

Case Report

Acute cholestatic hepatitis along with agranulocytosis: A rare side effect of carbimazole

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Abstract

Antithyroid drugs have been used for more than 50 years for the management of hyperthyroidism. Most patients tolerate treatment well but some may develop life-threatening side effects such as agranulocytosis, aplastic anemia and cholestatic hepatitis. A 45-year-old female was diagnosed with severe hyperthyroidism. Treatment with Carbimazole 30 mg/day was initiated. Within six weeks following the start of therapy, patient developed potentially life-threatening acute cholestatic hepatitis and agranulocytosis as adverse effects to carbimazole. The patient's symptoms and laboratory abnormalities resolved following withdrawal of offending drug. Agranulocytosis and cholestatic hepatitis together is an extremely rare idiosyncratic side effect of Carbimazole treatment and considered to be dose and age-related. Antithyroid drugs are deceptively easy to use, but because of the variability in the response of patients and the potentially serious side effects, all practitioners who prescribe the drugs need to have a working knowledge of their complex pharmacology.

Keywords: Agranulocytosis, carbimazole, cholestatic hepatitis, hyperthyroidism

Résumé

Antithyroïdiens de drogues ont été utilisés depuis plus de 50 ans pour la gestion de l'hyperthyroïdie. La plupart des patients tolèrent traitement bien, mais certains peuvent développer mortelles des effets secondaires tels qu'Agranulocytose, aplastic l'anémie et hépatite cholestatiques. Une femme de 45 ans a été diagnostiquée avec hyperthyroïdie sévère. Traitement avec Carbimazole 30 mg/jour) a été lancée. Dans les six semaines suivant le début de la thérapie, patient développé hépatite aiguë cholestatiques potentiellement mortelles et Agranulocytose comme des effets néfastes à carbimazole. Symptômes du patient et les anomalies de laboratoire résolu après le retrait de médicament incriminé. Agranulocytose et antihépatite cholestatiques ensemble est un effet secondaire d'idiosyncrasique extrêmement rare de traitement Carbimazole et considéré à dose et liée à l'âge. Antithyroïdiens de drogues sont trompeuse faciles à utiliser, mais en raison de la variabilité dans la réponse de patients et les effets secondaires potentiellement graves, tous les praticiens qui prescrivent les médicaments doivent avoir une connaissance de leur pharmacologie complexe.

Mots-clés: Agranulocytose, carbimazole, antihépatite cholestatiques, hyperthyroïdie

Introduction

Antithyroid drugs, which have been in use for more than half a century, remain cornerstones in the management of hyperthyroidism.^[1] Most patients tolerate treatment well but some may develop life-threatening side effects such as agranulocytosis,

aplastic anemia, vasculitis and cholestatic hepatitis. The most common adverse effect is a maculopapular pruritic rash, at times accompanied by fever.^[2] Adverse reaction of these thioamides occurs in 3–12% of treated patients. Agranulocytosis and cholestatic hepatitis together is an extremely rare idiosyncratic side effect of Carbimazole treatment

and are usually dose and age-related.

Here we share our experience of managing such a case of Carbimazole-induced acute cholestatic hepatitis along with agranulocytosis.

Case Report

A 45-year-old lady was presented to the emergency department of hospital in semi-conscious state. There was history of bluish discoloration of body, right hypochondriac pain and high-grade fever since one week. The patient was a diagnosed case of Hyperthyroidism (T4 - 20.1 μ g/dl, T3 - 3.2 ng/ml, TSH - 0.1 μ IU/ml) since six weeks and was on Carbimazole (30 mg/day) since then. General physical examination of patient showed blood pressure - 110/70 mmHg, pulse rate 96/min, Glasgow coma scale - 11/15. The patient was deeply jaundiced with tender hepatomegaly. Cardiac and respiratory system were unremarkable with regards to any important illness.

Blood picture showed Hemoglobin - 10 mg/dl, total leukocyte counts (TLC) - 1600/mm³, ESR - 80 mm/h (westergren method), Differential leukocyte counts - Neutrophil (N) 2%, Lymphocytes (L) 92%, Monocytes (M) 6%, peripheral blood smear showed normocytic normochromic RBC series, reduced total leukocyte count with neutropenia. LFT showed predominantly direct hyperbilirubinemia with raised enzymes (Total Biliubin - 12.4 mg/dl, Direct Bilirubin - 7.8 mg/dl, AST - 210 IU/ml, ALT - 123 IU/ml and ALP - 630 IU/ml). Ultrasonograph showed enlarged liver 16 cm with prominent portal vein at the porta hepatis. Blood tests proved negative for malaria, leptospirosis, Hepatitis A, B, C and E. So we reached to a diagnosis of Carbimazole-induced cholestatic hepatitis with agranulocytosis. She also had Herpes zoster lesions involving left C₂ dermatome.

As Carbimazole was the drug responsible for current patient status, it was discontinued and she was treated with IV ceftriaxone, oral Cloxacillin and antiviral Famciclovir. Her condition improved dramatically within three days of stopping the Carbimazole. The LFT and blood picture reverted to near normal range. At the end of seven days there was significant improvement in the laboratory parameters. (TBR - 3.5 mg/dl, DBR - 1.6 mg/dl, AST - 47 IU/ml, ALT - 58 IU/ml ALP - 296 IU/ml) or agranulocytosis (TLC-5500, N33, L65, E1, M1.)

Discussion

Six decades after their introduction, antithyroid

drugs continue to be important in the management of hyperthyroidism. Patients with Graves' disease, who have an approximately 40–50% chance of remission after 12 to 18 months of therapy, are the best candidates.^[1] Antithyroid drugs are associated with a variety of minor side effects, as well as potentially life-threatening or even lethal complications like severe liver failure and bone marrow toxicity.

Agranulocytosis (an absolute granulocyte count of less than 500 per cubic millimeter) is the most feared side effect of antithyroid-drug therapy occurring in 0.3–0.6% of patients.^[1] This reaction is rapidly reversible when the drug is discontinued, but antibiotic therapy may be necessary for complicating infections. Most of antithyroid drugs-induced agranulocytosis happens within the first 90 days of administration of antithyroid drug; however, this complication can occur even a year or more after starting therapy. Some, but not all, studies have suggested that the risk of agranulocytosis is greater in older patients and that they have a higher rate of death.^[1] It is important to note that agranulocytosis can develop after a prior uneventful course of drug therapy, a finding that is important since renewed exposure to the drug frequently occurs when patients have a relapse and undergo a second course of antithyroid therapy.^[1,3]

Although carbimazole-induced agranulocytosis is more common among patients over 40 years old and rare among patients receiving the dose less than 30 mg in a day, it can occur irrespective of the dose, age or duration of treatment. Analysis of the known cases suggests that older age of the patient and higher dose of the drug are risk factors for agranulocytosis and cholestatic injury.^[4]

Both classes of antithyroid agents, Propylthiouracil and Carbimazole, are known rarely to cause liver dysfunction, which is among the small number of their idiosyncratic toxic effects. Estimates regarding the frequency of this condition are imprecise, but it probably ranges from 0.1 to 0.2%.^[1] The antithyroid drugs have distinct patterns of liver injury: Propylthiouracil has hepato-cellular toxic effects and cholestatic changes are seen in case of Methimazole and Carbimazole.^[3] These unpredictable liver alterations occur presumably by hypersensitivity. There may be drug-related immune reactions, especially as it has been shown that sensitized lymphocytes may produce a cholestatic factor on stimulation with the antigen.^[5,4]

Sdoul^[6] studied 236 hyperthyroid patients treated with carbimazole from 1986 to 1992 and found that only two patients had cholestatic hepatitis and two

patients experienced a mild or severe neutropenia.

Eigtved *et al.*^[7] observed 476 hyperthyroid patients treated with Carbimazole and found that the total frequency of adverse effects, defined as symptoms leading to discontinuation of treatment, was 8% for Carbimazole. No cases of agranulocytosis were reported.

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To conclude, until this date only a handful of cases have been documented in literature, where a patient taking Carbimazole therapy develop acute cholestatic hepatitis,^[4-6,8,9] agranulocytosis^[3,4,6,10] or acute cholestatic hepatitis along with agranulocytosis.^[2] The key to diagnose these rare side effects lies in maintaining a high index of clinical suspicion, through history and clinical examination and performing appropriate laboratory investigations. Our case being one such point to the necessity not to over look such side effects, though rare!

Antithyroid drugs are deceptively easy to use, but because of the variability in the response of patients and the potential serious side effects, all clinicians who prescribe the drugs need to have a working knowledge of their complex pharmacology.^[1]

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