Agranulocytosis: A rare side effect of carbimazole and the function of Cholestyramine in Hyperthyroidism

Khaled Mohammed Alakhali1, Aziz UR Rahman2, Mohamad Zakour Khadari2, Ali Saleh Noori2, Yasameen Mahdi2

1 Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur, Malaysia
2 Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur, Malaysia

ABSTRACT
Agranulocytosis is a rare side effect of antithyroid drugs that usually develops within the few months after starting treatment. We report a 45-year-old Indian female who presented to the hospital with shortness of breath, lethargy, decreased appetite, pharyngitis, and fever after used of Carbimazole 30mg OD for 2 months due to hyperthyroidism which was prescribed by her clinician. Her full blood count revealed neutropenia with a count of 0.03 × 10⁹/L. Carbimazole was discontinued and she was given antibiotics. Cholestyramine was used to treat her hyperthyroidism. In conclusion, agranulocytosis induced by the Carbimazole is important to recognise and treat early to prevent morbidity and mortality.

Keywords: Carbimazole, Hyperthyroidism, Cholestyramine, Agranulocytosis, Neutropenia

INTRODUCTION

Hyperthyroidism is a very common disease, most likely caused secondary to Graves’s disease followed by toxic multi-nodular goitre. Thioamide drugs are one of the medicine categories used in the treatment of hyperthyroidism. It inhibits the thyroid peroxidases that catalyze the iodination of tyrosine residues in thyroglobulin and the oxidative coupling of iodinated tyrosines. Inhibition of iodination is competitively antagonized by iodide at low drug concentrations, but not at higher drug concentrations. It has been suggested that it also reduces the autoimmunity that underlies the Graves’ disease. Thioamides, which have been in use for more than half a century, remain cornerstones in the management of hyperthyroidism. Most patients tolerate treatment well, but some may develop life-threatening side effects such as agranulocytosis. Agranulocytosis is the most severe adverse hematologic reaction associated with the Thioamides. Agranulocytosis typically develops within the first 3 months of treatment, although it can occur at any time and as late as 12 months after starting Thioamide therapy.

The prevalence of agranulocytosis is about 0.2-0.5%. The risk factors for agranulocytosis are unknown. There is no predilection for either gender, and the reaction may be idiosyncratic, or dose related. Some reports suggest that patients older than 40 years or those taking high dosages of methimazole (e.g., >40 mg/day) might be more susceptible than those on any dosage of propylthiouracil. If agranulocytosis is diagnosed, the drug should be discontinued, the patient monitored for signs of infection, and antibiotics instituted if necessary. Although some cases of granulocytopenia have resolved with substitution or continuation of Thioamides, the risks of drug rechallenge clearly outweigh the benefits, and other treatments should be instituted.

Case Report:
A 45-year-old Indian woman with the known past medical history of hyperthyroidism was hospitalized in
Agranulocytosis: A rare side...

Malaysia hospital with shortness of breath, lethargy, decreased appetite, pharyngitis, and fever. She suffered also from major weight loss; her weight dropped down from 56 Kg to 47 Kg within 2 months. This incidence encouraged her to see a doctor and got the diagnosis of hyperthyroidism in April 2019. She denied any history of palpitation, sweating, or diarrhoea. She denied any allergy to medications. Her vital signs showed BP 92/58 mmHg, heart rate 132 bpm, respiratory rate 20 breaths/min, oxygen saturation 97%, weight 47 kg, and height of 161 cm. The patient is a non-smoker, non-alcoholic and does not abuse drugs. She is married and has one son (12 years old). Her occupation was a fruit seller. Her past medication history consists of once-daily Propranolol 20 mg and Carbimazole 30 mg.

Her blood test showed the values for Hemoglobin 8.2 mg/dl, total leukocyte counts 1240/mm³, platelet 166,000 per µL, SCr 47 µmol/L, K 3 mEq/L, PO4 0.3 mmol/L, and Albumin 20 g/litre. Differential leukocyte counts - Neutrophil 3 %, Lymphocytes 80 %, Monocytes (M) 2 %, Basophils 0 %, peripheral blood smear showed normocytic normochromic RBC series, reduced total leukocyte count with neutropenia. Initial thyroid function test showed TSH value of 0.27 mlU/L (0.4 - 4.5 mlU/L), FT4 of 30.47 pmol/L (9.0-24.0 pmol/L), and FT3 of 1.93 pmol/L (2.2 - 5.4 pmol/L).

The patient was diagnosed with neutropenic sepsis secondary to carbimazole induced agranulocytosis. As Carbimazole was the drug responsible for current patient status, it was discontinued, and she was treated in the ward from 9 to 24/06/2019 as shown in Table 1.

<table>
<thead>
<tr>
<th>Date</th>
<th>Name of the drug (Brand/Generic)</th>
<th>Dose</th>
<th>Route</th>
<th>Frequency</th>
<th>Stop date</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/06/2019</td>
<td>Rocephin (ceftriaxone)</td>
<td>2g</td>
<td>IV</td>
<td>OD</td>
<td>10/06/2019</td>
</tr>
<tr>
<td>10/06/2019</td>
<td>Tazocin (Piperacillin/tazobactam)</td>
<td>4.5g</td>
<td>IV</td>
<td>QID</td>
<td>24/06/2019</td>
</tr>
<tr>
<td>20/06/2019</td>
<td>Propranolol</td>
<td>20mg</td>
<td>Oral</td>
<td>OD</td>
<td></td>
</tr>
<tr>
<td>22/06/2019</td>
<td>Cholestyramine</td>
<td>4g</td>
<td>Oral</td>
<td>TDS</td>
<td></td>
</tr>
<tr>
<td>13/06/2019</td>
<td>Vit.C</td>
<td></td>
<td>Oral</td>
<td>OD</td>
<td></td>
</tr>
<tr>
<td>18/06/2019</td>
<td>Lithium</td>
<td>350 mg</td>
<td>Oral</td>
<td>BID</td>
<td>21/06/2019</td>
</tr>
<tr>
<td>12/06/2019</td>
<td>Ferrous Fumarate</td>
<td>200 mg</td>
<td>Oral</td>
<td>BID</td>
<td></td>
</tr>
<tr>
<td>10/06/2019</td>
<td>Dexamethasone</td>
<td>2 mg</td>
<td>IV</td>
<td>QID</td>
<td>10/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>Lugols Solution</td>
<td></td>
<td>Oral</td>
<td>BID</td>
<td>10/06/2019</td>
</tr>
<tr>
<td>10/06/2019</td>
<td>KH2PO4</td>
<td></td>
<td>IV</td>
<td>OD</td>
<td>12/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>MgSo4</td>
<td></td>
<td>IV</td>
<td>BID</td>
<td>11/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>Propylthiouracil (PTU)</td>
<td>600 mg</td>
<td>Oral</td>
<td>TDS</td>
<td>09/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>Hydrocortisone</td>
<td>200 mg</td>
<td>Oral</td>
<td>TDS</td>
<td>11/06/2019</td>
</tr>
<tr>
<td>11/06/2019</td>
<td>Noradrenaline</td>
<td></td>
<td>IV</td>
<td>OD</td>
<td>11/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>Paracetamol</td>
<td>1 g</td>
<td>Oral</td>
<td>OD</td>
<td>24/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>Thiamine</td>
<td>200 mg</td>
<td>IV</td>
<td>OD</td>
<td>10/06/2019</td>
</tr>
<tr>
<td>11/06/2019</td>
<td>KCL</td>
<td>1 mg in 100 cc</td>
<td>IV</td>
<td>OD</td>
<td>11/06/2019</td>
</tr>
<tr>
<td>12/06/2019</td>
<td>0.2% chlorohexidine</td>
<td></td>
<td>Oral</td>
<td>TDS</td>
<td>24/06/2019</td>
</tr>
<tr>
<td>12/06/2019</td>
<td>Slow K</td>
<td>1.2 g</td>
<td>IV</td>
<td>BID</td>
<td>12/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>Rocephin (ceftriaxone)</td>
<td>2g</td>
<td>IV</td>
<td>OD</td>
<td>10/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>MgSo4</td>
<td></td>
<td>IV</td>
<td>BID</td>
<td>11/06/2019</td>
</tr>
<tr>
<td>09/06/2019</td>
<td>PTU</td>
<td>600 mg</td>
<td>Oral</td>
<td>TDS</td>
<td>09/06/2019</td>
</tr>
</tbody>
</table>
Her condition improved within seven days of stopping the Carbimazole. On 17/06/2019 total white blood cell and neutrophil counts reverted to near normal range and symptoms like shortness of breath, lethargy, decreased appetite, pharyngitis, and fever disappeared. The patient was discharged from the hospital after 14 days and her discharge medications are shown in Table 2.

Table 2. Patient discharged medications list

<table>
<thead>
<tr>
<th>S. No</th>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cholestyramine</td>
<td>4 g</td>
<td>TDS</td>
</tr>
<tr>
<td>2.</td>
<td>Prednisone (0.5/kg)</td>
<td>20 mg</td>
<td>OD</td>
</tr>
<tr>
<td>3.</td>
<td>Propranolol</td>
<td>20 mg</td>
<td>OD</td>
</tr>
<tr>
<td>4.</td>
<td>Ferrous Fumarate</td>
<td>400 mg</td>
<td>OD</td>
</tr>
<tr>
<td>5.</td>
<td>Vit.C</td>
<td>100 mg</td>
<td>OD</td>
</tr>
<tr>
<td>6.</td>
<td>Vit.B</td>
<td>10 mg</td>
<td>OD</td>
</tr>
<tr>
<td>7.</td>
<td>Folate</td>
<td>5 mg</td>
<td>OD</td>
</tr>
</tbody>
</table>

Discussion:
Agranulocytosis is a rare but serious complication of antithyroid drug therapy. A study done by Van der Klauw et al.9 reported a relative risk of agranulocytosis among 115 for patients who received the antithyroid drugs (ATD), was found the highest risk among all others evaluated pharmacological agents. Similarly, in a study done by Tajiri et al., among 15,398 Japanese patients with Graves’ disease, there was no difference in the incidence of agranulocytosis between patients receiving propylthiouracil and those receiving the methimazole 10. The result of this case report is consistent with Van der Klauw et al and Tajiri et al 9,10.

, A study done by Nakamura et al.11 reported an analysis of 754 cases that published of ATD induced agranulocytosis in Japan11, the mean age of onset was 43.4
± 15.2 years and indicated that the females were more affected than males (6.3:1 ratio). Another, study done by Yang et al. reported an analysis of 114 cases with ATD induced agranulocytosis diagnosed in a single Chinese centre revealed a higher female-to-male ratio (10.4:1) and similar age of onset (41.7 ± 12.3 years) 12. Agranulocytosis usually develops in the first 3 months after antithyroid drugs therapy is initiated 11. In Japan, a 754 retrospectively reviewed cases of agranulocytosis after use of ATD found that more than 70% of patients who developed this side effect within 2 months, and nearly 85% showed this effect within 3 months9. The current case report of agranulocytosis manifest with 45 year old female patient and this consistent with the finding of Nakamura et al11 and Yang et al12.

The current case may have a difference in time of onset and may be related to the disease mechanism, with the immune-mediated process that leads to the more rapid destruction of neutrophils as opposed to direct toxicity. The previous studies recognised that the mean duration of treatment with propylthiouracil, carbimazole and methimazole needed to cause agranulocytosis was found to be 36, 41, and 42 days, respectively 13. Agranulocytosis can manifest not only after the first treatment with ATD but also in later courses. It can manifest up to eight courses later (with either the same or a different ATD) but usually occurs 5 months after finishing the previous treatment 14. Another study done by Kim et al. reported severe agranulocytosis developed after 3 weeks on carbimazole treatment15. In the present case report, agranulocytosis manifests 2 months after treatment with Carbimazole 30 mg OD. In summary, Agranulocytosis is life-threatening, but treatable within the opportunity, and the most important lesson for physicians in the future is to remain vigilant for ATD induced agranulocytosis regardless of treatment duration or dose.

REFERENCES


ندرة المحبيات: تأثير جانبي نادر للكريبيمازول ووظيفة الكوليستيرامين في فرط نشاط الغدة الدرقية
هلال محمد الأكحلي1، عزيز الرحمن2، محمد زغور خدروي2، علي صالح نوري2، باسمين مهدي2
1،2 قسم الصيدلة السريرية، كلية العلوم الصيدلانية، جامعة UCSI، كوالالمبور، ماليزيا

ملخص
ندرة المحبيات هو أحد الآثار الجانبية النادرة للأدوية المضادة للغدة الدرقية التي عادة ما تتطور في غضون بضعة أشهر بعد بدء العلاج. أبلغنا عن امرأة هندية تبلغ من العمر 45 عاماً قدمت للمستشفى في ضيق من التنفس والخمول وتراجع الشهية والتهاب البلعوم الحمى بعد تناولها لـ كاربمارول 30 ملغ مرة يوميا لمدة شهرين بسبب فرط نشاط الغدة الدرقية الذي وصفه الطبيب السريري لها. يعد كشف تعداد دمها الكامل وجود فرط في عدد الخلايا بنسبة 0.03 × 109 / لتر. تم إيقاف كاربمازول وتقليل استخدامه وتم إعطاء مضادات الفيروسات. تم استخدام كولستيرامين لعلاج فرط نشاط الغدة الدرقية لها بدلاً من كاربمازول. في الختام، ندرة المحببات التي يسببها كاربمازول من المهم التعرف عليها والعلاج في وقت مبكر لمنع المرض والوفيات.

الكلمات المفتاحية: كاربمازول، فرط نشاط الغدة الدرقية، كولستيرامين، ندرة المحببات، قلة العدلات.