Antithyroid Drug-induced Agranulocytosis

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Antithyroid drugs are widely used to treat hyperthyroidism, especially Graves' disease, but they tend to cause agranulocytosis, which increases the mortality rate. Granulocyte colony-stimulating factor decreases the duration of recovery from agranulocytosis. We retrospectively studied cases of antithyroid drug-induced agranulocytosis over the past 10 years in a northern Taiwan medical center. A clinical evaluation was conducted, including a review of complete blood cell counts and differential counts. Four cases were included in this analysis. Agranulocytosis persisted in 2 cases despite a change in therapy from propylthiouracil to methimazole. Fever, sore throat, and diarrhea were common symptoms of agranulocytosis. Initial white blood cell counts ranged from 450 to 1,710/μL. Only 1 case had a positive result from a throat swab culture (*Staphylococcus aureus*). Three of 4 cases received granulocyte colony-stimulating factor therapy, and the recovery time ranged from 3 to 13 days. All of the patients recovered from agranulocytosis. We concluded that: (1) conducting a routine complete blood cell count is beneficial in alerting caregivers to the possibility of agranulocytosis; (2) educating patients about the common symptoms of agranulocytosis may contribute to an early diagnosis; (3) providing granulocyte colony-stimulating factor therapy to patients results in good prognosis; and (4) monitoring for cross-reactions between drugs should be performed to prevent further episodes of agranulocytosis. [*J Chin Med Assoc* 2009;72(8):438–441]

Key Words: agranulocytosis, antithyroid drugs, methimazole, propylthiouracil, thioamide

Introduction

Antithyroid drugs are commonly used to control hyperthyroidism, especially when patients refuse other therapies such as radioiodine and surgery. Despite their acceptability, especially in Eastern countries, antithyroid drugs are associated with many complications. Of the known complications, antithyroid drug-induced agranulocytosis, although rare, is the most severe and life-threatening. We retrospectively studied cases of antithyroid drug-induced agranulocytosis over the past 10 years (1998–2008) in a Taiwanese medical center. We searched for patients who had used antithyroid drugs for the treatment of hyperthyroidism, had no other disease, had taken no other drugs that could have induced agranulocytosis, and had a neutrophil count < 500/μL. A clinical evaluation was conducted, including a review of complete blood cell counts and differential counts.

Case Reports

Case 1

Patient 1 was a 77-year-old woman with a history of hyperthyroidism for 20 years. She had received propylthiouracil therapy (50 mg thrice daily) for 1 year, which was switched to methimazole (5 mg thrice daily) 18 days before hospitalization. The patient had had a fever, headache and diarrhea since 10 days before hospitalization. White blood cell count was 940/μL, and the absolute neutrophil count was 60/μL. Granulocyte colony-stimulating factor and antibiotics were provided. White blood cell count recovered to 7,870/μL, and the absolute neutrophil count recovered to 3,856/μL on the 13th day. The symptoms also resolved.

Case 2

Patient 2 was a 53-year-old woman with Graves' disease with hyperthyroidism diagnosed 2 months before

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hospitalization. The patient had started treatment with methimazole (10 mg thrice daily) 46 days before hospitalization. Sore throat, fever, diarrhea, and epigastric pain developed 11 days before hospitalization. White blood cell count was 450/μL, and the absolute neutrophil count was 20/μL. Granulocyte colony-stimulating factor was provided with antibiotics. Blood and stool cultures were performed, which yielded negative results. White blood cell count recovered to 5,810/μL on the 7th day after the treatment began, and the symptoms also improved. A subsequent thyroid scan showed that the uptake of I-131 had increased. I-131 therapy, 5 mCi, was then provided.

Case 3

Patient 3 was a 43-year-old woman with a history of Graves' disease and hyperthyroidism for 2 years. The patient had initially been treated with antithyroid drugs for 3–4 months, but had stopped treatment because of mild leukopenia. About 1 year before this hospitalization, hand tremors were noted. The patient took propylthiouracil (50 mg twice daily) for 7 days. One month before hospitalization, the same symptoms were noted. Methimazole treatment (10 mg thrice daily) began. Fever and sore throat were noted 2 days before hospitalization. White blood cell count was 1,200/μL, and the absolute neutrophil count was 252/μL. A blood culture was negative. Treatment with granulocyte colony-stimulating factor (75 μg/day) and antibiotics began. The dosage was increased to 300 μg/day on the 4th day due to poor response. White blood cell count recovered to 4,090/μL on the 10th day. The patient's fever subsided when the agranulocytosis resolved. One month later, I-131 therapy, 6 mCi, was provided.

Case 4

Patient 4 was a 62-year-old woman with hyperthyroidism who had received propylthiouracil (100 mg thrice daily) since 24 days before this hospitalization. Fever and sore throat were noted 2 days before hospitalization, and pus formation was noted when she visited our ward. White blood cell count was 1,710/μL, and the absolute neutrophil count was 169/μL. A throat swab culture yielded *Staphylococcus aureus.* Blood and urine cultures were negative. Propylthiouracil was discontinued, and antibiotic therapy was initiated. White blood cell count recovered to 3,100/μL, and the absolute neutrophil count recovered to 1,758/μL on the 3rd day.

Discussion

Four cases were included in this analysis (Table 1). Two cases had symptoms of agranulocytosis even after therapy with propylthiouracil was switched to methimazole. Fever and sore throat were the most common

Table 1. Clinical characteristics of antithyroid drug-induced agranulocytosis

	Patient			
	1	2	3	4
Sex	Female	Female	Female	Female
Age (yr)	77	53	43	62
Duration of hyperthyroidism	20 yr	2 mo	2 yr	2 mo
Drug(s) used	Propylthiouracil/ methimazole	Methimazole	Propylthiouracil/ methimazole	Propylthiouracil
Duration of drug use	Propylthiouracil (1 yr)/ methimazole (18 d)	Methimazole (46 d)	Propylthiouracil (7 d)/ methimazole (28 d)	Propylthiouracil (24 d)
Initial WBC count (cells/μL)	940	450	1,200	1,710
Initial ANC (cells/μL)	60	0	252	169
Symptoms	Fever, headache, diarrhea	Fever, sore throat, diarrhea	Fever, sore throat	Fever, sore throat
GCSF duration (d)	11	7	11	Not used
GCSF dosage (μg)	75 for 5 d, 300 for 6 d	75 for 7 d	75 for 4 d, 300 for 7 d	Not used
Recovery time (d)	13	7	10	3

WBC = white blood cell; ANC = absolute neutrophil count; GCSF = granulocyte colony-stimulating factor.

symptoms, followed by diarrhea. The initial white blood cell counts ranged from 450/μL to 1,710/μL. Only 1 case had a positive result from throat swab culture (*S. aureus*). Three of 4 cases received granulocyte colony-stimulating factor therapy. The time to recovery ranged from 3 to 13 days. Mean recovery time in patients with granulocyte colony-stimulating factor therapy (Cases 1–3) was 10 days. Case 1, who was older than 65 years of age, took a longer time to recover than the other 3 patients, who were younger than 65 years of age. All 4 patients recovered from agranulocytosis.

Antithyroid drugs, especially thioamides—including propylthiouracil, methimazole and carbimazole—have adverse hematological effects, ranging from mild leukopenia to agranulocytosis and aplastic anemia. Mild leukopenia, defined as a total white blood cell count $<4{,}000/\mu L$, is noted in about 12% of adults and 25% of children taking propylthiouracil.[1] However, this phenomenon is usually transient and does not usually increase the risk of infection and herald the onset of agranulocytosis. Thus, it is not necessary to stop treatment with antithyroid drugs if mild leukopenia develops.[2] Agranulocytosis, defined as a marked decrease in the number of granulocytes, frequently $<500/\mu L$, is a rare complication. The incidence of antithyroid drug-induced agranulocytosis is 0.55% with propylthiouracil use and 0.31% with methimazole use.[3] The incidence of aplastic anemia caused by thioamides is very rare.[4] Only about 34 cases have been reported in the past 50 years.[5] However, of all the adverse reactions to antithyroid drugs, agranulocytosis and neutropenia account for 49% of mortality.[6]

Antithyroid drug-induced agranulocytosis occurs most frequently in the first 3 months of treatment, but it can occur after long-term treatment.[7,8] High doses of antithyroid drugs can increase the risk of agranulocytosis, but this notion is debatable.[8–10] Routine monitoring of white blood cell counts is recommended in patients taking antithyroid drugs; however, this practice is not foolproof because severe complications can occur suddenly and mild leukopenia does not necessarily herald the onset of agranculocytosis.[1,3] Educating patients about the prodromes of antithyroid drug-induced agranulocytosis (e.g. fever, sore throat, and cervical lymphadenopathy) may be more beneficial.[4]

Antithyroid drug-induced agranulocytosis is mediated by a variety of mechanisms, including direct toxic effects and immunological reactions. The direct toxic effects affect both mature circulating neutrophils and stem cells. The immunological reactions include the following: immunoglobulin E-mediated hypersensitivity reaction, drug-induced immunoglobulin G and M responses, and neutrophil-drug complex.[11,12] Fever and sore throat are common symptoms of antithyroid drug-induced agranulocytosis. Patients with an absolute neutrophil count $<100/\mu L$ tend to have a greater risk of infectious and fatal complications than do patients with a neutrophil count $>100/\mu L$. The mortality rate is greater in patients aged ≥ 65 years than in those aged <65 years.[6]

Bone marrow examinations have revealed signs of decreased generation of neutrophil granulocytes, including the observation of impaired generation of granulocyte precursor cells.[13] In patients with antithyroid drug-associated aplastic anemia, bone marrow examinations yielded hypocellularity.[12] Patients with granulocyte-to-erythrocyte count ratio (G:E) <0.5 in bone marrow took a significantly longer time to recover from agranulocytosis after granulocyte colony-stimulating factor therapy (mean, 9.8 days) than patients with G:E ≥ 0.5 (mean, 2.2 days; $p<0.001$).[14]

Treatment with granulocyte colony-stimulating factor decreases the time of recovery from agranulocytosis, the rate of complications from infection, and the mortality rate, even in patients with asymptomatic agranulocytosis.[13] Mean recovery time in patients with granulocyte colony-stimulating factor therapy is 6.8 days.[14] After recovery from agranulocytosis, doctors should be cautious about prescribing antithyroid drugs again, even another type of thioamide, due to common cross-reactions among thioamides.[1] Radioiodine therapy or surgery may be better choices than the use of another type of antithyroid drug. Our cases were similar to previous ones in that there was good prognosis after granulocyte colony-stimulating factor and empirical antibiotic therapy, and the most common symptoms were fever and sore throat. However, the recovery time in our cases was slightly longer than in previous cases (10 *vs.* 6.8 days).

In conclusion: (1) conducting a routine complete blood cell count is beneficial in alerting caregivers to the possibility of agranulocytosis; (2) educating patients about the common symptoms of agranulocytosis may contribute to an early diagnosis; (3) providing granulocyte colony-stimulating factor therapy to patients results in a good prognosis; and (4) monitoring for cross-reactions between drugs should be performed to prevent further episodes of agranulocytosis.

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