Discussion

Studies conducted elsewhere in the United Kingdom (Cathcart *et al.*, 1972; Gomez, 1972; Mason *et al.*, 1972) have indicated that in the dosage used in the present study Orudis is well tolerated, causes only occasional and minor side effects, and has statistically significant superiority ($P < 0.01$) in anti-inflammatory and analgesic activity when compared with placebo.

Indomethacin is a powerful anti-inflammatory and analgesic drug (Percy *et al.*, 1964; Hart and Boardman, 1965; Thompson and Percy, 1966), its principal disadvantage being a relatively high incidence of side effects.

The present studies suggest that in equal dosage clinical efficacy of Orudis is comparable with that of indomethacin. The results marginally favour the latter drug but side effects were less severe with the former. Preliminary results from studies with higher dosages of Orudis (Gomez, 1972; Mason *et al.*, 1972) indicate that 150 mg daily is well tolerated. This finding considered together with the above results suggests that Orudis is likely to have an important part to play in the clinical management of rheumatic disease.

We are indebted to Miss Ilse Tauber, of May & Baker Ltd., for the statistical analysis, and to May & Baker Ltd. for the drugs and record cards used in the two trials.

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Hypercalcaemia, Hypophosphataemia, and Inability to Excrete Hydrogen Ions

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British Medical Journal, 1972, 4, 400-403

Summary

Investigation of a patient with hypercalcaemia, hypophosphataemia, and nephrocalcinosis failed to lead to a clear diagnosis. Neither primary hyperparathyroidism nor primary incomplete renal tubular acidosis could explain all the biochemical features, and it seems that more than one fundamental abnormality may have been present.

Introduction

Biochemical changes produced by excessive parathyroid hormone and their effects on several organs and tissues are well known. Hypercalcaemia, hypophosphataemia, and nephrocalcinosis are common in advanced cases, and inability to eliminate hydrogen ions in the urine has been reported in a number of patients (Fourman *et al.*, 1960).

The case of a patient with all these conditions is reported here in whom a diagnosis of primary hyperparathyroidism was rejected on the basis of suppressed serum parathyroid hormone levels and normal response to parathyroid extract infusion (Becker *et al.*, 1964), prednisone administration (Thomas *et al.*, 1958), and intravenous calcium infusion (Goldsmith and Forland, 1964).

This patient's disorder, while similar to the late type of incomplete renal tubular acidosis (Elkinton *et al.*, 1960), was associated with hypercalcaemia, which has not been reported previously in that syndrome.

Case Report

An 18-year-old man was admitted to the Instituto Nacional de Cardiología for investigation of nephrocalcinosis. He had been well until six months previously, when he complained of dysuria and polyuria. His physician found a urinary infection and prescribed antibiotics. Nephrocalcinosis, hypercalcaemia, and hypophosphataemia were also discovered and the patient was referred to this Institute. There was no family history of renal disease but his father has essential hypertension. Physical examination showed nothing abnormal. His weight was 68 kg, height 178 cm, body surface area 1.82 m², blood pressure 120/80 mm Hg, heart rate 88/min, and ventilatory rate 18/min.

Serum calcium was high in numerous determinations, with levels varying from 11.0 to 12.0 mg/100 ml, while the serum phosphorus was low, with values ranging from 1.4 to 2.7 mg/100 ml. Alkaline phosphatase was 3.6 Bodansky units. Blood urea nitrogen was 42 mg/100 ml, and serum creatinine 1.0 mg/100 ml. Maximum tubular reabsorption of glucose was 191 mg/min, and maximum tubular secretion of para-aminohippurate (PAH) 56 mg/min. Glomerular filtration rate was 77 ml/min (inulin clearance), and renal plasma flow 286 ml/min (PAH clearance). Serum albumin was 4.55 g/100 ml, and globulins were 2.68 g/100 ml. Paper electrophoresis showed normal plasma proteins. Total serum carbon dioxide was 26 mEq/l, and pH was 7.42. Haemoglobin was 15.6 g/100 ml, and the haematocrit reading 49%. Leucocyte count was 7,400/mm³. Urine analysis showed low densities from 1004 to 1014. Urinary pH ranged from 6 to 7. Several urine cultures were negative.

A shortening of the S-T interval was present on the electrocardiogram. X-ray films of the chest, long bones, hands, feet, skull, and teeth showed no bone lesions. An intravenous pyelogram confirmed bilateral renal calcifications distributed diffusely on the parenchyma (Fig. 1) without alterations in the ureters or bladder.

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FIG. 1—Plain x-ray film of abdomen showing bilateral parenchymatous renal calcifications and normal structure of bones.

URINARY ACIDIFICATION TESTS

Alkaline urinary pH with no evidence of urinary infection prompted investigation of the renal capacity to acidify urine, since incomplete renal tubular acidosis is one of the causes of nephrocalcinosis (Elkinton *et al.*, 1960).

For this purpose ammonium chloride capsules were used in acute and chronic tests, as suggested by Wrong and Davies (1959) and Elkinton *et al.* (1960). In the acute test a single oral dose of ammonium chloride was used (100 mg/kg body weight). In the chronic test the substance was given for three days at 100 mg/kg/day divided into three doses.

The results are given in Tables I-IV. Both tests showed incapacity for urine acidification. Urinary pH did not decrease appreciably, despite increased urinary excretion of ammonium and titratable acidity and a decrease in urinary bicarbonate excretion.

TESTS FOR PRIMARY HYPERPARATHYROIDISM

As hypercalcaemia, hypophosphataemia, and defective urinary acidification have been reported in primary hyperparathyroidism (Fourman *et al.*, 1960) the diagnosis was investigated further.

While on a normal diet the tubular reabsorption of phosphate was 97%. An intravenous infusion of 200 U of bovine parathyroid extract (Eli Lilly & Co.), as described by Becker *et al.* (1964), reduced the tubular reabsorption of phosphate from 94% to 60% in the patient, and from 86% to 50% in a healthy control subject.

Serum calcium decreased from 11.4 mg to 10.8 mg/100 ml after six days of prednisone administration (20 mg/day) (Thomas *et al.*, 1958).

TABLE I—Urinary Response to Acute Administration of Ammonium Chloride. Values Before Treatment (60-0 min) are given in Parentheses

Time in min	Urine Volume in ml/min (2.59)	pH (6.86)	Titratable Acid in μ Eq/min (5.6)	NH_4^+ in μ Eq/min (6.0)	HCO_3^- in μ Eq/min (27.8)	Na ⁺ in μ Eq/min (118)	K ⁺ in μ Eq/min (52)	Cl ⁻ in μ Eq/min (138)	H ⁺ in μ Eq/min (-16.3)
0-59	2.37	6.85	6.0	7.8	20.0	224	47	127	-6.5
59-124	3.04	6.52	11.6	14.6	15.6	164	61	208	-10.5
124-183	3.55	6.42	14.3	10.1	16.1	206	92	272	8.3
183-249	3.75	6.48	16.5	21.4	17.4	203	105	295	20.5
249-308	2.40	6.43	13.4	14.4	10.7	130	62	174	17.1
308-367	3.99	6.55	18.5	19.2	19.0	217	104	286	18.7

H⁺ = Titratable acid + NH_4^+ - HCO_3^- .

TABLE II—Haematological Response to Acute Administration of Ammonium Chloride. Values Before Treatment are given in Parentheses

Time in min	pH (7.42)	Total CO ₂ in vol. % (22.07)	Na ⁺ in mEq/l. (136)	K ⁺ in mEq/l. (4.8)	Cl ⁻ in mEq/l. (101)	Haematocrit Value % (38)
120	7.36	21.48	137	4.0	102	36
240	7.34	19.80	137	4.0	100	36
360	7.36	21.16	138	3.7	101	36

TABLE III—Urinary Response to Chronic Administration of Ammonium Chloride. Values Before Treatment are given in Parentheses

Time in Days	Urine Volume in ml/min (1.55)	pH (6.8)	Titratable Acid in μ Eq/min (5.2)	NH_4^+ in μ Eq/min (1.9)	HCO_3^- in μ Eq/min (14.4)	Na ⁺ in μ Eq/min (73.6)	K ⁺ in μ Eq/min (46.5)	Cl ⁻ in μ Eq/min (79)	H ⁺ in μ Eq/min (-2.9)
1	—	—	—	—	—	—	—	—	—
2	2.62	5.94	25.7	29.1	38.0	152	115	246	16.8
3	2.62	5.72	34.7	33.0	5.5	136	115	217	62.2
4	1.98	5.79	26.6	41.6	4.4	87	75	148	63.7

H⁺ = Titratable acid + NH_4^+ - HCO_3^- .

TABLE IV—Haematological Response to Chronic Administration of Ammonium Chloride. Values Before Treatment are given in Parentheses

Time in Days	pH (7.44)	Total CO ₂ in vol. % (22.2)	Na ⁺ in mEq/l. (136)	K ⁺ in mEq/l. (4.7)	Cl ⁻ in mEq/l. (101)	Hematocrit Value % (43)
1	7.42	22.1	136	4.8	101	38
2	7.38	19.2	141	3.7	102	35
3	7.38	19.1	139	5.3	103	31
4	7.37	19.1	136	4.4	105	34

An intravenous infusion of calcium gluconate (15 mg/kg body weight) was given over four hours while the patient was on a daily diet containing 400 mg of calcium and 800 mg of phosphorus. The infusion resulted in a 17.5% decrease in urinary phosphate excretion on the day of the infusion followed by a 12.5% increase the next day (Fig. 2) (Goldsmith *et al.*, 1964).

Three days on a diet containing 120 mg of calcium and 800 mg of phosphorus decreased urinary calcium excretion from 218 mg to 50 mg/day, with no change in serum calcium (Fig. 3).

On a day when the serum calcium level was 9.4 mg/100 ml immunoassayable serum parathyroid hormone was undetectable in peripheral blood.

Finally, in the urinary concentration test in spite of water deprivation and antidiuretic hormone administration renal incapacity for urine concentration was shown (Fig. 4).

FIG. 2—Calcium infusion test with patient on daily diet containing 400 mg calcium and 800 mg phosphorus. Findings suggest normal inhibition of parathyroid activity by calcium.

FIG. 3—Absence of hypercalciuria during low-calcium diet (120 mg calcium, 800 mg phosphorus, 60 mEq sodium, 70 mEq potassium). Serum calcium level was unchanged.

FIG. 4—Urinary concentration test. Inability to concentrate urine was shown by minimal change in urinary osmolarity caused by dehydration followed by antidiuretic hormone.

Discussion

Some of this patient's symptoms suggested primary hyperparathyroidism. The combination of hypercalcaemia and hypophosphataemia is generally accepted as typical (Rasmussen, 1968). The inability maximally to decrease urinary pH in response to ammonium chloride has also been reported in patients with functioning parathyroid adenomas (Fourman *et al.*, 1960), and Hellman *et al.* (1965) showed that parathyroid hormone has a direct renal tubular effect inhibiting exchange of Na⁺ by H⁺.

Nevertheless, the diagnosis of primary hyperparathyroidism was excluded in this case in view of (1) the normal tubular reabsorption of phosphate, (2) the decrease in serum calcium when on prednisone, (3) the normal inhibition of parathyroid activity during intravenous calcium infusion reflected by decreased urinary phosphate excretion, (4) the normal response in tubular reabsorption of phosphate to parathyroid extract infusion, and (5) the undetectable serum parathyroid hormone.

On the other hand, the nephrocalcinosis and inability to acidify the urine in response to the ammonium chloride loads suggested the primary form of incomplete renal tubular acidosis (I.R.T.A.). This syndrome was initially described by Wrong and Davies (1959) in generalized nephrocalcinosis, without hypercalcaemia or hypercalciuria, as a deficit in the renal excretion of hydrogen ions and the incapacity maximally to decrease urinary pH, but without systemic acidosis. An infantile and a late variety have been recognized (Elkinton *et al.*, 1960).

Certainly, except for hypercalcaemia most of this patient's symptoms indicate the late variety of I.R.T.A. This disorder is usually found during investigations of nephrocalcinosis or renal lithiasis or both in patients in the second or third decade of life. Polyuria, low urinary density, hypophosphataemia, and inability to acidify the urine are the usual findings in this disease. A genetic defect with autosomal dominant inheritance is suspected, although in most cases no affected relatives are found.

I.R.T.A. can also be secondary to a large number of conditions, none of which appear to have been present in this patient, such as primary hyperparathyroidism, hypercalcaemia due to vitamin-D intoxication (Ferris *et al.*, 1961), amphotericin-B nephropathy (McCurdy *et al.*, 1964), ingestion of outdated tetracycline (Gross, 1963), and several dysproteinemias (Morris *et al.*, 1964).

If primary I.R.T.A. proves to be the correct diagnosis this will be the first such case reported with hypercalcaemia, for which no explanation can be offered. None of the common causes of a raised serum calcium level was present such as multiple myeloma, milk-alkali syndrome, metastatic bone disease, vitamin-D intoxication, or long-standing immobilization.

The response of serum calcium to prednisone administration might be interpreted as indicative of sarcoidosis (Thomas *et al.*, 1958). But even without the Kveim test the absence of hypergammaglobulinaemia, the normal level of alkaline phosphatase, and the lack of clinical or radiographical findings made it extremely unlikely that this disease was present.

The abnormalities presented by this patient may or may not have been interrelated. One possibility is: cause unknown → hypercalcaemia → secondary I.R.T.A. → nephrocalcinosis; a second possibility is: genetic alteration → primary I.R.T.A. → nephrocalcinosis → hypercalcaemia by an unknown mechanism.

This case is of interest since it presented several "typical" features of primary hyperparathyroidism and illustrates the differential diagnosis of nephrocalcinosis.

We are indebted to Dr. Herman Villarreal for his advice in the study of the patient. Dr. Claude D. Arnaud, Mayo Medical Laboratories, Rochester, Minn., performed the immunoassay of serum parathyroid hormone. R.V.D. is in receipt of a traineeship from Don Baxter Laboratories at the Instituto Nacional de Cardiología and E.Z. is in receipt of a research grant from Eli Lilly & Co. de México.

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MEDICAL MEMORANDA

Retroperitoneal Haemorrhage Simulating a Strangulated Inguinal Hernia

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British Medical Journal, 1972, 4, 403

The presence of a painful, irreducible swelling in the groin caused by a retroperitoneal haemorrhage after blunt trauma is reported, which offers an unusual differential diagnosis of a strangulated inguinal hernia.

Case Report

A 53-year-old man presented in the casualty department in March 1972 in the early morning with a painful, tender, irreducible lump in his left groin. He stated that on the previous evening he had fallen from a stool and landed on his back. He got up and shortly afterwards went to bed. Six hours later he woke up with a pain in the left groin. He also complained of pain over his left hip and down the left leg; he was nauseated, and vomited once. A diagnosis of left strangulated inguinal hernia was made, and the patient was referred to the surgical firm on duty for admission.

On examination he did not appear anaemic, shocked, or dehydrated, the pulse rate was 95/min, regular and good volume, and the blood pressure was 130/95 mm Hg. There were superficial bruises in the left flank of the abdomen, and with left-sided tenderness. Bowel sounds were diminished. Examination of the hernial orifices showed a right scrotal hernia, not tender, easily reducible, and with expansile impulse on coughing. On the left side there was a swelling above the midpoint of the inguinal ligament which was tense, tender, irreducible, and without a cough impulse. There was no discolouration of overlying skin, and the testes were normal.

Left hip flexion was limited by 30°; other movements were full. All pulses were present in both legs. X-ray pictures of the abdomen lumbar spine, pelvis, and left hip, and routine tests on the urine showed no abnormality.

A provisional diagnosis of a left strangulated inguinal hernia was made, and at operation one hour after admission the left groin was explored through an inguinal incision. On opening the canal a large haematoma was found deep to the external oblique aponeurosis and superficial to the transverse fascia. The cord appeared normal, and there was no evidence of a direct or indirect sac. The cord was mobilized and retracted; the haematoma was evacuated.

At this stage it was noticed that there was some fresh blood seeping through the deep inguinal ring. The index finger was introduced through the ring into the retroperitoneal space and a further clot was removed. As there was only very slight bleeding further exploration of the retroperitoneal space was not attempted. A Redivac drain was inserted into the deep ring and the canal was closed. A firm dressing was applied to the wound.

Postoperatively there was no evidence of bleeding disease. In-

vestigations were: haemoglobin 13.8 g/100 ml, bleeding time 2 min, clotting time 6 min, prothrombin ratio 1.3, platelet count 159,000/mm³. Liver function tests and an intravenous pyelogram, to exclude a renal injury, showed nothing abnormal.

His postoperative progress was uneventful; there was minimal loss from the Redivac drain, and it was removed on the second day. During the period of recovery he asked to have his right scrotal hernia attended to, and on the eighth day a right inguinal herniorrhaphy was performed. He was discharged from hospital 15 days after admission.

Comment

The common conditions which may simulate a strangulated inguinal hernia are: inguinal lymphadenitis, torsion of undescended testis, encysted hydrocele of the cord, lipomas, a tuberculous psoas abscess pointing above the inguinal ligament, pus in the inguinal hernial sac as a result of general peritonitis (Cronin and Ellis, 1959), and a dermoid cyst of the inguinal canal (Brightmore, 1971).

Handmaker and Mehn (1969) reported a case of haemorrhage into the spermatic cord and testicle simulating an incarcerated inguinal hernia. The patient presented on the sixth day after the start of anticoagulant therapy, with a tender irreducible swelling in the left inguinal canal and scrotum, and with signs of a small intestinal obstruction.

Nick, Zollinger, and Pace (1967) reviewed 65 cases of retroperitoneal haemorrhage secondary to blunt trauma. The causes in their series were renal injuries, fracture of the pelvis and transverse processes, rupture of the bladder, traumatic pancreatitis (4 cases), ruptured aorta (1 case), duodenal injury (1 case), trauma to the adrenal gland (1 case), with eight cases of unknown cause.

In another review of 75 cases by Allen, Eastman, Halter, and Conolly (1969) some causes were renal injuries (17 cases), pancreatic injury (16 cases), bladder laceration (10 cases), pelvic injury (7 cases), and vena cava rupture (4 cases). There were no cases of retroperitoneal rupture of the duodenum and no instances of aortic injury.

In neither series, however, was an extension of retroperitoneal haematoma into the inguinal canal reported.

I would like to thank Mr. R. P. Warren for allowing me to give details of the patient under his care, and for his help and encouragement to me in writing this report. My thanks are also extended to Mrs. M. Whitney, librarian, for her help.

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