Open Journal of
Clinical & Medical
Case Reports

Volume 7 (2021)
Issue 12

ISSN: 2379-1039

Suspected carbimazole induced acute cholestatic hepatitis: Case report

***Corresponding Author: Darshana Meanger**

Frankston Hospital Pharmacy Department, 2 Hastings Road, Frankston VIC 3199, Australia.
Email: dmeanger@phcn.vic.gov.au

Abstract

Background: Carbimazole (CBZ)-induced cholestatic hepatitis is rare, with only seven cases of this adverse drug reaction (ADR) reported to the Therapeutic Goods Administration since 1971 and less than 0.5% incidence overall of hepatotoxicity with antithyroid drugs (ATDs). A total of thirteen cases of CBZ-induced cholestatic hepatitis have been reported to the Food and Drug Administration as of March 2020.

Aim: This case report aims to highlight the clinical and biochemical findings of a patient who presented with CBZ-induced acute cholestatic hepatitis and the management provided.

Clinical details: A 62 year-old male presented to a tertiary hospital with general fatigue, dark urine, palpitation, pruritic rash and recent onset diarrhoea. He had started CBZ 10 mg twice a day, six weeks prior for amiodarone-induced thyrotoxicosis.

Outcomes: The patient was diagnosed with likely CBZ-induced acute cholestatic hepatitis, which resolved with the cessation of CBZ therapy and high dose corticosteroids.

Conclusion: ATDs are known to cause hepatitis or acute liver failure. However, most reports of this ADR are limited to case reports, small clinical studies or retrospective chart reviews. This case highlights the importance of clinical awareness of CBZ-induced cholestatic hepatitis and the need for prompt intervention and diagnosis to prevent long term liver damage. Despite the rare nature of CBZ-induced hepatitis, routine monitoring of LFT's before and during treatment with CBZ can be considered in practice to prevent drug induce liver injury. Caution should also be taken when using ATDs at higher doses and in patients with pre-existing mild-moderate hepatic insufficiency.

Keywords

carbimazole; drug induced liver injury; acute cholestatic hepatitis; adverse drug reaction.

Introduction

Carbimazole (CBZ)-induced cholestatic hepatitis is a rare adverse drug reaction (ADR), with only seven cases of CBZ-induced cholestatic hepatitis reported to the Therapeutic Goods Administration since 1971 and less than 0.5% incidence overall of hepatotoxicity with antithyroid drugs (ATDs) [1,2]. A total of thirteen cases of CBZ-induced cholestatic hepatitis have been reported to the Food and Drug Administration (FDA) as of March 2020 [2]. Propylthiouracil (PTU) is another ATD that is available in Australia and is known to cause toxic hepatitis with necrosis, where as Methimazole (MMI) and its prodrug CBZ are associated with cholestatic hepatitis [3-6].

The case presented here is of a patient who developed acute cholestatic hepatitis during CBZ administration for amiodarone-induced thyrotoxicosis. Amiodarone-induced thyrotoxicosis is caused by a large amount of iodine found in amiodarone [7]. It can develop over a long period of time or even several months after ceasing therapy, as amiodarone has a long half-life [8]. Amiodarone-induced thyrotoxicosis is treated by ceasing amiodarone and starting ATD with or without high-dose corticosteroids [1]. Patients who do not effectively respond to treatment within four to six weeks of treatment or those who suffer from ATD related ADRs may require a thyroidectomy [1]. This case report aims to highlight the clinical and biochemical findings of this rare ADR and the management provided. The patient's informed consent to publish the present case report was obtained and documented.

Case Report

In April 2020, a 62 year-old male presented to a tertiary hospital with symptoms of general fatigue, dark urine, palpitation, pruritic rash (on chest and upper back) and recent onset of diarrhoea. Two months prior to presentation he commenced treatment with CBZ 10 mg twice a day and prednisolone 25 mg daily (which was subsequently reduced to 12.5 mg daily) for amiodarone-induced thyrotoxicosis. His past medical history included atrial fibrillation (with a CHA2DS2Vasc score of 2), mild left ventricular systolic dysfunction, and mild coronary artery disease. He had failed a third cardioconversion and was re-started on amiodarone in February 2020. He had no known history of allergies to medications with a social history that included no smoking or illicit drug use and occasional alcohol consumption. His regular medications on admission included amiodarone 100 mg daily, carbimazole 10 mg twice a day, apixaban 5 mg twice a day, esomeprazole 20 mg daily, prednisolone 12.5 mg and sacubitril/valsartan 24 mg/26 mg twice a day. His bisoprolol therapy was ceased prior to the third cardioversion due to low blood pressure.

On admission the patient had the following remarkable pathology: Bilirubin of 155 micormol/L (<20 micromol/L), Alanine Transaminase (ALT) of 642 units/L (< 45 units/L), Aspartate Transaminase (AST) of 382 units/L (<35units/L), Gamma-Glutamyl Transferase (GGT) of 1,131 units/L (<50 units/L), Alkaline Phosphatase (ALP) of 497 units/L (30-110 units/L), Thyroid-Stimulating Hormone (TSH) of <0.03 mIU/L (0.5-4.00 IU/L), Triiodothyronine (T3) of 9.8 pmol/L (3.5-6.5 pmol/L) and Thyroxine (T4) of 62.2 pmol/L (10.0-23.0 pmol/L). During hospitalization, the treating clinical pharmacist had notified the medical team that amiodarone and CBZ can cause hepatotoxicity and that CBZ was recently initiated. The medical team decided to rule out other causes such as infective or autoimmune causes of hepatotoxicity before considering drug-induced hepatotoxicity. Hepatic viral screen came back negative, and ultrasound

of the liver, gallbladder and bile duct were all normal (Figure 1). Once all other causes were ruled out, amiodarone was changed to sotalol in consultation with cardiology team. Minimal Liver Function Test (LFT) improvement occurred (Table 1) after the cessation of amiodarone; however improvement was expected to take weeks given amiodarone's long half-life [1].

Given that CBZ-induced hepatotoxicity is rare, the endocrinology team initially decided to continue CBZ as the patients T4 remained significantly elevated [6]. However, several days later, it was decided that CBZ was to be ceased with Thyroid Function Tests (TFTs) and LFTs to be followed up in outpatient appointments. During hospitalisation, the patient had also received one day of 25 mg/day of prednisolone for thyrotoxicosis, followed by reduced dosing of 12.5 mg/day thereafter. Prednisolone was increased to 50 mg/day on discharge until review at endocrinology clinic, for the treatment of Drug-Induced Liver Disease (DILI). Six days after discharge from hospital, the patient was followed up in endocrinology clinic and was found to have markedly improved LFTs and TFTs. By early May 2020, his bilirubin and AST had normalised (see Table 1).

Table 1: Patients liver function tests and thyroid function tests from the end of January to the start of May 2020.

Pathology (normal range)	30/1	10/2	29/2	7/4	8/4	9/4	10/4	11/4	12/4	13/4	14/4	15/4	21/4	27/4	4/5
Bilirubin (<20 micromol/ L)	18	18	-	155	142	166	178	192	208	197	185	160	49	32	19
ALT (< 45 units/L)	22	32	-	642	497	593	594	588	612	586	554	503	168	75	61
AST (<35 units/L)	35	33	-	382	291	336	323	294	298	278	226	227	41	26	25
GGT (<50 units/L)	58	71	-	1,131	982	1,194	1,372	1,361	1,475	1,446	1,350	1,197	649	414	311
ALP (30-110 unit/L)	79	111	-	497	454	549	578	637	716	781	750	678	346	198	134
TSH (0.5-4.00 mIU/L)	-	-	<0.03	<0.03	<0.03	-	-	-	-	-	-	-	<0.03	<0.03	<0.03
T3 (3.5-6.5 pmol/L)	-	-	14.9	9.8	8.8	-	-	-	-	-	-	-	4.8	3.7	3.6
T4 (10.0-23.0 pmol/L)	-	-	86.3	62.2	53.2	-	-	-	-	-	-	-	41.9	30.0	24.4

*ALT: Alanine Transaminase; AST: Aspartate Transaminase; GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase; TSH: Thyroid-Stimulating Hormone; T3: Trii modothyronine; T4: Thyroxine.

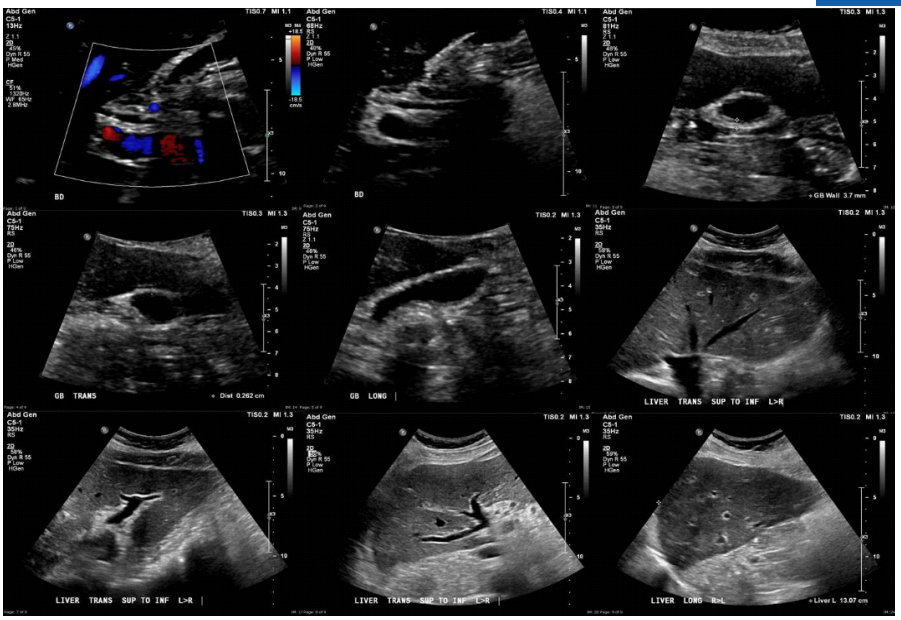

Figure 1: Patients normal ultrasound of the liver, gallbladder and bile duct.

Discussion

ATDs such as PTU, MMI and its prodrug CBZ are commonly used to treat amiodarone-induced thyrotoxicosis as either monotherapy or in combination with high dose corticosteroids [4]. ATDs are known to cause hepatitis or acute liver failure. However, most studies are limited to case reports, small clinical studies or retrospective chart reviews [9]. PTU-induced hepatotoxicity that has led to liver failure requiring liver transplantation has been on the rise [10]. In 2010, The USA's FDA issued a boxed warning on PTU for PTU-induced hepatotoxicity [10]. Studies comparing the incidence of ATDs' hepatotoxicity have found that MMI/CBZ versus PTU had a higher risk of hepatitis rates and a lower incidence of acute liver failure [9].

The patient presented here had developed significant acute cholestatic hepatitis with jaundice six weeks after commencing CBZ. A causality assessment of the ADR was done using the Naranjo's scale [11]. The calculated Naranjo's scale score was four, indicating that CBZ possibly could have caused the ADR [11]. This was based on the known ADR occurring after administration of CBZ, improvement in the patients ADR after cessation of CBZ and a possibility that amiodarone and hyperthyroidism could have also induced hepatitis [11].

MMI and its prodrug CBZ have a similar side effect profile. It is still unknown the exact mechanism of MMI/CBZ-induced cholestatic hepatitis, however, it is presumed that unpredictable alterations to liver enzymes could be due to a hypersensitivity reaction [12]. This may be due to a drug-related immune reaction, as sensitised lymphocytes have been shown to produce cholestatic factors upon stimulation with antigens [12]. CBZ has been rarely associated with intrahepatic cholestasis, and there have been very few reports of CBZ-induced liver damage in the medical literature. Most CBZ liver toxicity published cases had histological changes that were consistent with cholestasis [13]. Many rates of ATD-related hepatotoxicity have been found to peak in the first thirty days of treatment, with mostly high doses of MMI/CBZ leading to an increase in the risk of hepatitis [9].

Currently, the most effective way to treat DILI is to cease the suspected offending medication and to

prevent re-exposure. Some studies have also found that corticosteroids can also be effectively used to treat DILI [14]. In this case, both CBZ and amiodarone were ceased, and high dose of prednisolone was initiated on discharge. Amiodarone induced hepatotoxicity is uncommon; however, serum enzyme elevations are reported in 15-50% of patients who are on long-term therapy [12]. It is possible that amiodarone may have contributed to the liver impairment in the case presented; however, amiodarone causes a more alcoholic liver disease picture, with markedly elevated ALT and AST (10 to 100 fold) [8]. Amiodarone also has a long half-life which generally leads to liver enzymes improvement over several months rather than days [8].

Furthermore, this patient also presented with no changes in liver enzymes when initially being admitted to hospital for thyrotoxicosis and only had signs of acute cholestatic hepatitis after being initiated on CBZ (Table 1). However, these factors alone cannot exclude amiodarone's contribution to the patient's acute liver impairment. Following the cessation of CBZ and initiation of high doses corticosteroids, LFTs and TFTs markedly improved after six days (Table 1). Corticosteroid therapy was weaned down to 25 mg daily for two weeks then 12.5 mg daily thereafter once LFTS and TFTs were stable. LFTs remained stable one month after prednisolone was weaned down, but TFTs began to increase indicating that alternative treatment such as a thyroidectomy may need to be considered to treat the patient's thyrotoxicosis.

The case presented here highlights the importance of clinical awareness of CBZ induced cholestatic hepatitis and the need for prompt intervention and diagnosis to prevent long-term liver damage. Despite the rare nature of CBZ-induced hepatitis, routine monitoring of LFT's before and during treatment with CBZ can be considered in practice to prevent DILI in addition to medication counseling on this ADR.

Declaration of conflict of interest: The author declares that there is no conflict of interest.

Patient consent: The patient has signed consent to publication form and the form is held by the treating institution.

Acknowledgements: This case report was originally prepared in part fulfilment of course requirements for the Masters of Clinical Pharmacy degree at Monash University, Faculty of Pharmacy and Pharmaceutical Sciences. The author would like to thank Iouri Banakh and Amy McCrae for there assistance in reviewing this manuscript.

References

1. Therapeutic Goods Administration. Australia Government, Department of Health. Australia. Available from: https://apps.tga.gov.au/PROD/DAEN/daen-report.aspx.

2. U.S. Food and Drug Administration [Internet]. U.S. Food and Drug Administration. 2020.

3. Akmal A, Kung J. Propylthiouracil, and methimazole, and carbimazole-related hepatotoxicity. Expert Opin Drug Saf. 2014; 13: 1397–406.

4. Endocrinology [revised Jan 2019]. In: eTG complete[internet]. Melbourne: Therapeutic Guidelines Limited. 2017.

5. Liaw YF, Huang MJ, Fan KD, Li KL, Wu SS, Chen TJ. Hepatic injury during propylthiouracil therapy in pa-tients with hyperthyroidism. A Cohort Study. Ann Intern Med. 1993; 118: 424–8.

6. Arab DM, Malatjalian DA, Rittmaster RS. Severe cholestatic jaundice in uncomplicated hyperthyroidism treated with methimazole. J Clin Endocrinol Metab. 1995; 80: 1083–5.

7. Australian medicines handbook online. Adelaide (S. Australia): Australian Medicines Handbook Pty Ltd; 2018.

8. LiverTox: Clinical and Research Information on Drug- Induced Liver Injury [Internet]. Bethesda (MD): Na-tional Institute of Diabetes and Digestive and Kidney Diseases. 2012.

9. Wang MT, Lee WJ, Huang TY, Chu CL, Hsieh CH: Antithyroid drug-related hepatotoxicity in hyperthyroidism patients: a population-based cohort study. Br J Clin Pharmacol 2014; 78: 619–62.

10. US Food and Drug Administration MedWatch. FDA Drug Safety Communication: New Boxed Warning on severe liver injury with propylthiouracil. 2010.

11. Naranjo C, Busto U, Sellers E, Sandor P, Ruiz I, Roberts E et al. A method for estimating the probability of adverse drug reactions. Clinical Pharmacology and Therapeutics. 1981; 30: 239-245.

12. Jain K, Chakrapani M, Smitha K.Acute cholestatic hepatitis along with agranulocytosis: A rare side effect of carbimazole. Annals of African Medicine. 2010; 9: 102-104.

13. Sadoul JL, Canivet B, Freychet B. Toxic hepatitis induced by antithyroid drugs: four cases including one with cross-reactivity between carbimazole and ben- zylthiouracil. Eur J Med. 1993; 2: 473–477.

14. Hu P, Xie W. Corticosteroid therapy in drug- induced liver injury: Pros and cons. Dig Dis. 2019; 20: 122-126.

Manuscript Information: Received: July 10, 2021; Accepted: September 03, 2021; Published: September 15, 2021

Authors Information: Darshana Meanger
Frankston Hospital Pharmacy Department, 2 Hastings Road, Frankston VIC 3199, Australia.

Citation: Meanger D. Suspected carbimazole induced acute cholestatic hepatitis: Case report. Open J Clin Med Case Rep. 2021; 1787.

About the Journal: Open Journal of Clinical and Medical Case Reports is an international, open access, peer reviewed Journal focusing exclusively on case reports covering all areas of clinical & medical sciences.
Visit the journal website at www.jclinmedcasereports.com
For reprints and other information, contact info@jclinmedcasereports.com