Thioamide-resistant Graves' Disease: Successful total thyroidectomy

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Introduction

Graves' disease in adults can be treated with radioactive iodine, antithyroid drugs or, rarely, total thyroidectomy[1]. If a patient elects for antithyroid medication, thioamides (carbimazole or prophythiouracil) are used, either as a titration regimen or as part of a block and replace regimen, for 12-18 months before withdrawal of treatment and further assessment of any disease recurrence. It is rare that Thioamides do not achieve disease suppression with this usually associated with concordance issues. We present a case of a patient with true thioamide-resistant Graves' disease who, following extensive pre-operative intervention, went on to achieve a successful total thyroidectomy.

History

A 35-year-old woman was referred for tertiary advice with a six year history of difficult to manage severe Graves' thyrotoxicosis. She had been previously treated with carbimazole and propylthiouracil, but had never achieved normal thyroid function tests. She had had significant symptoms throughout, with insomnia, anxiety, weight loss of 22kg in total, and bilateral moderate active and chronic thyroid eye disease. She had achieved a successful pregnancy three years prior.

Concordance was not thought to be an issue as the patient showed empty blister packs - and accidentally took both carbimazole and propylthiouracil for a time. Thyroid function tests had never normalised.

Radioactive iodine had previously been decided against due to her young children at home and significant thyroid eye disease. Preparation for thyroidectomy with Lugol's iodine had been attempted before but the operation was cancelled as she remained thyrotoxic.

On examination, she was floridly thyrotoxic with fine tremor on outstretched hands and sinus tachycardia at 140bpm. She had a large diffuse goitre with bruit. Eye examination demonstrated bilateral proptosis, lid lag, and limited lateral eye movement with diplopia on left lateral gaze.

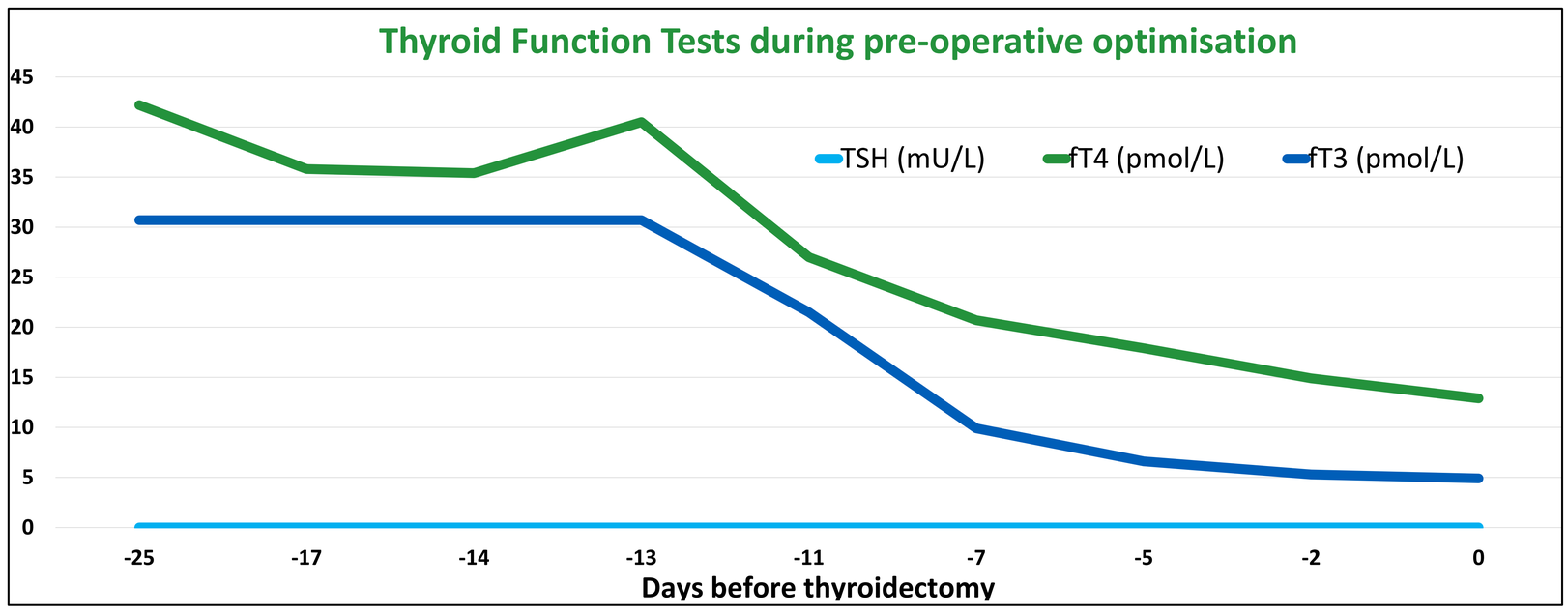
A multi-disciplinary decision was made with the patient to proceed with admission for pre-operative optimisation, which achieved biochemical control. Urgent thyroidectomy was then performed without complication. The patient was discharged home a few days later on levothyroxine 125mcg OD and has remained well since.

Results at referral to NNUH

Parameter	Result	Normal range
TSH	<0.01 mU/L	0.35 – 4.94
Free T4	43.6 pmol/L	9.0 – 19.1
Free T3	>30.7 pmol/L	2.4 – 6.0
Thyroid stimulating antibody (TSI)	6.18 iu/L	<0.56

MRI Orbits

Bilateral symmetrical proptosis. Fatty infiltration of the inferior and superior rectus muscles bilaterally, in keeping with a degree of chronic thyroid eye disease. Marginal increase in signal intensity of the medial rectus muscles bilaterally, suggestive of subtle disease activity.



Medication for pre-operative optimisation of thyrotoxicosis

Name	Dose	Mechanism of action	Notes
Carbimazole	20mg TDS & 10mg nocte	Inhibits TPO-mediated iodination of thyroglobulin Decreases type 1 deiodinase activity, reducing conversion of T4 to T3 Reduces TSI titre with possible immunosuppressive effects	Can try total daily (divided) dose of 70-80mg Often limited by arthropathy once >60mg daily
Prednisolone	30mg OD	Prevents peripheral conversion of T4 to T3	
Lithium	250mg TDS	Inhibits iodine uptake into follicular cells Inhibits thyroid hormone secretion	
Propanolol	80mg TDS	Improves peripheral effects of thyrotoxicosis Inhibits T4 to T3 conversion (mild effect)	
Cholesytramine	5mg TDS	Blocks enterohepatic circulation of thyroid hormones so increases clearance	
Lugol's iodine	5 drops TDS	Inhibits thyroid hormone synthesis and release Blocks peripheral conversion of T4 to T3 Decreases thyroid blood flow & vascularity -> reduces intra-op blood loss	Start 10-14 days before surgery Administer orally with milk or orange juice Can get escape from effects after ~3 weeks
Iopanoic acid (considered but not used for this patient)	*0.5g BD or TDS*	*Inhibits conversion of T4 to T3*	*Will normalise fT3 within 48-72h* *No pharmaceutical formulations produced worldwide so only unlicensed laboratory grade powder available* *Needs very careful counselling with patient*

Discussion

- True thioamide-resistant hyperthyroidism is rare but confers significant risk to the patient, both during the period of hyperthyroidism and at the time of thyroidectomy. Multiple medications in combination can be offered to gain biochemical control to reduce peri-operative risks[2].
- The mechanism of thioamide resistance is not clear with suggested mechanisms including malabsorption, rapid drug metabolism, anti-drug antibodies and impaired intrathyroidal drug accumulation or action[3].
- In this case, TSI was only mildly elevated despite significant disease activity, including systemic symptoms and thyroid eye disease. The TSI assay can a poor predictor of the bioactivity of the stimulating antibody and disease severity[4].
- Treatment of active thyrotoxicosis by thyroidectomy requires a multi-disciplinary approach to ensure appropriate pre-operative optimisation of the patient. This is especially challenging given the current pressures faced by the NHS. The timing of surgery for this patient had to be carefully planned especially once a junior doctors' strike was called for that day.

References

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Thyroid
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