CASE REPORT

A Case of Graves' Disease Resistant to Carbimazole

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ABSTRACT

We describe a case of a patient with Graves' disease who failed to respond to carbimazole. Our patient remained thyrotoxic despite maximal carbimazole dosage. Our patient was switched to propylthiouracil which subsequently made the patient euthyroid. The patient was then definitively treated with radioiodine treatment. This case highlights the need to increase awareness of carbimazole resistance to prevent patients from being given escalating doses of carbimazole which increases the probability of adverse effects and extend their time in the hyperthyroid state.

Keywords: Carbimazole, Graves' disease, resistance.

INTRODUCTION

Thionamides which include methimazole and carbimazole are the usual first-line treatments in patients with Graves' disease (1–3). Propylthiouracil (PTU) is usually used as a second-line treatment (exception being in the first trimester of pregnancy) due to its association with severe hepatotoxicity (3). Most patients usually respond favourably to treatment with thionamides. Our patient, however, did not respond to carbimazole and had carbimazole resistant thyrotoxicosis (3).

CASE REPORT

Ms. VT is a 40-year-old female from Trinidad, West Indies. She is of Afro-Caribbean descent and presented with weight loss, palpitations and anxiety when examined by her family physician. Her thyroid test was as follows:

Free t3:13.9 (1.5–4.1 pg/mL)
Free t4: 34.6 (0.35–6 ng/dL)
Thyroid stimulating hormone (TSH): 0.008 (0.4–4 μIU/mL)

The patient had a diffuse non-tender goitre which was confirmed by thyroid ultrasound with no nodules. She had a thyroid bruit and no signs of ophthalmopathy. She was subsequently diagnosed with Grave's disease. She was started on Carbimazole 30 mg twice daily and propranolol 40 mg three times daily, and thyroid function tested 2 months later showed:

Free t3:15.1 (1.5–4.1 pg/mL)
Free t4: 36.2 (0.35–6 ng/dL)
TSH: 0.006 (0.4–4 μIU/mL)

Carbimazole was then increased to 40 mg twice daily with no biochemical or clinical improvement in thyroid function. The patient was subsequently referred to the endocrinologist, who questioned the compliance with medications. However, after being satisfied with the patient's compliance, carbimazole was discontinued and the patient's medication switched to PTU 300 mg twice daily. After 6 weeks of treatment, her thyroid function testing returned with normal results and she became clinically euthyroid. Our patient was subsequently treated with radioiodine therapy and is presently euthyroid on no medications 1 year later.

DISCUSSION

The prevalence of hyperthyroidism is approximately 2% for women and 0.2% for men (1) with the most common cause being Graves' disease. Graves' disease is an autoimmune condition comprising features of hyperthyroidism, diffuse goitre, ophthalmopathy and dermopathy (2).

Thionamides which include methimazole and carbimazole are the usual first-line treatments in patients

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with Graves' disease. Propylthiouracil is usually used as a second-line treatment (exception being in the first trimester of pregnancy) due to its association with severe hepatotoxicity (3).

Both of these treatments reduce thyroid hormone synthesis, and euthyroidism is usually achieved within several weeks. (3) Most patients usually respond favourably to treatment with thionamides. Our patient, however, did not respond to carbimazole and had carbimazole resistant thyrotoxicosis (3). The literature has shown that patients with Graves' disease can be refractory to high-dose thionamides (4–7) but the prevalence of carbimazole resistance is unknown (7).

There are various reasons for possible resistance to carbimazole. These include malabsorption of the drug, rapid metabolism of the drug, anti-drug antibodies and defects in intrathyroidal drug accumulation or action (4).

Any patient with drug-resistant Graves' disease should be questioned on compliance (6). We evaluated this by direct questioning of the patient and by supervised pill administration by her relative and was satisfied that our patient was in fact compliant with her medications. Also, since the patient responded to PTU, it is unlikely that the patient was non-compliant.

Our patient had no features suggestive of malabsorption on history or physical examinations. Hence, patient was not further investigated for this. In this case, the patient was unable to afford private lab testing for drug levels or anti-drug antibodies. The perchlorate discharge test was not done due to unavailability in our country but has been used in the literature to differentiate resistance to carbimazole from non-compliance (8). Also, the measurement of urinary iodine is also advised to exclude iodine contamination as a possible cause of resistance (8). However, financial constraints prevented this test from being done as well.

This case features an important aspect of the treatment of Graves' disease. Our patient was resistant to treatment with carbimazole but responded favourably to switching the treatment to PTU. Physicians should be made aware of this possibility when treating hyperthyroid patients. Since if not aware, patients may be given unwarranted escalating doses of carbimazole. Our patient was given higher than the recommended dose of 60 mg of carbimazole (3) by her family physician in a desperate attempt to control her hyperthyroidism. The use of high doses of carbimazole consequentially is associated with increased probability of adverse effects and also lengthened patients' time in the hyperthyroid state.

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