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Symptomatic Hypercalcaemia in Thyrotoxicosis

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Summary: In three patients with thyrotoxicosis and with symptomatic hypercalcaemia antithyroid therapy restored the plasma calcium concentration to normal, though initially in one case intravenous and oral neutral phosphate solution were required to curtail intractable vomiting.

Nine cases have been recorded in which the plasma calcium concentration returned to normal after antithyroid treatment was started; all but one became normocalcaemic within eight weeks. It is suggested that in hypercalcaemic thyrotoxicosis a second pathological condition should be considered only if the plasma calcium concentration fails to return to normal within eight weeks.

Introduction

In the past 15 years an increasing number of case reports linking thyrotoxicosis with hypercalcaemia have appeared in the literature. The combination, though forming only a small proportion of all patients with thyrotoxicosis, can result in a serious situation arising from acute and potentially fatal hypercalcaemic complications. We have recently studied three cases of hypercalcaemic thyrotoxicosis. In each case there was intractable vomiting, which in one case could be relieved only by lowering the plasma calcium concentration by intravenous inorganic phosphate infusion. In the other two cases treatment with carbimazole alone resulted in cessation of vomiting and lowered the plasma calcium level to within normal limits.

Case 1

A 33-year-old man gave a history of recurrent vomiting for 24 hours. Three weeks earlier he had felt nauseated for several days and had been transiently jaundiced. The relevant abnormal findings were hepatosplenomegaly, mild icterus, and a serum bilirubin concentration of 2·5 mg./100 ml.; there was no evidence of haemolysis. Plasma calcium levels were consistently raised (Fig. 1).

Despite continued vomiting polyuria persisted with increasing dehydration. Further inquiry showed that he had lost over 20 lb. (9 kg.) in weight during the preceding six months. No direct thyroid function test was done at this time, but on the basis of the history and biochemical findings (Table I) a presumptive diagnosis of thyrotoxicosis was made. Treatment with carbimazole 10 mg. eight-hourly was instituted. The vomiting gradually stopped and the plasma calcium concentration returned to normal in three weeks. The blood urea concentration returned to normal levels (39 mg./100 ml.), and creatinine clearance rose from 46 to 85 ml. per minute. Treatment with carbimazole was continued for 18 months.

A year and a half later the patient relapsed. He lost 8 lb. (3·6 kg.) in weight in three weeks and became mildly jaundiced: P.B.I. 9·8 μg./100 ml., and bilirubin 2·1 mg./100 ml. The plasma calcium and inorganic phosphate levels were both normal.

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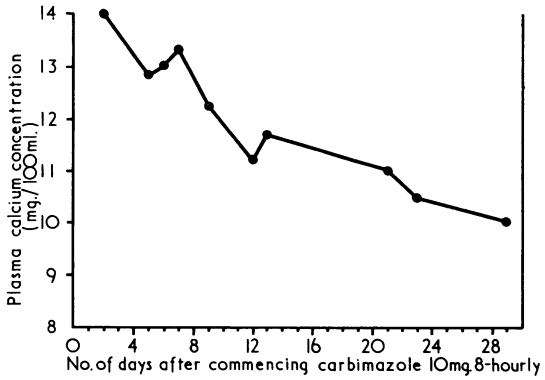

Fig. 1.—Case 1. Plasma calcium concentration during treatment.

TABLE I.—*Initial Findings in Three Patients with Hypercalcaemic Thyrotoxicosis*

	Case 1	Case 2	Case 3	Mean Normal ± 50
Haemoglobin (g./100 ml.)	14·0	12·0	11·7	14·8 ± 0·9
Plasma urea concentration (g./100 ml.)	180	59	24	Range 15–45
Protein (g./100 ml.)	7·0	6·0	7·1	6·8 ± 0·3
Calcium (mg./100 ml.)	14·0	13·9	13·0	9·7 ± 0·4
Inorganic phosphate (mg./100 ml.)	2·9	4·5	3·5	4·7 ± 0·4
Cholesterol (mg./100 ml.)	110	140		Range 150–320
P.B.I. (μg./100 ml.)		20	23	5·0 ± 0·45
^{131}I 4-hour neck uptake			87%	Range 12–31%
Urinary calcium (mg./day)	520	560		300

A further course of carbimazole was begun and an elective subtotal thyroidectomy was carried out some months later. The histology of the gland was compatible with partially treated thyrotoxicosis. Since operation (August 1967) the patient has kept well.

Case 2

A 22-year-old woman was admitted to hospital because of recurrent vomiting five weeks after she had developed typical thyrotoxic symptoms. The diagnosis was confirmed biochemically (Table I). The plasma calcium concentration was 13·9 mg./100 ml. Despite treatment with carbimazole, 10 mg. six-hourly, vomiting became more severe and the patient became increasingly dehydrated. This was corrected with intravenous fluid. Intravenous neutral phosphate curtailed the vomiting, but a week later this recurred and the plasma calcium concentration was 16 mg./100 ml. Further intravenous neutral phosphate, followed by oral supplements and cortisone acetate, led to a permanent cessation of vomiting and gradual restoration of normocalcaemia (Fig. 2).

Six weeks after starting carbimazole therapy oral phosphate and cortisone acetate were stopped without reappearance of hypercalcaemia. Two months later an elective subtotal thyroidectomy was performed. Histology was compatible with partially treated thyrotoxicosis. Since the operation (July 1967) the patient has remained well.

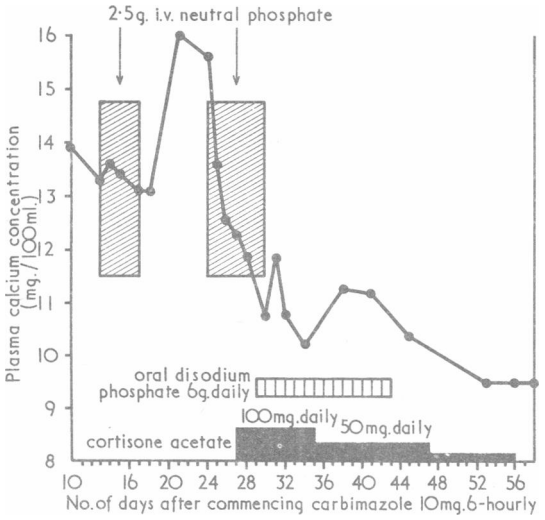

Fig. 2.—Case 2. Plasma calcium concentration during treatment.

Case 3

A 24-year-old married woman developed a puerperal schizo-affective psychosis. The response to electric convulsion therapy, insulin therapy, and phenothiazines was poor. Some weeks after admission she began to vomit up to four times a day. Her weight fell by 28 lb. (12·7 kg.) in the ensuing six weeks. Thyroid function tests confirmed thyrotoxicosis (Table I). The plasma calcium concentration was 13·0 mg./100 ml. Treatment with carbimazole 10 mg. eight-hourly was started and after a few days the vomiting stopped. Plasma calcium concentration returned to normal within four weeks. Six months after diagnosis the patient remained well and normocalcaemic on maintenance doses of carbimazole.

Discussion

Vomiting in thyrotoxicosis has long been recognized (Lahey, 1932), though only comparatively recently has the occasional dominance of this symptom been emphasized (Nikkilä and Pitkänen, 1960). Such dominance may delay diagnosis, as in Case 1. In this case coexistent jaundice further confused the picture and initially a diagnosis of viral hepatitis was entertained. Recurrence of jaundice three years later, during a thyrotoxic relapse, supports a causal relationship between the two conditions (Werner, 1962). Hypercalcaemia, though not always the cause, should be suspected whenever vomiting complicates thyrotoxicosis (Nikkilä and Pitkänen, 1960). In life-threatening situations, as in Case 2, a direct attack on the plasma calcium concentration may be indicated. Exogenous calcitonin may be the treatment of choice (Buckle *et al.*, 1969), but when this is not available intravenous phosphate therapy may have to be used, despite the actual and theoretical complications of such therapy (Goldsmith and Ingbar, 1966).

Up to 1960 only a few cases of hypercalcaemic thyrotoxicosis had been recorded (Noble and Borg, 1936; Wijnbladh, 1937; Miller and Evans, 1942; Koenig *et al.*, 1957; Epstein *et al.*, 1958; Hubble, 1958). In half the cases the hypercalcaemia was attributed to thyrotoxicosis alone, but in the remainder there was associated hyperparathyroidism. In the past decade more than 20 further cases of coexistent thyrotoxicosis and hyperparathyroidism have been reported (Breuer and McPherson, 1966; Ahuja and Chopra, 1968). This has led to the unwarranted assumption that finding unequivocal hypercalcaemia in a patient with thyrotoxicosis should always lead to a search for a parathyroid adenoma (Klotz *et al.*, 1968) despite the evidence that a tendency towards hypercalcaemia is normal in uncomplicated thyrotoxicosis (Nikkilä and Pitkänen, 1960; Baxter and Bondy, 1966; Frizel *et al.*, 1967).

That thyrotoxicosis per se can alter calcium metabolism has been known for many years. In 1891 von Recklinghausen described the case of a young woman suffering from osteitis fibrosa cystica and thyrotoxicosis. More recently Follis (1953) observed pathological changes resembling osteitis fibrosa in each of 20 thyrotoxic subjects examined at necropsy. Aub *et al.* (1929) observed consistently increased faecal and urinary loss of calcium in thyrotoxic patients despite normocalcaemia. The plasma ionized calcium concentration has been shown to be consistently raised in thyrotoxicosis (Frizel *et al.*, 1967). A reduction in the protein-bound calcium, consequent on hypoalbuminaemia (Adams *et al.*, 1967; Klotz *et al.*, 1968) accounts for the comparative infrequency of overt hypercalcaemia.

In about 10% of cases the rise in ionized calcium concentration more than offsets the reduction in plasma protein-bound calcium concentration and hypercalcaemia results (Nikkilä and Pitkänen, 1960; Baxter and Bondy, 1966). Occasionally this is severe enough to cause nausea, vomiting, polyuria, dehydration, and hypercalcaemic nephropathy, all of which were seen in one or more of our three patients.

The cause of hypercalcaemia in thyrotoxicosis is still obscure. Morbid anatomical (Follis, 1953), clinical, and kinetic studies in patients with thyrotoxicosis (Krane *et al.*, 1956) suggest that there is increased bone catabolism leading to increased calcium mobilization. Pribek and Meade (1957) have suggested that hypercalcaemia will occur only when there is concomitant failure to suppress parathyroid hormone secretion in the face of a rise of plasma calcium concentration. Nevertheless, hypercalcaemia in thyrotoxicosis probably occurs despite parathyroid suppression. In a case of hypercalcaemic thyrotoxicosis recently reported (Buckle *et al.*, 1969), plasma immunoreactive parathyroid hormone concentration was unrecordably low (under 0·1 ng./ml.). Later, when euthyroidism and normocalcaemia had been re-established, the plasma immunoreactive parathyroid hormone concentration was found to be within the normal range (0·1 to 0·25 ng./ml.). The calcitonin content of the hyperplastic thyroid gland is reputedly lower than in the normal thyroid gland (Aliapoulios *et al.*, 1966; Klotz *et al.*, 1968), and impaired secretion of calcitonin could conceivably account for the appearance of hypercalcaemia in thyrotoxicosis.

Treatment by conventional means is usually sufficient in thyrotoxicosis complicated by overt hypercalcaemia, but in rare cases more direct measures, aimed at lowering the plasma calcium level, may have to be used. Search for a second pathological condition to explain the hypercalcaemia is unnecessary and may be confusing. For example, the cortisone acetate suppression test has been reported as positive (Sataline *et al.*, 1962) or negative (David *et al.*, 1962) in thyrotoxicosis.

The time taken for the complete return of plasma calcium levels to normal after initiating antithyroid therapy varies.

TABLE II.—*Duration of Hypercalcaemia in Nine Cases of Thyrotoxicosis*

Patient No.	Duration of Hypercalcaemia	Treatment Given
1	13 weeks	4·17 mCi ^{131}I and propylthiouracil 300 mg. daily (Epstein *et al.*, 1958)
2	8 ,,	2-mercaptomidazole 60 mg. daily for three weeks followed by propylthiouracil, 300 mg. daily and low calcium diet (Stanley and Fazekas, 1949)
3	6 ,,	Carbimazole 40 mg. daily, neutral phosphate, and cortisone acetate (Fig. 2)
4	6 ,,	Propylthiouracil 400 mg. daily (Pribek and Meade, 1957)
5	4 ,,	Carbimazole 30 mg. daily (Case 3)
6	4 ,,	Propylthiouracil 600 mg. daily (Kleeman *et al.*, 1958)
7	3 ,,	Carbimazole 30 mg. daily (Fig. 1)
8	2 ,,	Carbimazole 40 mg. daily, intravenous porcine calcitonin and hydrocortisone (Buckle *et al.*, 1969)
9	2 ,,	Potassium iodide (Nikkilä and Pitkänen, 1960)

Unfortunately, in most cases reported serial plasma calcium levels during treatment are not given. The relevant details in the present three cases, and six others in which the relevant information is available, are shown in Table II. In all but one the plasma calcium concentration had returned to normal within eight weeks of beginning treatment. Thus it would seem reasonable to wait at least this long before considering a second pathological condition to explain concomitant hypercalcaemia.

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Clinical and Bacteriological Studies with Clindamycin

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Summary: Fifty patients have been treated with clindamycin, a chemical analogue of lincomycin. Forty-four responded satisfactorily to treatment. Gastrointestinal side-effects were rare though five patients developed rashes. Most recently isolated staphylococci are clindamycin-sensitive.

Introduction

Clindamycin (7 (S)-chloro-7-deoxylincomycin) is a derivative of lincomycin obtained by chemical replacement of the 7 (R)-hydroxyl group of lincomycin by a 7-chloro substituent. It is four to eight times more active than lincomycin against most Gram-positive organisms and is better absorbed from the gastrointestinal tract (McGehee *et al.*, 1968). We report the results of treatment with clindamycin of a group of patients known or suspected to be suffering from infections caused by Gram-positive organisms. In-vitro sensitivity studies were also carried out and the results are reported.

Patients and Methods

Fifty patients (29 female and 21 male) aged 9 months to 82 years were selected for treatment with clindamycin; 25 were children. Thirteen presented with bone or joint infection (Table I), 17 had a variety of infections caused by penicillin-resistant *Staphylococcus aureus* species, and 20 suffered from pneumonia. The 17 miscellaneous staphylococcol infections were: cellulitis 4, wound infection 5, suppurative lymphadenopathy 3, chronic bronchitis 2, breast abscess 1, and skin infection 2.

The antibiotic was administered in capsules at six-hourly intervals as clindamycin hydrochloride hydrate (Dalacin C). The six-hourly dose was 300 mg. for adults, 150 mg. for children under 12 years, and 75 mg. for babies, who were given the antibiotic in powder form in milk. Parenteral preparations of clindamycin are not available at present, and four patients who were judged on clinical grounds to be septicaemic were given intramuscular lincomycin for the first three to four days of their illness. Septicaemia was subsequently confirmed in all four patients. The duration of clindamycin therapy ranged from 7 to 187 days, depending on the severity and chronicity of the infection. Liver function tests, full haematology, urine analysis and measurement of serum urea and electrolytes were performed at least once during treatment in all adults and most children. The patients were observed for clinical evidence of possible untoward reactions to the drug.

Before treatment was started appropriate specimens were taken for bacteriological examination. The clindamycin sensitivity of all organisms cultured was determined with a 2-μg. disc. The disc sensitivities to clindamycin of 500 *Staph. aureus* and 100 *Haemophilus influenzae* isolates were also recorded. The minimum inhibitory concentrations for 34 *Staph. aureus* strains were determined by the tube dilution technique.

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