

Carbimazole Resistant Graves Disease- Its Not Always Poor Compliance

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Introduction:

- Graves Disease is a common cause of thyrotoxicosis particularly in female.
- The response to treatment with thionamides is usually excellent.
- The commonest cause of treatment failure is poor drug adherence.
- We present a patient with Graves Disease who did not respond to Carbimazole despite a good compliance suggesting resistance to the drug.

Case Presentation:

- A 54 years old female referred with symptoms of clinical and biochemical thyrotoxicosis which were not improving on Carbimazole 40 mg daily inspite of good compliance for 3 months.
- TRAb was strongly positive confirming diagnosis of Graves Disease.
- She was otherwise fit and well and was not taking any other medications. There was no evidence of malabsorption. She had negative duodenal biopsies for Coeliac disease in the past.
- The dose of Carbimazole was increased to 60 mg daily with addition of beta-blockers.
- She remained symptomatic with no improvement in her TFTs as shown in Table 1.
- She even develop a mild leucopenia with WBC 3.1 and Neutrophil count 1.5 most likely related to Carbimazole which further strengthened the evidence of her drug compliance.
- There was a risk of her going into thyroid storm and therefore she underwent uneventful total thyroidectomy after she was made euthyroid with Lugol's Iodine for 10 days.
- The histology confirmed changes consistent with Graves Disease.

Discussion:

- Thionamides resistant Graves disease is rare but cases have been reported in literature.
- The exact cause of drug resistance is unknown but possible mechanisms include drug malabsorption, anti-drug antibodies, rapid drug metabolism, impairment of intra-thyroidal drug accumulation or action and predominant T3 toxicosis.
- Resistance to drugs can be tested by performing perchlorate discharge test 4 hours after administration of carbimazole. A negative test indicate inadequate blockade of iodine organification and thus possible Carbimazole resistance.
- Urinary Iodine excretion can be measured to rule out exogenous iodine exposure.
- The following can be used either alone or in combination to achieve euthyroidism prior to definitive therapy.
 - Iopanoic Acid** – Oral radio-contrast material which inhibit conversion of T4 to T3.
 - Glucocorticoids** - Inhibit the conversion of T4 to T3 and in Graves disease decreases the secretion of thyroid Hormones.
 - Lithium** - Increases intrathyroidal iodine content, inhibits the coupling of iodotyrosine residues to form iodothyronines, and inhibits the release of T4 and T3.
 - Cholestyramine** – Interfere with enterohepatic circulation and recycling of thyroid hormone.
- In our patient we used Lugol's iodine which block the release of T3 and T4 from thyroid gland as well as its synthesis by blocking iodine organification (Wolff- Chaikoff effect).

Conclusion:

- This case highlights the importance of recognising the rare possibility of thionamides resistant Graves disease and physicians needs to be aware of this.
- Lugols iodine can be used safely to achieve euthyroidism prior to definitive therapy.

Date	T3	T4	TSH	CMZ dose
Aug 2014		49	<0.01	20mg
Oct 2014	19.9	41	<0.01	20mg
Nov 2014	24.7	54.5	<0.01	40mg
Nov 2014	23.1	55.0	<0.01	40mg
1 st Dec 2014	14.8	38.5	0.01	60mg
16 th Dec 2014	19.2	50.1	0.01	60mg
29 th Dec 2014	5.2	12.1	0.01	Lugol Iodine
Jan 2015	Surgery			

Table 1:TFTs from Diagnosis to surgery.