Carbimazole and autoantibody synthesis in Hashimoto's thyroiditis

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Summary and conclusions

Serum thyroxine, thyrotrophin, and thyroid microsomal antibody levels were measured in 20 patients with Hashimoto's thyroiditis and hypothyroidism before, during, and after treatment with carbimazole or placebo. Thyroid microsomal antibody levels fell during treatment in the 10 patients who received carbimazole, while serum thyroxine and thyrotrophin levels did not change. There were no changes in the placebo group.

The study proves support for the concept that carbimazole may act directly on autoantibody synthesising lymphocytes localised in the thyroid. Such an effect might be valuable in influencing the autoimmune process in autoimmune thyroid disease.

Introduction

Several studies have indicated that thyroid autoantibody levels fall during antithyroid drug treatment of patients with Graves's disease.¹⁻⁵ This phenomenon could reflect spontaneous changes in autoantibody levels or some direct or indirect effect of antithyroid drugs on the autoimmune process. Recent observations suggest, however, that antithyroid drugs may have a direct action on autoantibody synthesis⁶ and to investigate this possibility further we studied the influence of carbimazole on thyroid microsomal antibody levels in patients with Hashimoto's thyroiditis.

Patients and methods

Twenty patients with Hashimoto's thyroiditis and hypothyroidism (diagnosed on clinical, biochemical, and immunological grounds) were studied. The patients were taking thyroxine replacement therapy (0.15 mg/day), which was continued throughout the investigations. An initial blood sample was taken and three weeks later the patients were divided into two similar groups, 10 being treated with carbimazole (15 mg three times daily) and 10 with placebo. Patients in the carbimazole-treated group had a mean ($\pm$ SEM) age of 54 ± 3 years, and nine were women. All 10 of the placebo-treated group were women, and their mean age was 51 ± 2 years. Blood samples were taken every three weeks and analysed for serum thyroxine,⁷ serum thyrotrophin,⁸ and thyroid microsomal antibody.⁹ After 12 weeks treatment with carbimazole or placebo was stopped and a final blood sample taken three weeks later.

The statistical significance of the changes in thyroxine, thyrotrophin, and microsomal antibody levels was assessed using a paired *t* test.

Results

Serum microsomal antibody levels fell in nine of the 10 patients treated with carbimazole. The fall was statistically significant for the group after six weeks' drug administration and maximal after nine weeks (see figure). Thereafter the mean antibody levels rose slightly and this trend continued over the three weeks after withdrawal of carbimazole treatment. These increased values reflected increases in antibody titres in only three patients, however, the levels remaining unchanged in six and decreasing in one patient; overall the mean increases for the group were not statistically significant ($p > 0.1$).

Influence of carbimazole and placebo treatment on microsomal antibody levels in Hashimoto's thyroiditis.

There was no significant change in serum thyroid hormone or thyrotrophin levels during antithyroid drug treatment (see figure), although two patients showed an approximately twofold increase in serum thyrotrophin levels after nine weeks' carbimazole.

Serum microsomal antibody, thyroxine, and thyrotrophin levels showed no changes in the placebo-treated group (see figure).

Discussion

Thyroid microsomal antibody levels fell in patients with Hashimoto's disease who were treated with carbimazole. This effect appeared to be independent of thyroxine or thyrotrophin levels as these values did not change during antithyroid drug administration. Our observations therefore support the suggestion⁶ that carbimazole has a direct effect on the immune cells that synthesise thyroid autoantibodies. As the active metabolite of carbimazole (methimazole) is concentrated in the thyroid,^{10 11} and lymphocytes localised in the thyroid seem to be a major site of thyroid autoantibody synthesis,¹²⁻¹⁴ the drug probably acts on these immune cells. Furthermore, recent studies in vitro have shown that methimazole, at concentrations similar to those which might be expected in the thyroid during treatment, strongly inhibits thyroid autoantibody synthesis by lymphocyte cultures from patients with Hashimoto's thyroiditis.

The effects of carbimazole on thyroid autoantibody levels in patients with Graves's disease¹⁻⁶ are similar to those described here for Hashimoto's thyroiditis. Consequently in-vivo and in-vitro studies in both Hashimoto's and Graves's diseases suggest that carbimazole has a direct, inhibitory action on thyroid auto-

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antibody production. This effect could be of potential value in influencing the autoimmune process in these conditions.

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Thyroxine replacement therapy: prescribing patterns and problems in 2710 patients

SCOTTISH AUTOMATED FOLLOW-UP REGISTER GROUP

Summary and conclusions

The use of thyroxine replacement therapy was studied in 2710 patients with a previous diagnosis of either thyrotoxicosis or primary hypothyroidism. The patients, who were treated in five centres, were followed-up continuously using an automated register. Seventy per cent of patients had been prescribed daily doses of thyroxine of 200 µg or more. The estimated 10-year cumulative incidence of detected undertreatment was 13.2% (95% confidence limits 10.9-15.6%). The median cumulative incidence of recognised overtreatment was 6.2%.

Improved patient education and the dissemination of guidelines to doctors on the use of thyroxine replacement may reduce the incidence of undertreatment or overtreatment.

Introduction

Overt spontaneous hypothyroidism is a relatively common condition with a prevalence of up to 2% of the general population aged 18 and over.¹ To this must be added patients with congenital hypothyroidism, currently estimated at between 1 in 3000 to 1 in 9000 live births.² Hypothyroidism is common in patients who have been treated for thyrotoxicosis; in a recent study in four different teaching hospital centres, the prevalence

of hypothyroidism ranged from 24% to 63% in a total of 1902 patients after radioiodine therapy and from 23% to 52% in 1428 patients after subtotal thyroidectomy (unpublished observations).

Many studies³⁻⁴ have shown that patients often do not take long-term medication in the recommended dosage and sometimes stop taking it altogether either on their own initiative or because of the intervention of another doctor. The prevalence of inadequate treatment with thyroxine was as high as 75% in one study.⁵ This problem was re-examined in thyroxine-treated patients who were under continuous surveillance through a follow-up register⁶ and were offered an assessment of their thyroid status every 12 to 18 months over 10 years.

The Scottish Automated Follow-up Register (SAFUR) has been providing follow-up facilities for patients treated for thyroid disease since 1967, as a joint venture between hospital and primary care. The system is used by hospital doctors in five Scottish centres and 1547 general practitioners to follow-up patients treated by radioiodine, subtotal thyroidectomy, and thyroxine replacement. There are now over 6000 patients on the register. Follow-up examinations are usually carried out by general practitioners, and biochemical analyses, processing, and reporting of results are performed by a central registry with laboratory and computing facilities.

Patients and methods

Analysis of 2710 computer-held patient follow-up records produced information about 2926 prescriptions for thyroxine. Twenty-seven prescriptions (0.9%) were for less than 100 µg/day and 204 (7%) for 300-500 µg/day. Lists of these patients were sent to the centres concerned for checking for possible errors in recording and for appropriate action. In the remaining group of prescriptions only 861 (29%) were for doses in the range of 100 to 150 µg, 1714 (59%) were for 200 µg, and 120 (4%) for 250 µg.

When undertreatment was detected at the follow-up examinations⁷

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