Rapid improvement of thyroid function by using glucocorticoid indicated for the preoperative preparation of subtotal thyroidectomy in Graves' disease

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Abstract

Glucocorticoid therapy is not considered as an authentic method for obtaining euthyroid in Graves' disease. We tried the administration of prednisolone as a preoperative preparation for subtotal thyroidectomy in 4 hyperthyroid patients with Graves' disease who had suffered adverse effects of thionamide antithyroid drugs, including agranulocytosis, liver damage and skin eruptions.

Following oral administration of a 30 mg daily dose of prednisolone, with or without other antithyroid reagents, both serum T4 and T3 concentrations decreased rapidly and reached the normal range within 2 weeks. The clinical signs and symptoms of hyperthyroidism also improved rapidly and subtotal thyroidectomies were performed uneventfully in all cases.

These results suggest that 1) glucocorticoid medication can normalize the circulating hormone levels rapidly in Graves' disease, 2) it is a useful method as preoperative preparation for subtotal thyroidectomy, especially when other conventional methods are not available or effective in obtaining euthyroid, and 3) mechanisms other than thyroid stimulation by circulating immunoglobulin seem to play an important role in causing hyperfunction of the gland.

Methods used in treating hyperthyroidism of Graves' disease seem to have become well established. By the appropriate use of conventional therapies, namely, thionamide medication, radiiodine therapy and subtotal thyroidectomy, it is not difficult to treat hyperthyroidism in the majority of cases. Nevertheless, not infrequently, embarrassing cases are experienced because of the adverse effect of antithyroid drugs. In this paper we show the usefulness of glucocorticoid therapy in obtaining euthyroid rapidly for uneventful subtotal thyroidectomy in such cases.

Case 1

A 44-year-old female was referred to us for the treatment of persistent thyrotoxicosis. She had been in good health until February 1974, when she noticed weight loss, palpitation, heat intolerance and short breath on exercise. She also noticed the retraction of her upper eye lids and bulging in the anterior neck. In March 1974, she was examined at a local dispensary and diffuse goiter was noticed. Blood examination revealed that serum T4 and RT3U were 22.6 µg/100 ml and 44%, respectively. A diagnosis of Graves' disease was made and treatment with methimazole (30 mg daily) was instituted. Four
weeks later, she had a severely sore throat with high fever. Palpitation and sweating recurred. She was carried to a university hospital by ambulance. The WBC count was 800/cmm and neutrophil was 1%, indicating that she had agranulocytosis probably induced by methimazole. She was treated with a large dose of antibiotics and prednisolone. The WBC count normalized two weeks later. After discharge, her hyperthyroidism was treated with 10 mg of oral iodine per day alone, and her thyroid function remained hyperthyroid. In October 1975, palpitation and excessive sweating recurred again. Serum T₄ and RT₃U were 15.0 µg/100 ml and 35.4 %, respectively. Although the dose of oral iodine was increased to 100 mg per day, the thyroid function was not rendered euthyroid. She became very restless, and began to imagine that she would be caught and hurt by someone. Because of this fear, she changed the place where she was staying almost every day. She was referred to us in December 1975, because of the abnormal behavior and the cohabitation.

On admission, she had typical symptoms and signs of Graves' hyperthyroidism. She was hyperkinetic with marked finger tremor. Her pulse rate was 120 per minute. She had a diffuse goiter, estimated to weigh approximately 60 g. Other physical findings were not remarkable. Serum T₄, T₃ and RT₃U were 16.0 µg/100 ml, 645 ng/100 ml and 45 %, respectively. Antimicrosome and antithyroglobulin hemagglutination antibodies were 1:2400 and 1:24, respectively. Other hematological and biochemical routine examinations revealed no abnormality except for a low serum cholesterol level.

Thionamide medication was not indicated because of her history of agranulocytosis. Regarding isotope therapy, she had a strong fear of isotopes, and additionally, her psychic symptoms urged us to make her euthyroid as soon as possible. We selected subtotal thyroidectomy as the fastest and surest therapy to get her euthyroid. To facilitate the thyroidectomy, it was required to make her euthyroid prior to the operation.

Iodine, which is usually used for this purpose, had been already prescribed in a large dose for a sufficiently long period. She had already escaped from the suppressive effect of iodine on the thyroid hormone

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**Case 1**

![Fig. 1. Clinical course of Case 1, a 44-year-old female.](image)
release. Then, the oral administration of prednisolone, 30 mg daily, was started. As shown in Fig 1, serum levels of T₄ and T₃ were decreased rapidly concomitant with the relief of her symptoms. The examination on the 11th day of administration of prednisolone showed that serum T₄ and T₃ were 10.5 µg/100 ml and 250 ng/100 ml, respectively. On the 17th day, serum T₄ and T₃ were 6.2 µg/100 ml and 99 ng/100 ml, respectively, which were completely within the normal range.

The titers of antimicrosome and antithyroglobulin hemagglutination antibodies were not changed. The size of the goiter was found to be reduced to approximately 50 g on palpation.

After confirming a normal basal metabolic rate (+10%), subtotal thyroidectomy was performed with general anesthesia. On the day of the operation, 200 mg of hydrocortisone was used to protect against acute adrenal insufficiency due to surgical stress. The operation and postoperative course were uneventful. She was discharged 6 days after the operation. The serum concentrations of T₄, T₃, Ca and P have been within the normal range.

**Case 2**

A 23-year-old woman was referred to us for treatment of Graves’ disease. In 1973, she suffered from fulminant hepatitis when she was at 6 months of gestation. She survived following vigorous treatment including steroid hormone and blood exchanges. In 1975, she became aware of excessive sweating, heat intolerance and weight loss. Her condition was diagnosed as Graves’ disease on the basis of an enlarged nontender thyroid gland, symptoms and signs of thyrotoxicosis and elevated serum thyroid hormone levels (T₄ and RT₃U were 14.1 µg/100 ml and 53%, respectively). Methimazole in a 30 mg daily dose, was prescribed. Two months after the institution of the treatment, a number of skin eruptions appeared on the extremities. On the following day, she had a high fever of 40°C and a severely sore throat. The WBC count was 1000/cmm and the granulocyte count was less than 50/cmm. She was admitted to a hospital and treated with large doses of antibiotics and recovered. After this episode, propranolol was prescribed to control her hyperthyroidism, but without success. Propylthiouracil, 150 mg daily, was then added in January 1976, because the symptoms of thyrotoxicosis got worse. A few weeks later, however, the serum levels of transaminase increased markedly and propylthiouracil was stopped. After the cessation, the liver function improved. She was referred to us for treatment of hyperthyroidism and hospitalized on May 28, 1976.

On physical examination she had markedly excessive perspiration. Her pulse rate was 100/min and the thyroid gland was diffusely enlarged to approximately 60 g on palpation. There was a vascular bruit over the goiter. Neither apparent exophthalmos nor pretibial myxedema was present.

Routine hematological and biochemical examinations revealed a slight increase in alkaline phosphatase, transaminase and gamma globulin, and mild anemia. Serum concentrations of T₄ and T₃ were 18.4 µg/100 ml, respectively. RT₃U was 44%. Twenty-four hours’ ¹²³I-thyroid uptake was 67%. Antimicrosome and antithyroglobulin antibodies were 1 : 24000 and negative, respectively. Because she was most anxious to have a baby as soon as possible and strongly nervous about the “harmful” effect of isotope therapy, we determined to try to make her euthyroid by prednisolone and perform subtotal thyroidectomy. In addition to propranolol which had been already given, prednisolone, 30 mg daily, was administered orally. As shown in Fig 2, the serum levels of T₄ and T₃ decreased rapidly and had reached the normal range when examined on the 15th day of the administration of
prednisolone. The size of the goiter was reduced to about 50 g on palpation. The antimicrosome and antithyroglobulin antibodies maintained the same titers as before the administration of prednisolone. After confirming a normal basal metabolic rate (+5 %), subtotal thyroidectomy was performed. Prior to the operation, 30 mg of iodide was also prescribed. The operation and postoperative course were uneventful. On the day of the operation, 100 mg of hydrocortisone was given twice and the dose was decreased on the following days. She was discharged 8 days after the operation.

Case 3

A previously healthy 43-year-old woman became aware of palpitation, finger tremor, general malaise and excessive sweating in the summer of 1978. In August, 1980, a goiter and tachycardia were noted by a health consultant physician and she was referred to us for the evaluation of the thyroid. She had a diffuse nontender goiter, estimated to weigh approximately 60 g. Her pulse rate was 120 per minute and her skin was warm and moist. Her eye signs for Graves’ disease were present to a mild degree. She had no pretibial myxedema. The values for T4 and T3 concentrations in serum were 18.9 µg/100 ml and 395 ng/100 ml, respectively. RT3U was 38%. Twenty-four hours thyroid uptake of radioactive iodine was 69%. A diagnosis of hyperthyroidism due to Graves’ disease was made and treatment with propylthiouracil, 300 mg daily, was instituted. In the fourth week of the administration of propylthiouracil, severe skin eruptions appeared on the trunk and face, associated with the elevation of the value for serum transaminase. Propylthiouracil was switched to methimazole and the eruptions faded. However, in the 5th week of the administration of methimazole, generalized eruptions appeared again and methimazole was stopped. She was hospitalized for the control of hyperthyroidism. On examination, she seemed to still have hyperthyroidism as evidenced by finger tremor, moist skin and tachycardia. Serum levels of T4 and T3 were 15.8 µg/100 ml and
Case 3

A 43-year-old female was seen as an outpatient on May 28, 1982, because of a four-month history of palpitation, finger tremor, general malaise, and excess sweating. On examination, tachycardia, finger tremor, and a diffuse nontender goiter, estimated to weigh approximately 90 g, were noted. The levels of T4 and T3 concentrations in serum were 21.0 μg/100 ml and 690 ng/100 ml, respectively. A diagnosis of Graves' disease was made and treatment with methimazole (30 mg daily) and propranolol (30 mg daily) was instituted. In spite of this treatment, his symptoms got worse and he was admitted on June 23, in order to take enough rest. On the twelfth hospital day, methimazole was replaced by propylthiouracil, 300 mg daily, because of the development of urticaria.

Although the eruptions disappeared once

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**Case 4**

A 22-year-old male was seen as an outpatient on May 28, 1982, because of a four-month history of palpitation, finger tremor, general malaise, and excess sweating. On examination, tachycardia, finger tremor, and a diffuse nontender goiter, estimated to weigh approximately 90 g, were noted. The levels of T4 and T3 concentrations in serum were 21.0 μg/100 ml and 690 ng/100 ml, respectively. A diagnosis of Graves' disease was made and treatment with methimazole (30 mg daily) and propranolol (30 mg daily) was instituted. In spite of this treatment, his symptoms got worse and he was admitted on June 23, in order to take enough rest. On the twelfth hospital day, methimazole was replaced by propylthiouracil, 300 mg daily, because of the development of urticaria.
after changing the drug, they appeared again a few weeks later. In spite of the presence of urticaria, propylthiouracil was continued with antihistamine drug because thyrotoxicosis persisted. After a month, subtotal thyroidectomy was recommended, since these treatments did not exert enough therapeutic effect on his thyrotoxicosis. To induce a euthyroid state before operation, prednisolone (30 mg daily) was added to propylthiouracil and propranolol. After the administration of prednisolone, serum levels of $T_4$ and $T_3$, which had been fluctuating in the hyperthyroid range, decreased steadily and rapidly and his symptoms improved. On the 10th day of the administration of prednisolone, the basal metabolic rate was $-5\%$ and inorganic iodine (30 mg daily) was added to the treatment to reduce the vascularity of the gland.

The titers of antimicrosome and antithyroglobulin antibodies (1:2,400,000 and 1:240, respectively) were not changed when a euthyroid state was obtained, although they declined to 1:240,000 and 1:24, respectively, just before the operation. Fifteen days after the institution of prednisolone administration, subtotal thyroidectomy was performed. The goiter weighed 78 g.

During the operation and the following four days, hydrocortisone was given by injection or orally, and the doses tapered and finally stopped. The operation and postoperative course were uneventful. The patient is in now good health without any medication.

**Discussion**

In this communication, we presented four cases of Graves' disease whose hyperthyroidism was successfully controlled by glucocorticoid therapy as the preoperative preparation for subtotal thyroidectomy. In three of cases (Case 1–3), thionamide drugs could be used no longer because of severe or life-threatening adverse effects. In another case (Case 4), prednisolone was used because propylthiouracil or methimazole did not exert a therapeutic effect and its dose could not be increased because of persistent urticaria. In all the cases, serum levels of $T_4$ and $T_3$ decreased rapidly and reached the normal range within 2 weeks following the administration of prednisolone, and consequently, subtotal thyroidectomies were performed uneventfully.
Iodine or propylthiouracil had also been given with prednisolone in Case #1, #3 and #4 when the normalization of thyroid function was obtained. These reagents had been proved no longer effective by long term administration (Case #1) or not effective enough to produce a euthyroid state (Case #4), when the prednisolone therapy was instituted. However, the possibility that the rapid improvement in thyroid function was due to the combined effects of prednisolone and these reagents, instead of the effect of prednisolone alone, cannot be excluded. In Cases #2, #3 and #4, iodine was added because it was expected to reduce the vascularity of the gland to facilitate the operation and make it safe.

The rapid decline in the circulating thyroid hormones following prednisolone treatment agrees well with the results of short term administration of dexamethasone reported by Williams et al. (1975). They gave 4 doses of dexamethasone, 2 mg orally every 6 h, to hyperthyroid Graves' disease patients and noted significant lowering of levels of T₄, T₃ and thyroglobulin. The effect of glucocorticoid developed within 24 to 48 h after the first dose of dexamethasone and the thyroid hormone and thyroglobulin values returned to or toward the basal level in the subsequent 5 to 6 days. In their studies, the magnitude of decrease in T₄ and T₃ levels was only 19% and 40% of their basal levels, respectively, at the maximum. A similar decrease in the amount thyroid hormone was obtained when dexamethasone was given for 5 days, as reported by Chopra (1975). However, our results indicate that circulating thyroid hormone levels could be normalized when prednisolone is administered longer.

Although the mechanism responsible for the improvement of the hyperthyroidism in Graves' disease by glucocorticoid is still unclear, its effects on the peripheral metabolism of thyroid hormone and on the immune mechanism of this decrease could be involved. The inhibitory effect of glucocorticoid on the conversion of T₄ to T₃ in peripheral tissue has been well known (Chopra. 1975). Although the ratio of T₃ to T₄ in the circulation decreased during the administration of prednisolone in our studies, it is difficult to determine to what extent the decline in T₃ levels was due to this mechanism, because the half life of circulating T₃ is much shorter than that of T₄.

The second is the effect on the immune mechanism of the disease. Since the discovery of LATS (Adams, 1956, 1958), the thyroid stimulating IgGs have been measured and named variously based on their assay methods (Adams, 1958, 1967; Onaya et al., 1973; Shishiba et al., 1973; Smith and Hall, 1974; Orgiazzi et al., 1975). Although these stimulating IgGs seem to be responsible for the hyperfunction of the thyroid gland in Graves' disease, it is difficult to explain the acute effect of glucocorticoid shown in our study on the basis of a fall in the level of circulating IgG thyroid stimulator, since the half-life of IgG is estimated to be about 3 weeks. In fact, the decline in thyroid hormone levels was demonstrated in our study without or before the decline in the titers of antimicrosome or antithyroglobulin antibodies. An alternative possibility will be the effect on cellular immunity. While the role of cellular immunity in this disease has not been well elucidated, it is likely that thyroid stimulation through this mechanism is altered acutely by glucocorticoid therapy. Recently, the thyroid-stimulating action of lymphocytes in the thyroid in situ has been extensively studied though no clear evidence has been obtained yet.

Apart from the experimental observations on the pharmacological effect of glucocorticoid on hyperthyroidism, the attempts to treat hyperthyroidism of Graves' disease by glucocorticoid were reported in a few papers (Hill et al., 1950; Wikholm and Einhorn, 1963; Werner and Platman, 1965). All of them were before the development of the precise radioimmunoassays for thyroid hor-
Nowadays, glucocorticoid therapy does not seem to be considered as an authentic method to treat hyperthyroidism of Graves’ disease except for cases of thyroid storm. A large dose of iodine is usually recommended when thionamide antithyroid drugs are not available or not effective in producing a euthyroid state. However, patients often escape from the thyroid-suppressive action of iodine, and it is not effective in patients who have previously been exposed to a large amount of iodine. We demonstrated that treatment with the ordinary dosage of prednisolone (30 mg daily) could be an alternative or additional method to use in achieving euthyroidism in those patients, especially as the preoperative preparation of subtotal thyroidectomy.

References


