Treatment of thyrotoxicosis resistant to carbimazole with corticosteroids

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Summary

We report two patients whose thyrotoxicosis failed to respond to conventional treatment with carbimazole. The patients remained persistently hyperthyroid, both clinically and biochemically, despite several months of carbimazole therapy at the maximum recommended doses. Prednisolone 20 mg per day was then given in addition to the antithyroid drug and a dramatic response observed in both cases. They were then successfully treated with radioiodine.

Prednisolone has not been previously used to treat patients with hyperthyroidism who have not responded to thionamide drugs. Our experience suggests that corticosteroids may be potentially useful for controlling thyrotoxicosis in combination with carbimazole before definite treatment can be instituted.

Keywords: thyrotoxicosis, prednisolone, carbimazole resistance

Thionamides have been used in the treatment of hyperthyroidism for over 50 years. Most patients respond within four to six weeks of initiating treatment and the dose is reduced to a maintenance level for a further six to 12 months. Rarely, patients are found not to respond to antithyroid drugs (carbimazole or propylthiouracil) and this poses a difficult management problem. Such patients are usually thought to have failed to comply with their medication.

Corticosteroids are often used in the management of thyroid crisis.¹ However, they have not been recognised as useful therapy in the management of patients not responding to antithyroid drugs alone. We report two patients who remained persistently thyrotoxic despite treatment with carbimazole at the recommended dose for four months.

Case 1

A 30-year-old woman had had symptoms of thyrotoxicosis with palpitations, mood changes, heat intolerance, weight loss and diarrhoea for six months. On examination she was lean (body mass index 19), and had sinus tachycardia with a heart rate of 120 beats/min. She had a diffuse goitre with a bruit and fine tremor of her hands, but no eye signs apart from lid lag. Thyroid function tests confirmed hyperthyroidism with free thyroxine of

37 pmol/l (normal 1–24 pmol/l), free triiodothyronine of 12.7 pmol/l (4.2–7.1 pmol/l) and thyroid stimulating hormone of 0.2 mU/l (0.3–3.8 mU/l). Thyroid antimicrosomal and antithyroglobulin antibody titres were 1:400 and negative, respectively. She was treated with carbimazole 30 mg daily but two months later she was still clinically thyrotoxic and her free thyroxine was 41.6 pmol/l. The carbimazole was increased to 60 mg daily. She was also prescribed propranolol but it had to be discontinued owing to respiratory wheeze. Four months later, on the maximum recommended dose of carbimazole, she felt no better and her free thyroxine was 46 pmol/l. Non-compliance with the prescribed medication was suspected, but on repeated questioning she asserted that she was taking her treatment regularly. She was then started on prednisolone 20 mg daily in addition to the carbimazole. There was marked improvement in her symptoms within four weeks and she was clinically euthyroid, which was confirmed with a free thyroxine of 28.8 pmol/l. At this stage she was given radioactive iodine 400 MBq. Two months later her free thyroxine was 17.7 pmol/l (figure). The carbimazole was then stopped and prednisolone was gradually withdrawn; 15 months hence she is euthyroid and clinically well.

Case 2

A 46-year-old woman presented with symptoms of tremors, weight loss, tiredness, increased sweating, irritability and inability to concentrate at work. On examination she had a

Figure Serum free thyroxine concentrations for Case 1 (●) and Case 2 (○) during treatment with carbimazole and the effect of adding prednisolone. RAI=radioactive iodine

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diffuse goitre with an audible bruit, but no eye signs of Graves' disease. Her pulse rate was 100 beats/min, regular. She had fine tremors of her fingers and mild proximal muscle weakness. Thyroid function tests confirmed thyrotoxicosis (serum free thyroxine 73.8 pmol/l, free triiodothyronine >43.2 pmol/l and thyroid stimulating hormone <0.1 mU/l). Her antimitochondrial and antithyroglobulin antibody titres were 1 : 25 600 and negative, respectively. She was started on carbimazole 45 mg daily which, three months later was increased to 60 mg daily because of persistent hyperthyroidism. Two months later her serum free thyroxine was >125 pmol/l and her symptoms had worsened. She denied noncompliance to treatment. She was then commenced on prednisolone 20 mg daily in addition to the carbimazole. In the next two weeks her symptoms had improved and she was able to go back to work. Four and eight weeks later her free thyroxine was 71.2 and 63.6 pmol/l, respectively. In view of the considerable improvement in symptoms and since the free thyroxine level was down to 50% of her levels prior to prednisolone, she received radioactive iodine 400 MBq. Four and six months later her free thyroxine was 44.9 pmol/l and 5 pmol/l (figure). The carbimazole was therefore discontinued and prednisolone was gradually withdrawn. She is now being treated with thyroxine owing to hypothyroidism and is well.

Discussion

Carbimazole is widely used in the management of hyperthyroidism. It acts by inhibiting the oxidation and organic binding of thyroid iodide^{1,2} as well as having an immunosuppressive effect upon the thyroid itself. It is some months before the patient is rendered euthyroid, therefore compliance with treatment is essential. Failure to take the medication is generally thought to be the reason for lack of response to treatment, but the true prevalence of carbimazole resistance is unknown. There are few reports in the literature of patients not responding to the maximum recommended dose of 60 mg carbimazole daily.³ It is not clear why such patients do not respond. Both our patients denied noncompliance. Our first patient also had diarrhoea but there was no clinical evidence to suggest malabsorption. Although it is possible to measure drug levels, this is rarely done in clinical practice and was not performed in our patients. However, the observation that both patients demonstrated significant improvement once given prednisolone suggests that compliance was unlikely to have been the problem.

Before definitive treatment of thyrotoxicosis with subtotal thyroidectomy or ablation with radioiodine, it is necessary to control hyperthyroidism so as to reduce the risk of precipitating thyroid crisis.¹ Hence patients not responding to carbimazole need further

Summary/learning points

- resistance to antithyroid drugs in the treatment of thyrotoxicosis is not unknown
- prednisolone has been shown to ameliorate the symptoms of hyperthyroidism and hence can be used as an adjunct in the treatment of thyrotoxicosis when patients do not respond to antithyroid drugs alone
- prednisolone can also be useful in the rapid control of symptoms in the elderly and when definitive treatment for thyrotoxicosis has been planned, such as radioiodine

measures to reduce their serum free thyroxine concentration. In our two patients we used prednisolone to good effect. The addition of prednisolone as an adjunct to carbimazole produced significant clinical improvement and made it safe for the patients to have radioiodine treatment.

Prednisolone is not used as a mode of achieving euthyroid status in patients with hyperthyroidism, though it is often used in thyroid crisis. Studies have shown a rapid decline in serum thyroid hormone concentration following the acute administration of glucocorticoids.⁴⁻⁷ The effect of corticosteroids on the thyroid gland in hyperthyroidism is obscure. Graves' disease is an autoimmune disorder,¹ both cell- and antibody-mediated.⁸ The latter is a syndrome complex due to the action on the thyroid of IgG immunoglobulins that may be antibodies against components or regions of the thyroid plasma membrane, possibly regions that include the receptor for thyroid stimulating hormone itself. Thus, the reason why patients respond to corticosteroids could be two-fold. The more immediate effect could be the inhibition of conversion of thyroxine to triiodothyronine in the peripheral tissue,⁵ blocking the release of thyroxine from the thyroid. It may also lead to suppression of the immune response and hence decreased stimulation of the thyroid gland by the altered immune response and cell-mediated immunity. Clearly, further studies are needed to examine the effect of such immunosuppressive therapy in Graves' disease.

Our experience suggests that there are some patients who may benefit from the use of corticosteroids as an adjunct to antithyroid drugs in the treatment of Graves' disease. Such patients would include those in whom the response to carbimazole has been poor and also those patients in whom rapid remission of the disease is required, such as in the elderly and in patients with thyrotoxic heart disease. These cases demonstrate the potential value of prednisolone in rapid control of thyrotoxicosis, where a decision has been made to proceed with definitive treatment such as surgery or radioiodine.

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Congestive cardiac failure following laxative withdrawal

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Summary
We report the case of a 60-year-old woman who presented with weakness and hypokalaemia due to excessive use of laxatives. When the laxatives were withdrawn, she developed severe congestive cardiac failure requiring treatment with a diuretic and angiotensin-converting enzyme inhibitor. There was no underlying cardiac abnormality, and these drugs were eventually stopped with no recurrence of the cardiac failure. The possible mechanisms of heart failure following laxative withdrawal is discussed.

Keywords: laxative abuse, hyperaldosteronism, cardiac failure

Laxatives account for a significant proportion of over-the-counter (OTC) pharmacy sales (£37m in 1994 out of a total of £1268m OTC pharmacy and grocery sales). The wide variety and easy availability can lead to excessive use, inappropriate dosage, and even abuse of these medicines. Loss of fluid and electrolytes in diarrhoea may result in secondary hyperaldosteronism and hypokalaemia. Oedema may be a feature of the recovery phase after laxative withdrawal.

We describe a patient whose excessive laxative intake led to life-threatening cardiac failure after the laxatives were withdrawn.

Case report

A 60-year-old woman underwent a bilateral salpingo-oophorectomy for endometrial carcinoma in December 1987. She made a good recovery and routine follow-up showed no evidence of recurrence. Following the operation, she was told to avoid straining at stool and was prescribed Fybogel sachets and senna tablets. She felt this laxative regimen did not have the desired effect and some months later, on the advice of a friend, she started to take Fam-Lax (phenolphthalein and rhubarb) which she bought over-the-counter. Starting

with the recommended adult dose of two tablets, she soon increased this to five tablets per day. This produced a liquid, easily passed stool within a few hours.

Whilst on holiday in Spain in 1993 she felt weak and exhausted and was told she had a low blood pressure. By the time of her return home the symptoms had become more severe and eventually resulted in her admission to hospital.

On admission, her blood pressure was 105/60 mmHg. Clinically her heart was normal and there was no evidence of cardiac failure. Urea and electrolytes were within the normal range except for serum potassium which was found to be low at 2.6 mmol/l. Her prescribed medication consisted of medroxyprogesterone, sucralfate, ranitidine and co-dydramol.

In the absence of any other obvious cause for her hypokalaemia, laxative abuse was suspected. She admitted to taking the Fam-Lax – she had simply been following instructions not to strain at stool.

The laxatives were withdrawn and oral potassium supplements started (Sando-K 2 bid). Serum potassium rose rapidly to normal levels over the next four days (figure).

Figure Serum potassium and aldosterone levels

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