

# A Case Report of Carbimazole Induced Agranulocytosis

Anns Mariya<sup>1,\*</sup>, Sreenath R<sup>2</sup>, Dona Maria<sup>3</sup>

<sup>1</sup>Nirmala College of Pharmacy, Muvattupuzha, Kerala, INDIA.

<sup>2</sup>Department of Endocrinology, Caritas Hospital, Thellakom, Kottayam, Kerala, INDIA.

<sup>3</sup>Department of Pharmacy Practice, Nirmala College of Pharmacy, Muvattupuzha, Kerala, INDIA.

## ABSTRACT

Carbimazole is an antithyroid medication used to treat an overactive thyroid gland. Agranulocytosis is a rare but potentially serious adverse effect that cannot be predicted by routine measurement of white blood cell count but which is reversible on stopping treatment. Patients should be warned to stop the drug and seek medical advice immediately, if severe sore throat, infections or fever develop while on treatment. Here a 52-year-old female patient was admitted with complaints of painful swelling in the scalp, neck and right hand. She was hyperthyroid and taking neomercazole 10 mg twice daily. Laboratory examination shows the possibility of carbimazole induced agranulocytosis. The drug was stopped, and with the treatment she received, her counts gradually showed an improving trend and she was discharged.

**Keywords:** Carbimazole, Agranulocytosis, Colony stimulating factor, Infections.

## Correspondence:

**Ms. Anns Mariya**

Pharm D Intern, Nirmala College of Pharmacy, Muvattupuzha, Ernakulam-686661, Kerala, INDIA.  
Email: annsmariya83@gmail.com

**Received:** 26-12-2022;

**Revised:** 21-04-2023;

**Accepted:** 23-05-2023.

## INTRODUCTION

Carbimazole is a medicine that is used to treat hyperthyroidism. This condition occurs when thyroid gland making too much hormones. Carbimazole is a prodrug, after absorption it is converted to the active form, methimazole.<sup>1</sup> Methimazole prevent thyroid peroxidase enzyme from iodinating and coupling with the tyrosine residue on thyroglobulin, hence reducing the amount of thyroid hormones. Minor adverse reactions with methimazole have 25% depending on the dose and the drug, whereas major adverse effects occur in 4.6% of patients receiving drug. Agranulocytosis is the most serious adverse effect of carbimazole drug therapy and is characterized by fever, malaise, gingivitis, oropharyngeal infection, and a granulocyte count less than 250/mm.<sup>2</sup> This drug is concentrated in granulocytes, and this reaction can represent a direct toxic effect rather than hypersensitivity. The toxic effect is higher in patients older than age 40 years receiving a MMI dose greater than 40 mg/day and is linked to HLA class II genes containing the DRB1\*08032 allele. Agranulocytosis almost always develops in the first 3 months of therapy. Because the onset is sudden, routine monitoring is not recommended. Colony-stimulating factors have been used with some success to restore cell counts to normal, but it is unclear how effective this form of therapy is to routine supportive care.<sup>3</sup> Once antithyroid drugs are discontinued, clinical improvement is seen over several days to weeks.<sup>4</sup>

## CASE REPORT

A 52-year-old female patient was consulted with fever, symptomatic gall stone disease and complaints of painful swelling in the scalp, neck and right hand. She had a history of hypothyroidism; 6 months ago, and she took thyroxin 25mcg then stopped after three months. She was taking propranolol BD. On further evaluation, found that she was hyperthyroid and the condition was managed with neomercazole 10mg twice daily. Routine investigation showed anaemia, leukopenia, neutropenia, lymphocytosis, eosinophilia, increased ESR and C-reactive protein elevation. Peripheral smear report showed carbimazole induced agranulocytosis.

The drug was stopped and she was empirically started with intravenous antibiotics in the view to decrease vulnerability to infections. Treatment started to cure agranulocytosis with filgrastim 300mcg as Stat medication. An Endocrinology opinion was taken during the hospital stay for modification of anti-thyroid medications. A thyroid function test was done, and it was not within the normal range; as anti-thyroid medications were not able to start at this time, they looked for another possibility, so she was done with radioiodine ablation. White Blood Cell (WBC) count and neutrophil count became normal within few days. With the treatment she received, her counts gradually showed an improving trend and she was discharged.

## DISCUSSION

Hyperthyroidism is a common endocrine disorder. Carbimazole and propylthiouracil are thionamide drugs. Although carbimazole induced agranulocytosis is a rare condition.<sup>5</sup> The risk factors for



DOI: 10.5530/ijopp.16.3.44

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**Table 1: Lab investigations.**

	DAY 1	DAY 2	DAY 3	DAY 4	DAY 5	DAY 6	DAY 7	REFRANGE
TSH	0.01						0.01	0.5-5Miu/L
FT3							18.6	2.3-4.1
FT4	22.6						45.3	12-28
LYMPHOCYTES	78	70	69	63	43			20-50%
TOTAL WBC (cu mm)	4100	3760	5820	5760		5840	5890	4000-11000
EOSINOPHIL	7	7	4	4	5			1-6%
HAEMOGLOBIN	11.5	12.2						12-16 g/dl
CRP	3.1	2.2		1.0	0.2	0.2		<0.3
ESR	42							0-20 mm/hr

agranulocytosis are unknown. There is no prediction for either sex, and the reaction may be idiosyncratic or dose related. Some reports suggest that patients older than 40 years or those taking high dosages of carbimazole (e.g., >40 mg/day) might be more susceptible.<sup>6</sup>

The mechanism for agranulocytosis is assumed that, 1) when drug get attached with granulocyte, and antibody production starts results in the destruction of granulocytes, 2) antibodies may target the drug metabolites complex absorbed on the neutrophil granulocyte in the presence of plasma component, 3) the drug may trigger the autoantibodies production.<sup>7</sup>

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 carbimazole therapy. A delayed reaction is also common with carbimazole therapy.<sup>8</sup> If agranulocytosis is diagnosed, the drug should be discontinued, the patient monitored for signs of infection, and antibiotics instituted if necessary. Granulocyte colony-stimulating factors may shorten the recovery period. If the patient recovers, granulocytes begin to reappear in the periphery within a few days to 3 weeks; a normal granulocyte count occurs shortly thereafter. Although some cases of granulocytopenia have resolved with substitution or continuation of thionamides, if the risks of drug rechallenge clearly outweigh the benefits, then other treatments should be instituted. Changing to an alternative thionamide should also be avoided because of possible cross-sensitivity between these agents.<sup>7</sup>

## CONCLUSION

Hyperthyroidism is an endocrine disorder, with prevalence of subclinical and overt hyperthyroidism were present in 1.6% and 1.3% of subjects.<sup>8</sup> Anti thyroid medication was commonly used to control this condition. Carbimazole is one of those medications with rare side effect of agranulocytosis. Carbimazole-induced

agranulocytosis occurs generally within few weeks or months of taking the anti-thyroid medication but onset may be delayed by one year with in incidence of 0.1%-0.3%.<sup>9</sup> Dechallenge resulted in normalization of blood parameters.<sup>5</sup> This drug induced agranulocytosis is a lethal condition but reversible if recognized early and treated accordingly.

## ACKNOWLEDGEMENT

We gratefully thank the health care staff of Caritas Hospital Thellakom, Kottayam, Kerala-686630, India.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

MMI: Methimazole; HLA: Human leukocyte antigen gene complex.

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**Cite this article:** Mariya A, Sreenath R, Maria D. A Case Report of Carbimazole Induced Agranulocytosis. Indian J Pharmacy Practice. 2023;16(3):262-3.