Hypercalcaemia induced by increased thyroxine substitution in a patient treated with dihydrotachysterol

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Abstract. The metabolism of vitamin D is essential in the control of bone and mineral metabolism. Hyperthyroidism as well as hypothyroidism affect the metabolism of bone tissue and vitamin D. We present a dihydrotachysterol-calcium treated patient with post-operative hypothyroidism, who developed hypercalcaemia, when the thyroxine dosage was increased.

The metabolism of vitamin D is essential in the control of bone and mineral metabolism (Haussler & McCain 1977a,b). Hyperthyroidism as well as hypothyroidism effect the metabolism of bone tissue and vitamin D (Bouillon et al. 1980; Krane et al. 1956; MacFarlane et al. 1982; Mosekilde et al. 1977; Mosekilde & Melsen 1978). Recently, Lamber & Tikkainen (1981) reported 3 patients with post-operative hypothyroidism and hypoparathyroidism, who were treated with thyroxine and dihydrotachysterol as well as calcium. When thyroxine was withdrawn in order to perform a total body scan for metastases of thyroid carcinoma hypercalcaemia developed.

We present a dihydrotachysterol-calcium treated patient with post-operative hypothyroidism, who developed hypercalcaemia, when the thyroxine dosage was increased.

Case Report

The patient is a female born in 1930. Since 1948 she has been known to have goitre. No treatment was given until the spring of 1970, when she developed classical signs of hyperthyroidism. After pre-treatment with methimazole-thyroxine she underwent a subtotal thyroidectomy in October 1970. A multinodular goitre was found. Post-operatively she developed hypocalcaemia and treatment with dihydrotachysterol (Atecen®, Bayer AG, Leverkusen, FRG) and calcium tablets was instituted. Serum calcium levels were normalized but in January 1971, being on a dosage of Atecen® of 3.5 mg daily, she was hospitalized because of severe hypercalcaemia 5.0 mmol/l (reference range 2.0–2.6 mmol/l; serum calcium values are not adjusted for changes of serum proteins) and renal insufficiency (serum creatinine 480 µmol/l; reference range 60–120 µmol/l). Dihydrotachysterol and calcium were discontinued and the serum calcium levels decreased gradually to subnormal values. The renal function improved (serum creatinine 120 µmol/l). Because of hypocalcaemia, dihydrotachysterol (Dygratyl®, Ferrosan, Malmö, Sweden) and calcium (Solvecalc®, Draco, Lund, Sweden) were instituted. In the spring of 1971 thyroxine (Levaxin®, Nyegaard, Oslo, Norway) was added because of hypothyroidism. The patient continued with Levaxin 0.1 mg, Dygratyl® 0.8 mg and Solvecalc® 2.25 g Ca²⁺ daily for 2 years and the serum calcium level remained within normal limits, average level 2.25 mmol/l.

In October 1973 there were symptoms and signs of hypothyroidism and Levaxin® was increased to 0.15 mg daily for 3 weeks and then to 0.2 mg. The patient improved, her weight decreased 8 kg in 5 months and the symptoms and signs of hypothyroidism disappeared. Serum T₄ increased from 59 to 102 nmol/l (reference range 38–125 nmol/l). To find the optimal dosage of thyroxine substitution, Levaxin® was increased to 0.25 mg daily in July 1974, while Dygratyl® 0.8 mg and Solvecalc® 2.25 g Ca²⁺ were unchanged. The serum calcium in October 1973 was 2.15 mmol/l, in January 1974 2.15 mmol/l and in July 1974 2.45 mmol/l (Fig. 1).

In late August 1974 the patient experienced fatigue, thirst, polyuria and epigastric pain. In the middle of
September 1974 she became worse and was admitted to hospital. On admittance there was severe hypercalcaemia (3.75 mmol/l) (Fig. 1), renal insufficiency (serum creatinine 544 µmol/l) and anaemia (haemoglobin 85 g/l). Dygratyl® and Solvecale® were discontinued, the serum calcium levels were normalized after 10 days and renal function improved (serum creatinine 117 µmol/l). After 11 days the patient developed laboratory and clinical signs of hypocalcaemia and Dygratyl® 0.4 mg daily without calcium tablets was re-instituted. Levaxin® was reduced to 0.2 mg daily.

The course has following this incident been uncomplicated, the patient is now in a good condition, has a normal serum calcium level and a normal renal function (serum creatinine 67 µmol/l). She is maintained on Levaxin® 0.2 mg and Dygratyl® 0.6 mg daily.

**Discussion**

The described patient had two periods of severe hypercalcaemia on treatment with dihydrotachysterol and calcium. In the first incidence, which occurred 3 months after subtotal thyroidectomy, it cannot be excluded that the patient had a subclinical hypothyroidism, which might have made her more prone to develop hypercalcaemia on dihydrotachysterol treatment (Lowe et al. 1962). As discussed by Lamberg & Tikkanen (1981) there may be delayed elimination of dihydrotachysterol from the plasma in the hypothyroid state. This may lead to increased calcium absorption from the gut and hypercalcaemia (Lekkerkerker & Doorenbos 1973). A possible additional mechanism for the development of hypercalcaemia in hypothyroidism is decreased glomerular filtration (Lekkerkerker & Doorenbos 1973).

In contrast, the second incidence of hypercalcaemia occurred after thyroxine substitution was increased from 0.2 to 0.25 mg daily, while the dose of dihydrotachysterol and Ca²⁺ remained constant. Thyroid hormones cause an increase in bone resorption (Mosekilde et al. 1977; Mundy et al. 1976), which tends to increase serum calcium and phosphate concentrations, and this might explain why our patient developed hypercalcaemia at the second incidence. An alternative explanation could be increased bioavailability of dihydrotachysterol when the thyroxine dosage was increased. Altered metabolism of drugs in thyroid disorders has been discussed by Eichelbaum (1976).

In patients with normal parathyroids and normal renal function, the increased bone resorption accompanying hyperthyroidism tends to increase serum calcium, which causes a decrease in parathyroid hormone secretion (Mosekilde & Christensen 1977). This homeostatic mechanism suppresses the renal 1-hydroxylase enzyme and the serum concentration of 1,25-dihydroxycholecalciferol is reduced (Bouillon et al. 1980). Both the reduced release of parathyroid hormone and the decreased production of 1,25-dihydroxycholecalciferol tend to lower serum calcium.

In patients with clinical hyperparathyroidism there is at present no possibility to discriminate between a total loss of parathyroid hormone secretion and an insufficient secretion. In those patients with insufficient parathyroid hormone secretion the discussed regulatory mechanism could theoretically play some role. However, this is probably of minor importance, since the treatment with pharmacological doses of dihydrotachysterol tends to suppress the secretion of parathyroid hormone. Pharmacological doses of vitamin D or equivalents increase serum calcium via an increased gastrointestinal absorption and an osteolytic effect on the bone tissue. It remains incomprehensible, however, that treatment with pharmacological doses of vita-
min D or equivalents can maintain a normal serum calcium in view of the fact that the known homeostatic mechanisms regulating calcium metabolism are no longer in play. Alterations with regard to other factors which influence calcium metabolism may therefore be very important.

The described patient and the 3 patients reported by Lamberg & Tikkanen (1981) demonstrate that it is important to carefully monitor serum calcium concentrations in dihydrotachysterol treated patients when the thyroxine dosage is changed.

References


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