed in our second case. Lafferty & Pearson (1964) found this break in most of their studies and at high accretion rates, the break usually occurred before five days. In some of their studies even a slight rise in the serum specific activity was observed at the time of the break. In their opinion this rise could be explained by a sudden enrichment of the exchangeable calcium pool from a source of calcium with a higher specific activity than the pool, and most likely represented resorption of bone laid down shortly after injection of the tracer. As compared with $^{45}$Ca the rapid excretion of $^{85}$Sr causes a more rapid loss of this tracer from the exchangeable pool, and its incorporation into the non-exchangeable portion of the skeleton is therefore more sharply defined (Bauer
1964). Resorption of short living bone labelled by $^{85}\text{Sr}$ may thus result in a more enrichment rise in the serum specific activity. Thus the observed break and enrichment of the exchangeable pool in our first case could be due to resorption of bone with a short-life span independent of the operation. It is also possible that back diffusion of $^{85}\text{Sr}$ from the skeletal mineral stores to the rapidly exchangeable compartment has taken place (Nordin et al. 1962), leading to a rise in the serum concentration. In Fig. 5 (case II) it is shown, however, that although a slight break in the concentration curves occurred spontaneously after seven days, due to either resorption of short living bone or to back diffusion, a steep rise was observed immediately after operation which seemed directly related to the surgical intervention. Therefore it is very likely that the rise in case I is also largely an effect of the operation.

As the rapid decrease in serum and urine calcium can only be due to a high bone accretion rate, one would expect that if the skeleton does not discriminate between $^{85}\text{Sr}$ and calcium, this high accretion rate would have caused a reduction in the $^{85}\text{Sr}$ concentration instead of the observed rise.

Apparently a considerable part of $^{85}\text{Sr}$ was not yet incorporated into the deeper layers of the bone crystals and was flushed out by the large amount of calcium entering the bone after operation. Other investigators (Bronner et al. 1963) have also found that the skeletal clearances of Sr and Ca are not completely identical and it is likely that this difference becomes more manifest when the bones have a high avidity for calcium. Obviously one cannot estimate the postoperative change in bone accretion rate from the $^{85}\text{Sr}$ data.

REFERENCES


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