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Severe Neutropenia and Hepatotoxicity After Carbimazole Drug Therapy for Hyperthyroidism in a Pediatric Patient: A Case Report

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Patient: Female, 17-year-old
Final Diagnosis: Severe neutropenia and hepatotoxicity
Symptoms: Fever • body aches • headache • nausea • abdominal pain
Clinical Procedure: —
Specialty: Endocrinology and Metabolic • Pediatrics and Neonatology
Objective: Unusual clinical course

Background: Hyperthyroidism is an overproduction of thyroid hormones. Carbimazole is an anti-thyroid medication used to treat hyperthyroidism in adults and children. It is a thionamide associated with rare adverse effects such as neutropenia, leukopenia, agranulocytosis, and hepatotoxicity. Severe neutropenia is a life-threatening event characterized by a sharp drop in absolute neutrophil count. Severe neutropenia can be treated by discontinuation of the precipitating medication. Administration of granulocyte colony-stimulating factor provides longer protection against neutropenia. Elevated liver enzymes indicate hepatotoxicity, which usually normalize after discontinuation of the offending medication.

Case Report: A 17-year-old girl was treated with carbimazole since the age of 15 for hyperthyroidism secondary to Graves' disease. She initially received 10 mg of carbimazole orally twice daily. After 3 months, the patient's thyroid function reflected residual hyperthyroidism and was then up-titrated to 15 mg orally in the morning and 10 mg orally in the evening. She presented to the emergency department reporting fever, body aches, headache, nausea, and abdominal pain for 3 days. She was diagnosed with severe neutropenia and hepatotoxicity induced by carbimazole after 18 months of dose modification.

Conclusions: In hyperthyroidism, it is important to maintain patients in a euthyroid state for a long period to minimize the autoimmunity and hyperthyroid relapse, which often requires long-term use of carbimazole. However, severe neutropenia and hepatotoxicity are rare and serious adverse effects of carbimazole. Clinicians should be aware of the importance to discontinuation of carbimazole, administration of granulocyte colony-stimulating factors, and supportive treatment to reverse the consequences.

Keywords: Carbimazole • Drug-Related Side Effects and Adverse Reactions • Hyperthyroidism • Neutropenia • Chemical and Drug Induced Liver Injury
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Background

Hyperthyroidism is the overproduction of thyroid hormones by the thyroid gland [1]. It occurs about 8 times more often in women than in men. Pharmacologic treatment options include thionamides. This class includes 3 well-known medications: carbimazole, methimazole, and propylthiouracil. Carbimazole is more commonly used in the United Kingdom and Commonwealth countries compared to methimazole [2]. Carbimazole is a prodrug that converts to methimazole [3]. It inhibits formation of iodide and causes a decrease in the production of thyroid hormones thyroxine (T4) and triiodothyronine (T3). Carbimazole is rarely associated with adverse effects, but is life-threatening in some cases [4]. Patients should be made aware of possible adverse effects at the time of drug initiation, and close monitoring in subsequent visits is required.

Hematological toxicities, including aplastic anemia, hemolytic anemia, thrombocytopenia, and/or neutropenia have been associated with thionamide mediations [5-7]. Neutropenia is defined as absolute neutrophil count (ANC) less than 1.5×10^9/L and severe neutropenia is defined as ANC less than 0.5×10^9/L. Neutropenia is a known risk factor for susceptibility to bacterial infection. Thionamide medications may induce antibodies to differentiated granulocytes, which may be antineutrophil cytoplasmic antibodies (ANCA) that cause apoptosis of specific granules in neutrophils and lead to a decrease in neutrophil count [8].

Treatment of neutropenia can be accomplished by discontinuing the causative medication and using hematopoietic growth factors such as granulocyte-macrophage colony-stimulating factor (sargramostim) or granulocyte colony-stimulating factor (G-CSF) (filgrastim, pegfilgrastim) [9].

Carbimazole has rarely been associated with hepatotoxicity [1]. There are few reports of carbimazole-induced liver injury in the medical literature; most cases involve adults [10]. Although most of these cases presented with hepatotoxicity in the first 3 months of treatment, Burgin et al reported a case with late-onset hepatotoxicity [11]. Cases of anti-thyroid medications-induced hepatotoxicity were reversed by discontinuation of the anti-thyroid medication [12].

Here, we report the case of a 17-year-old girl treated with carbimazole for Graves' disease, severe neutropenia, and hepatotoxicity due to carbimazole toxicity.

Case Report

This 17-year-old girl had a past medical history of hyperthyroidism due to Graves' disease, at the age of 15 years. She started treatment with carbimazole 10 mg orally twice daily and was up-titrated to 15 mg in the morning and 10 mg in the evening based on her repeated laboratory tests that reflected residual hyperthyroidism 3 months after initiation of treatment. Her symptoms and thyroid function improved accordingly. Her physician planned to start radioactive iodine therapy when she reaches 18 years of age.

The patient presented to the Emergency Department (ED) with fever, body aches, headache, nausea, and abdominal pain for 3 days. She was diagnosed with severe febrile neutropenia; the diagnosis was based on a temperature of 39°C and ANC of 0.34×10^9/L ells/µL. Laboratory analysis of the thyroid gland revealed thyroid-stimulating hormone (TSH) value of 0.124 uIU/mL (normal range 0.480-4.170 uIU/mL) and free thyroxine (T4) 10.2 pmol/L (normal range 10.70-18.40 pmol/L). Biochemical analysis showed elevated alanine aminotransferase (ALT) 195 U/L, aspartate aminotransferase (AST) 299 U/L, direct bilirubin 0.7 umol/l, and total bilirubin 4.5 (**Table 1**). C-reactive protein test was not performed and urine culture and blood culture were sent to the laboratory for further analysis.

Vital signs on admission showed a respiratory rate of 19 breaths/minute, heart rate of 100 beats/minute, oxygen saturation of 89% on room air, blood pressure of 104/71 mmHg, and weight of 61 kg. She was hospitalized and treated with intravenous fluids and ceftriaxone and received the same dose of carbimazole.

On the first day in the hospital, her temperature was stable, but her neutrophil count was 0.24×10^9/L, which is below the reference range. Accordingly, ceftriaxone was discontinued after infectious disease consultation, and she received 2 grams of cefepime intravenously every 8 hours as empiric antibiotic treatment for febrile neutropenia. Later that same day, her carbimazole was discontinued because carbimazole-induced agranulocytosis was suspected.

Granulocyte colony-stimulating factor (G-CSF) was initiated. A single dose of pegfilgrastim 6 mg subcutaneously was administered on the second day of hospitalization. It was effective in reversing the neutrophil count and showed a return to the normal range of neutrophil count within 48 hours, with a transient leukocytosis.

During her hospitalization, liver function tests showed a marked increase in serum aminotransferase levels. The levels gradually improved after discontinuation of carbimazole treatment: ALT 134-81 U/L, AST 194-91 U/L (**Table 1**). Tests for hepatitis B and hepatitis C were negative. Urine culture and blood culture were negative for bacterial growth.

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Table 1. Changes in laboratory data during admission and after discharge.

Variable	Normal values	On admission	Day 2	Day 3	Day 4	Day 5	Day 6	Day 55
Alanine aminotransferase	0-35 U/L	195 U/L	134 U/L	113 U/L	99 U/L	90 U/L	81 U/L	29 U/L
Aspartate aminotransferase	0-35 U/L	299 U/L	194 U/L	151 U/L	125 U/L	108 U/L	91 U/L	35 U/L
Alkaline phosphatase	47-119 U/L	89 U/L	84 U/L	76 U/L	79 U/L	90 U/L	124 U/L	93 U/L
Direct bilirubin	0-3.4 µmol/L	0.7 µmol/L	0.7 µmol/L	1.4 µmol/L	0.9 µmol/L	1 µmol/L	0.8 µmol/L	1.3 µmol/L
Total bilirubin	5-21 µmol/L	4.5 µmol/L	5.9 µmol/L	5.8 µmol/L	6.8 µmol/L	7 µmol/L	5.6 µmol/L	8 µmol/L
White blood cells	4.00-12.00 $\times 10^9$/L	1.0$\times 10^9$/L	0.90$\times 10^9$/L	1.30$\times 10^9$/L	7.10$\times 10^9$/L	17.7$\times 10^9$/L	23.50 $\times 10^9$/L	2.7$\times 10^9$/L
Neutrophils	1.40-7.70 $\times 10^9$/L	0.37$\times 10^9$/L	0.24$\times 10^9$/L	0.16$\times 10^9$/L	5.11$\times 10^9$/L	13.61$\times 10^9$/L	18.54$\times 10^9$/L	0.57
Neutrophils%	40-60%	37%	27%	12%	5.8%	76.9%	78.9%	21%
Lymphocytes	1.00-5.50 0.37$\times 10^9$/L	0.58$\times 10^9$/L	0.60$\times 10^9$/L	1.07$\times 10^9$/L	1.53$\times 10^9$/L	3.04$\times 10^9$/L	3.5$\times 10^9$/L	2.03 10^9/L
Lymphocytes%	20-40%	58%	67%	82%	21.6%	17.2%	14.9%	75%
Monocytes	0.10-0.80 $\times 10^9$/L	0.03$\times 10^9$/L	0.03$\times 10^9$/L	0.05$\times 10^9$/L	0.41$\times 10^9$/L	0.92$\times 10^9$/L	1.2$\times 10^9$/L	0.11 10^9/L
Monocytes%	2-8%	3%	3%	4%	5.8%	5.2%	5.1%	4%
Thyroid-stimulating hormone	0.480-4.170 uIU/ml	0.124 buIU/ml	NA	0.71 uIU/ml	NA	NA	0.05 uIU/ml	0.05 uIU/ml
Free T4	10.70-18.40 pmol/L	10.2 pmol/L	NA	11.3 pmol/L	NA	NA	12.70 pmol/L	12.7 pmol/L

Her physical condition progressively improved after 6 days of hospitalization. She was discharged and was referred to a specialized medical center to receive radioactive iodine therapy. Follow-up at 7 weeks, while she was off carbimazole treatment, showed improved laboratory test results (**Table 1**).

Discussion

We report the case of a girl with severe neutropenia and hepatotoxicity who was diagnosed with hyperthyroidism and treated with carbimazole. In general, an initial daily dose of 15-30 mg of carbimazole orally is recommended to reduce the elevation of thyroid hormones [4]. Carbimazole-induced neutropenia or agranulocytosis is a more serious adverse effect than hepatotoxicity [1].

Severe neutropenia is a life-threatening adverse event associated with carbimazole use [13] and can be idiosyncratic [14]. After discontinuation of the harmful medication, the leukocyte count usually normalizes within 2 weeks, but in some cases, it can take up to 56 days [15,16]. Neutropenia usually occurs during the first 3 months of carbimazole treatment, but late onset has been reported [17]. Our case presented as late onset of severe neutropenia.

Severe neutropenia induced by anti-thyroid medications can be successfully treated with G-CSF, which improves normalization of peripheral granulocytes and reduces life-threatening complications related to immunocompromised status, such as severe bacterial and fungal infections [15,18]. In our case, we had used 1 dose of the pegylated filgrastim (pegfilgrastim). The decision to administer pegfilgrastim was made due to its longer protection against neutropenia and the availability of the medication in our pharmacy at that time. to the best of our knowledge, this is the first case of carbimazole-induced neutropenia treated with pegfilgrastim. The patient developed transient leukocytosis, which is an adverse reaction to pegfilgrastim [19].

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Hepatotoxicity is a rare but serious reaction to carbimazole, occurring in about 0.1-0.2% of treated cases [20]. Previous reports have described cases of carbimazole-induced hepatotoxicity as cholestatic jaundice [21]. However, our patient presented as a case of liver injury without biochemical suggestions of cholestatic jaundice. She had a significant elevation in ALT and AST to 134 and 194 U/L, respectively, whereas direct and total bilirubin were within normal ranges, at 0.7 and 4.5 umol/l, respectively (**Table 1**). The mechanism that seems to cause drug-induced hepatotoxicity can be divided into 3 main pathways of initial injury: direct cell stress, direct mitochondrial damage, and specific immune responses [22]. In the few reported cases of hepatotoxicity caused by thyroid medications, the condition was resolved by discontinuation of the damaging agent [23].

Our case illustrates many of the difficulties and controversies in the treatment of pediatric thyrotoxicosis. The patient became neutropenic and developed acute hepatotoxicity 18 months after starting carbimazole (3 months after increasing the dose). She was started on carbimazole 10 mg orally twice daily and was up-titrated to 15 mg in the morning and 10 mg in the evening 3 months before admission. The increase in dose may have triggered the adverse events. However, her TSH level was low at admission, which rules out carbimazole overdosing.

The limited therapeutic options available at that time were surgery or administration of radioiodine. Beta-blockade and administration of iodine-containing preparations can reduce the likelihood of thyroid crisis at the time of thyroidectomy, but it was felt that radioiodine offered a better balance of safety and efficacy [1].

Conclusions

Our 17-year-old patient had rare and serious delayed severe neutropenia and hepatotoxicity induced by carbimazole administration. It is essential to maintain such patients in a euthyroid state and to consider the rare adverse effects of carbimazole. In such patients who experience severe neutropenia or hepatotoxicity, physicians should consider an alternative method of treatment rather than switching to another anti-thyroid medication to avoid the recurrence of those serious adverse effects. Overall, discontinuation of carbimazole, administration of 1 dose of pegfilgrastim 6 mg subcutaneously, and supportive intravenous treatment achieved a favorable outcome in our case and reversed the severe neutropenia and hepatotoxicity.

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