

Case Report

Cholestatic Jaundice Induced by Carbimazole in Grave's Disease

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Kuwait Medical Journal 2007, 39 (3): 281-283

ABSTRACT

Antithyroid medications are one of the treatment options for Grave's disease. Carbimazole (the pro drug for methimazole) is widely used as the drug of choice, except in pregnancy where propylthiouracil is preferred by many. It is generally well-tolerated. Its side-effects include allergy, upper gastrointestinal upset, the rare

occurrence of a granulocytosis and others. Hepatitis is another rare but serious side-effect. We report a previously healthy 65-year-old female patient with Grave's disease who developed cholestatic jaundice after carbimazole therapy. She made a full recovery after the drug was discontinued.

KEYWORDS: carbimazole, cholestatic jaundice, Grave's, thyrotoxicosis

INTRODUCTION

Grave's disease is the most common cause of hyperthyroidism. It accounts for approximately 80-90% of cases. Treatment options include radioiodine, antithyroid medications, and surgery. The former is now considered the treatment of choice by most endocrinologists in the United States. Antithyroid medications are still widely used in younger patients with mild disease, pregnant or lactating patients. It is usually continued for about 12-24 months. The chance of remission is around 40-50%. It has several side effects; the majority is mild and reversible such as allergic reaction, and upper GI disturbances. Other rare side effects include agranulocytosis and vasculitis like reaction particularly with propylthiouracil. Hepatic toxicity is a rare but serious side effect with both methimazole (and its pro drug, carbimazole) and propylthiouracil (PTU)^[1-3]. Fatal cases have been documented with both drugs^[4]. The hepatohistopathological findings with PTU are toxic hepatitis with necrosis^[5], whereas they resemble cholestatic hepatitis with methimazole (and carbimazole)^[6]. We present a case of carbimazole induced cholestatic hepatitis in a patient with Grave's disease. We describe the clinical and biochemical findings in this patient and review the relevant literature.

CASE REPORT

A 65-year-old female patient was admitted to the medical department with long standing

bilateral eye proptosis. In addition she gave history of palpitation, tremor and weight loss of seven kilograms over three months. She also admitted to having frequent loose motions and heat intolerance. She was known to have chronic stable angina, and was taking atenolol and aspirin. There was questionable history of iodine allergy. She had no history of liver disease. She was not a known diabetic or hypertensive. She was neither smoker nor an alcohol consumer.

On physical examination, she had fine tremors of both hands. Her weight was 62 kg. Her pulse rate was 120 beats/minute, regular and her blood pressure was 150/70 mmHg. Eye examination showed bilateral exophthalmos, with conjunctivitis and periorbital edema. There was diplopia on looking to both sides indicating ophthalmoplegia. Thyroid was soft and mildly diffusely enlarged. The liver and spleen were not palpable. Other systemic examination was unremarkable.

Her initial FT4 was 59.1 pmol/l (normal range = 12 - 22) and TSH < 0.005 uIU/ml (normal range = 0.2 - 4.2). Other laboratory results are shown in Table 1.

She was diagnosed as Grave's disease and started on propranolol with prednisolone for Grave's ophthalmopathy. Carbimazole was also initiated at a dose of 30 mg per day in three divided doses. She neither did thyroid scan nor took I 131 because of concern with iodine allergy and exacerbation of the eye manifestations respectively. Three weeks later, FT4 was normal at 16.9 pmol/l

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Table 1: Showing date wise laboratory results (normal range)

Lab. test		Date-wise results					
		03/01/05	31/01/05	08/02/05	09/03/05	30/03/05	25/04/05
Albumin g/l	(34-50)	24.9	34	34	38	37	40
Alk.p u/l	(50-136)	83	206	224	106	83	61
T.Bilirubin mmol/l	(3-20)	2.3	135	413	48	16	18
D.Bilirubin mmol/l	(0-5)			230	20		
Gamma GT u/l	(5-85)	29		399	79	145	
ALT u/l	(30-65)	32	165	164	159	117	41
AST u/l	(10-42)		67	69	92	40	31

and TSH < 0.03 uIU/ml. She complained of blue discoloration of the sclera, associated with nausea and vomiting. Results of the liver function tests were as shown in Table 1. The laboratory findings were consistent with cholestatic jaundice. She had marked elevation of bilirubin and alkaline phosphatase. Aspartate and alanine amino transferase were less markedly elevated. Prothrombin time was within normal limits. Test for antinuclear antibodies was negative. Abdominal ultrasound showed normal liver size and texture. Intrahepatic biliary ducts were normal and no obstruction was detected. Hepatitis serology was negative for hepatitis A, B and C. Patient refused to do liver biopsy. Carbimazole was stopped and she received radio active iodine under the cover of prednisolone to minimize risk of eye signs deterioration. Her liver functions normalized within two months. She developed post-radioiodine hypothyroidism and was started on thyroxin therapy. She was seen again after four and six months and her liver functions were still normal.

DISCUSSION

Hyperthyroidism *per se* can affect liver function tests. It causes mild elevation in liver enzymes that normalizes with treatment^[7]. In addition, cholestatic jaundice can happen solely due to severe hyperthyroidism^[8]. All antithyroid drugs (methimazole, carbimazole and propylthiouracil) can affect the liver on rare occasions. A cohort study on 50 patients by Liaw found that subclinical liver injury is common during PTU treatment^[5]. Thirty percent patients had transient, asymptomatic rise in aminotransferase level with no elevation in bilirubin after two months of therapy. Despite continuation of PTU, liver enzymes normalized in most patients within five months. He suggested cautious continuation of PTU in the absence of symptoms and hyperbilirubinemia. Despite this, PTU induced liver disease can be severe and fatal^[9,10]. Carbimazole and methimazole, on the other hand have been typically associated with cholestatic jaundice (mainly hyperbilirubinemia)

without evidence of hepatic necrosis on liver biopsy^[2,6,11]. Most patients recover on drug discontinuation. Nevertheless, there are occasional reports of severe and fatal cases with methimazole induced liver disease^[12]. Review of the literature revealed around 22 cases of cholestatic jaundice due to both methimazole and carbimazole^[11]. The mean time of onset after starting treatment is 36 days^[1]. The majority of patients are female, reflecting the predominance of thyrotoxicosis in female sex. The proposed mechanism of carbimazole-induced cholestasis is not fully understood but is thought to be an allergic reaction^[13]. Cross reaction between PTU and carbimazole is still a concern when a switch from one to another is considered, in spite of some reports to the contrary^[6]. The hepatotoxic effect is dose-independent^[14].

Our patient developed significant hyperbilirubinemia within three weeks of starting carbimazole, despite normalization of thyroxin level. It continued to rise for one more week after stopping the offending drug, until complete normalization over two months. Aminotransferase level was mildly elevated, reaching 2-3 times the normal.

Although she received steroid from the start for reasons discussed above, it did not affect the course of the liver disease. In fact, previous reports of using steroid in methimazole induced hepatitis did not show any benefit^[15]. This coincides with the fact that most patients recover once the drug is stopped. Our patient showed a good response to drug withdrawal. She received radioiodine with no significant complications of the eyes.

CONCLUSION

Hepatic toxicity is a rare but serious side effect of antithyroid medications. Doctors dealing with thyroid patients should be aware of such complication. Routine liver function test during therapy is not cost effective, but should be done when this complication is suspected. The drug should be withdrawn immediately and alternative therapy for hyperthyroidism such as radioiodine must be considered.

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