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Oxyphenbutazone-induced goitre

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Summary

A woman who had taken oxyphenbutazone for 4 years because of back pain presented with goitre and hypothyroidism. This was shown to be due to an organification defect, caused or aggravated by oxyphenbutazone.

Introduction

An adverse effect of some drugs lies in their goitrogenic action (de Groot and Stanbury, 1975). Phenylbutazone has this property and several reports of goitre and hypothyroidism associated with its administration have been published (Morgans and Trotter, 1955; Benedek, 1962; Kleint, 1971; Ruiz-Torres, 1971; Vermulen and Schoot, 1972). It is not, however, widely appreciated that one of its major metabolites, oxyphenbutazone (Tanderil®, Geigy) is also goitrogenic (Norrell, 1967; Miracco and Orlando, 1972). The following case of oxyphenbutazone-induced goitre is the first to be reported in Britain.

Case history

A 63-year-old woman was referred to surgical out-patients with a 2-month history of progressive thyroid

enlargement and symptoms of hypothyroidism. On examination, she had a large, firm, vascular, non-tender goitre and was clinically hypothyroid. There was no family history of thyroid disease and she ate a normal, balanced diet. She gave a long history of low back pain and 5 years previously she had taken phenylbutazone and dihydrocodeine for about 1 year. She had subsequently been found to have marked hyperuricaemia and had been put on allopurinol 100 mg t.d.s. and oxyphenbutazone 100 mg t.d.s., which she had taken regularly for 4 years. Thyroid function tests confirmed hypothyroidism (see Table 1) and no anti-thyroid antibodies were detectable.

Assuming iodine deficiency to be unlikely, the results suggested that the hypothyroidism was due to an organification defect. This was confirmed by a perchlorate discharge test (see Fig. 1). Uptake of ¹³¹I was very high (32% at 30 min) but following the administration of potassium perchlorate at 40 min there was a discharge of isotope from the gland, so that at 70 min, only 28% of the administered radioactivity remained in the thyroid.

All medication was withdrawn and over the next 4 weeks the patient became clinically and biochemically euthyroid (PBI 549 nm/l, TSH 4.6 nu./l). Twenty-one months later she remained euthyroid and the thyroid

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TABLE 1. Thyroid function tests

Test	Result (SI units)	Normal range (SI units)
PBI	116–248 nm/l	310–630 nm/l
Free thyroxine index PBI/Thyopac 3	150	337–537
Serum thyroxine (thyopac 4)	0 nm/l	58–167 nm/l
TRH test	0 min 35 mu./l	0.5–4.0 mu./l
(serum TSH response to 200 µg TRH, i.v.)	20 min 47 mu./l	6.5–20.5 mu./l
	60 min 46 mu./l	4.0–15.6 mu./l
¹³¹ I-uptake	6 hr 52% Scan—diffusely enlarged gland	11–40%

Fig. 1. Perchlorate discharge test.

gland was no longer visible or palpable (PBI 571 nm/l, Thyopac-3 111%, FTI 514, TSH 1.7 mu./l). The oral perchlorate discharge test was repeated; ¹³¹I uptake had fallen to 13% at 30 min but administration of potassium perchlorate again caused a discharge of isotope from the gland at about the same rate as before, indicating persistence of the organification defect.

Discussion

Phenylbutazone is a potent anti-rheumatic agent having analgesic, sodium-retaining and uricosuric properties. It is metabolized, by hydroxylation in the liver, to two compounds, one of which is oxyphenbutazone (Burns *et al.*, 1960).

Since Morgans and Trotter's first report of phenylbutazone-induced goitre in 1955, several mechanisms have been proposed to explain its action on thyroid function, including iodine binding (Green *et al.*, 1953) and displacement of thyroid hormone from binding proteins with subsequent TSH suppression (Melholm-Hansen, 1962) but it is now agreed that

the action is on the thyroid gland itself causing an organification defect, reduced thyroid hormone secretion and consequently excessive TSH secretion and goitre formation (Keinsorg and Kruskemper, 1955; Hillman, 1957; Kruskemper, 1959; Abiodun *et al.*, 1973).

In 1967, Norrell described a case of goitre and hypothyroidism due to an organification defect, caused by oxyphenbutazone. This phenomenon has been reported only once since, to our knowledge, and in that case the patient was also receiving para-aminosalicylic acid, itself a goitrogen. Experiments have shown that the action of oxyphenbutazone on the thyroid is similar to that of phenylbutazone (Ege and Fernholz, 1965; Hoffman, 1967).

The cause of the persistently abnormal perchlorate discharge test following withdrawal of oxyphenbutazone in the present case remains conjectural; in Norrell's case, no organification defect persisted. The present patient was taking allopurinol in addition to oxyphenbutazone but no anti-thyroid activity has been ascribed to the drug. Other possibilities include a pre-existing organification defect aggravated by administration of oxyphenbutazone or persistence of the metabolic defect caused by the drug despite its withdrawal.

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Coeliac disease and goitre

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Summary

Two cases of coeliac disease associated with thyroid enlargement are presented. One had a large simple adenomatous goitre which was removed surgically and the other had histological confirmation of lymphadenoma (Hashimoto's disease).

Introduction

There have been a number of recent reports of cases in which coeliac disease has been associated with another disease complex. Thus coeliac disease has been reported in association with diabetes (Walker-Smith, Vines and Grigor, 1969), Sjögren's syndrome (Maclaurin, Matthews and Kilpatrick, 1972; Pittman and Holub, 1965), thyroiditis (Maclaurin *et al.*, 1972) and bird fancier's lung (Berrill *et al.*, 1975). Two cases in which thyroid disease was associated with coeliac disease are now described.

Case 1

A 55-year-old unmarried woman who was born and lived all her life in an area endemic for goitre was

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admitted to hospital with weakness, loss of appetite, diarrhoea and weight-loss. She had had a large multinodular goitre for many years.

On examination she was in mild congestive heart failure with fast atrial fibrillation. She was clinically anaemic and investigations showed Hb 4 g/100 ml; WCC 1900/mm³; platelet count $4.6 \times 10^4/\text{mm}^3$; reticulocyte count 0.5%; film reported as showing macrocytosis; protein-bound iodine 460 mmol/l (normal range 300–600); bone marrow showed a megaloblastic anaemia; serum vitamin B₁₂ 30 pg/ml (normal range 150–900); serum folic acid 2.3 ng/ml (normal range 3.5–24.0); serum carotene 15 mg/100 ml (normal 60–120); faecal fats were normal; D-xylose excretion was only 1.6 g of a 25-g dose in 5 hr; jejunal biopsy showed an atrophic mucosa with prominence of lymphoid tissue and subtotal villous atrophy.

A diagnosis of coeliac disease was made and she was started on a gluten-free diet. With treatment of the anaemia her general condition improved sufficiently for her to have a partial thyroidectomy and a total of 515 g of thyroid tissue was removed which was shown on histology to be an adenomatous