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# Carbimazole-Induced Agranulocytosis - A Report of 2 Recent Cases

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## ABSTRACT

**Carbimazole is a useful antithyroid drug with a rare potentially fatal complication of agranulocytosis. We report 2 cases presenting with this problem. One was treated supportively with barrier nursing and broad spectrum antibiotics, and the other needed use of a haemopoietic growth factor, granulocyte colony stimulating factor (G-CSF). As it is indeed possible for thyrotoxic patients who developed agranulocytosis with carbimazole to have the same complication with propylthiouracil, once agranulocytosis had resolved, both patients were treated with radioiodine to maintain euthyroidism.**

**Carbimazole-induced agranulocytosis usually spontaneously resolves within 1 to 2 weeks of stopping the drug. The use of haemopoietic growth factors to stimulate the proliferation and differentiation of progenitor cells, accelerates neutrophil recovery, as in our first case discussed.**

**We recognise that agranulocytosis from carbimazole is a rare, life-threatening complication. Instead of awaiting spontaneous recovery, the use of haemopoietic growth factors certainly seems a justifiable option, with a promise of a reduction in morbidity and mortality.**


**Keywords: carbimazole, agranulocytosis, haemopoietic growth factor, G-CSF**

## INTRODUCTION

Thyrotoxicosis is a common problem with a prevalence of about 1.9% - 2.7% females, and males being affected five times less often[1]. Patients are usually treated with antithyroid drugs, the commonest of which is carbimazole. It is an effective drug which blocks the synthesis of thyroid hormone, and also has extrathyroidal immune modulatory effects. Unfortunately, 0.3% - 0.5% of patients on this drug have a potentially fatal complication of agranulocytosis[1], defined as granulopaenia of < 250 cells/mm$^3$, almost always occurring within 3 months of initiating therapy.

Agranulocytosis, despite advances in antibiotics and supportive care, has a mortality nearing about 20%[7]. There are 2 main mechanisms suggested as the cause of agranulocytosis. The first is the interference of the drug with protein synthesis and cell replication; the second is suggested as an allergic reaction whereby Immunoglobulin G binds to the granulocyte-macrophage colony forming units in the marrow and suppresses granulocyte formation[7,8]. We recently encountered 2 patients with this rather uncommon complication, 1 recovered spontaneously with supportive therapy, and the other required granulocyte colony stimulating factor (G-CSF).

### Case 1

A 45-year-old man was diagnosed to have Graves' disease in April 1995 when he presented with a 2-month history of weight loss and diarrheoa. He was started on carbimazole and his symptoms responded well to therapy. After 2 months of therapy, he was admitted with a 3-day history of swinging fever and sorethroat. He was clinically noted to have tonsillitis and pharyngitis. His full blood count showed granulopaenia with a neutrophil count of <0.10 x $10^9$/L. The septic workout did not reveal any infecting organism, and he was treated empirically with broad spectrum antibiotics, after stopping the carbimazole. After one week of antibiotics, his total white count still remained at 1.1 x $10^9$/L, with neutrophils still <0.1 x $10^9$/L. He had a bone marrow examination done on day 6 of antibiotic therapy, and this showed suppression of granulocyte cell lines. The following day, the patient continued to have a spiking temperature, and his counts did not appear to be improving. He was then started on subcutaneous G-CSF, at 300$\mu$g daily. A 5-day course was planned, but as the total white count had risen to 9.4 x $10^9$/L (3.1 x $10^9$/L of neutrophils ) just after 2 doses, the rest of the G-CSF was omitted. His counts improved thenceforth and normalised within 3 days. He was subsequently referred for radioiodine therapy and is currently well on follow-up.

### Case 2

A 37-year-old Indonesian lady was treated with a 6-month course of antithyroid drugs 4 years previously for thyrotoxicosis. In August 1995, she developed a relapse and was started on carbimazole. She then presented in early October with a 3-day history of fever, chills, rigors associated with sorethroat. A septic workout was done and she was promptly started on broad spectrum intravenous antibiotics. Her full blood count revealed leucopaenia, with white cells only 1.9 x $10^9$/L, predominantly lymphocytes. This leucopaenia persisted until day 9 of antibiotic therapy (day 9 of stopping carbimazole), when the counts

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improved to 7.3 x $10^9$/L with polymorphs 3.0 x $10^9$/ L. After completion of the empirical course of antibiotics, she was referred for radioiodine therapy and has since returned to her homeland.

## DISCUSSION

Although rare, agranulocytosis is the most serious side effect of antithyroid drugs, especially carbimazole. As septicaemia rapidly supervenes in untreated cases, the fatality from agranulocytosis just cannot be overemphasised. All patients starting on antithyroid drugs must thus be instructed to have a white blood count checked if fever or sorethroat develops, especially during the first 3 months of starting therapy. If the counts are normal, the drug should be resumed.

Both patients in our recent experience were in the prime of their lives. They had responded to carbimazole and were actually euthyroid at the time of agranulocytosis. The first patient had a marked neutropaenia and had an obvious focus of sepsis. The G-CSF was used because he remained septic and ill, and the neutropaenia showed no signs of resolving. It may be argued that the white cell count rising just after 2 doses of G-CSF was actually due to the drug, or the natural history of carbimazole-induced agranulocytosis. It is however, well known that G-CSF can mount a substantial rise in granulocyte count even 24 hours after its administration[2]. Carbimazole-induced agranulocytosis usually spontaneously resolves within 1 to 2 weeks of stopping the drug, with a range of 7 to 56 days[8]. The use of haemopoietic growth factors to stimulate the proliferation and differentiation of progenitor cells, is now gaining popularity. G-CSF stimulates the proliferation of the granulocyte cell line, while granulocyte-macrophage colony stimulating factor (GM-CSF) promotes the survival and differentiation of the early haemopoietic cells into monocytes and neutrophils[10-11]. A number of trials have reportedly shown the successful acceleration of neutrophil recovery in post-chemotherapy induced neutropaenia. This benefit is also now being seen in several case reports of their use in drug induced agranulocytosis, as in our first case.

The second patient received antithyroid therapy 4 years ago in Indonesia and did not experience any side effects from the drug. We were unable to confirm the drug used, but it would most likely be propylthiouracil, as it is extremely uncommon for carbimazole to cause agranulocytosis when used again to treat relapses. Like our first patient, she had severe neutropaenia, but her counts showed definite signs of recovery after only 4 days of supportive therapy. As such, we continued to manage her with expectant treatment till complete resolution 3 days later.

Once agranulocytosis had resolved, we were left with 2 options for long-term antithyroid treatment. As it is indeed possible for thyrotoxic patients who developed agranulocytosis with carbimazole to have the same complication with propylthiouracil[11], we chose not to use this drug. Both patients had no contraindications to radioiodine and this was felt to be the ideal option.

In conclusion, we recognise that agranulocytosis from carbimazole is a rare, life-threatening complication with a possibility of spontaneous recovery. Until recently, we could do little more than wait during this variable recovery period. Now, the use of haemopoietic growth factors certainly seems a justifiable option, with a promise of a reduction in morbidity and mortality.

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