Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Metoprolol Induced Jaundice : A Case Report

Sneha Joy[1], Lakshmi R[1]*, Sujith Kumar S[2]

1 Department of Pharmacy Practice, St. Joseph's College of Pharmacy, Cherthala, Kerala, India - 688524.
2 Department of Cardiology, Lourdes Hospital, Post Graduate Institute of Medical Science &Research, Kochi, Kerala, India - 682012.

ARTICLE HISTORY

Received: 15.04.2022

Accepted: 14.05.2022

Available online: 30.03.2022

DOI:

10.5530/ajphs.2022.12.14

Keywords:

Beta blockers, drug induced liver injury, jaundice, metoprolol.

***Corresponding author:**

Email : lakshmir87@gmail.com

ABSTRACT

Drug induced liver injury is a common cause of acute liver failure. Beta blockers are a widely prescribed class of drugs; however, hepatotoxicity is a rare adverse effect. Here we report a case of 54 years old female patient with Metoprolol induced hyperbilirubinemia and transaminitis. Drug induced liver injury (DILI) is an important differential diagnosis in many patients in clinical hepatology. DILI is the leading cause of acute liver failure and is an important safety issue when new drugs are developed.

INTRODUCTION

Metoprolol is a cardio selective beta blocker used for treatment of angina pectoris, coronary artery disease, acute myocardial infarction and systemic hypertension. The usual dose of extended release preparation of metoprolol is 25-100 mg PO per day initially; may be increased at intervals of 1 week or longer; usual range, 50-100 mg/day; not to exceed 400 mg/day.[1] Common side effects include bradycardia, hypotension, fatigue, dizziness, depression and impotence.[2] Despite its wide scale use, metoprolol induced liver injury is exceedingly rare. [3] Metoprolol pharmacokinetics are significantly altered between genotype-inferred phenotypes of CYP2D6, but the impacts on the inter-patient clinical response have not been detailed. [4]

CASE REPORT

A 54 year old female patient with past history of acute coronary syndrome (ACS)- non ST elevated myocardial infarction (NSTEMI)/ acute pulmonary edema, hypertension, coronary artery disease (CAD) - triple vessel disease (TVD) with moderate-severe mitral valve regurgitation(MR), coronary artery bypass grafting (CABG) done with 5 grafts and mitral valve annuloplasty in 2020, presented with complaints of persisting hyperbilirubinemia and transaminitis which was persisting despite treatment from another hospital.

She was currently on Tab. Clopidogrel/Aspirin 75mg OD, Tab. Metoprolol succinate extended release 50mg BD, Tab. Ivabradine 5mg 1/2 BD, Tab. Torsemide10mg OD, Tab.Eplerenone 25mg OD, Tab.Sacubitril/Valsartan 50mg BD.

Prior to her admission with us, she was on treatment elsewhere for previous 2 weeks with complaints of recurrent jaundice. She was treated withInj. Acetylcysteine 600mg, Inj. Meropenem 1g, Inj. Pantoprazole 40mg, Tab. Metoprolol succinate 50mg, Tab.Eplerenone 25mg, Multivitamins, Tab. Tenofovir Alafenamide 25mg, Tab. Ursodeoxycholate 300mg, Tab.S-Adenosyl L-Methionine Disulfate Tosylate 400mg.

In that hospital, all other past medications except Tab.

Table 1 : Lab Investigations

	NORMAL RANGE	DAY 1	DAY 3	DAY 6	DAY 10	DAY 13	DAY 15
Total Bilirubin	<1.0mg/dL	14.9	15.7	14.6	10.2	6.4	5.8
Direct Bilirubin	<0.3mg/dL	13.4	14.6	14	9.8	6	5.5
ALP	35-104 U/L (F)	134			144		133
SGOT	Upto 40 U/L	470	470	294	233	121	113
SGPT	Upto 40 U/L	510	454	291	207	118	95

All viral markers were negative except ANTIHBV-CORE antibody.

HBV DNA was negative

Metoprolol succinate and Tab. Eplerenone were withheld. However, no improvement in clinical and biochemical parameters was observed and patient got discharged on demand.

After being admitted in our hospital, Tab. Eplerenone, Tab.Sacubitril/Valsartan and Tab.Torsemide were withheld and all other medications from the past were continued along with- Tab. Ursodeoxycholic acid 300mg 1-1-1**,** Tab.Digoxin 0.25mg 1/2 OD (5/7**)**, Tab.Furosemide 20mg 0-1-0**,** Tab.Ivabradine 7.5mg 1-0-1.

The lab investigations on the day of admission (Day 1) showed Total bilirubin: 14.9mg/dl [normal range: <1mg/dl]; Direct Bilirubin: 13.4mg/dl [normal range: <0.3mg/dl]; SGOT: 470 U/L [normal range: upto 40U/L]; SGPT: 510 U/L [normal range: upto 40U/L].

Next day, (Day 2), Tab. Metoprolol succinate 50mg BD was discontinued. In the following days, a significant and sharp decrease in elevated bilirubin levels and transaminase levels were observed. Lab values after 2 weeks (Day 15) *(Table 1)* showed Total bilirubin: 5.8mg/dl; Direct Bilirubin: 5.5mg/dl; SGOT: 113 U/L; SGPT: 95U/L; ALP- 133 U/L.The patient was diagnosed with ' *jaundice -likely to be of drug induced etiology'***.** Significant improvement was seen when Tab. Metoprolol succinate was stopped.

DISCUSSION

Hepatic injury due to Metoprolol therapy is quite rare and only a few reports have been published. In this case, delayed adverse effect of Metoprolol affecting quality of life is strongly evident. There were no underlying factors supporting the cause of liver injury. However, once the culprit drug was discontinued, the abnormally elevated liver function test reports exhibited a steady decline. In a case report by Hansen T and Fynne L, an 80-year-old woman developed cholestatic liver injury and jaundice after two months of treatment with Metoprolol succinate. There was no evidence of other underlying disease and liver function normalized in the following months after discontinuation of Metoprolol. [5] A similar scenario was observed in this case too.

Similarly, according to a case summary by Kathleen O Hagmeyer, a 40-year-old white man who had been taking carvedilol for the treatment of cardiomyopathy presented to the emergency department with pruritus over his entire body. Laboratory tests showed elevated serum transaminases. Carvedilol was discontinued and the liver function test results returned to normal in three weeks. Later the patient was started on metoprolol and within 10 days again developed pruritus, following which metoprolol was discontinued and subsequently liver function tests normalized. [6] The etiology of this adverse reaction remains unknown but suggests a possible adverse

Table 2 : Causality and Severity assessment of the ADR

Causality assessment	**Score**
WHO-UMC*Scale	Probable
Naranjo Scale	Probable – Score 5
Hartwig's severity assessment	Moderate - Level 4

*WHO-UMC - *World Health Organization- Upsala Monitoring Centre.*

reaction that may recur if the patient is switched to another β-adrenergic blocker.

Also, a study done using rabbits by Maysaa Banay Zubairi, to determine the hepatotoxicity associated with Metoprolol, resulted in histopathological changes of liver injury in all metoprolol-treated rabbit.[7]

A report by Natalie E. Mitchell, details the case of A 30-year-old man on carvedilol started 1 month prior to presentation. On admission, the patient was hypotensive and physical examination was notable for trace sublingual icterus with nontender hepatomegaly and no stigmata of chronic liver disease. Liver function tests were abnormally high. An evaluation for autoimmune and infectious causes of acute hepatitis was unrevealing. Carvedilol was withheld and over the next 3 following days, the patient's laboratory results significantly improved. Moreover, the patient was prescribed with Metoprolol in the follow-up as he was found hypertensive. This subsequently resulted in transaminitis and hyperbilirubinemia. However, once the drug was stopped, values went back to normal range. [8] Eventually this raises a question against the class of beta blockers as a whole rather than one specific agent. A drastic decrease of elevated hepatic parameters was observed in this case as well.

In a case report by Somnath Mondal, where atenolol (beta blocker) induced episodes of chronic and acute hepatotoxicity in 2 elderly hypertensive patients were studied, the 1st patient manifested liver dysfunction after 8 months of 50 mg daily atenolol therapy and in the 2nd patient liver dysfunction was revealed within 3 weeks of 100 mg daily atenolol intake. There was no underlying evidence of hepatotoxicityand was 'probably' drug (atenolol) induced. Withdrawal of the offending drug resulted in reversal of the diseased states. [9] This necessitates routine liver function tests in patients on beta blocker therapy. There is a coinciding differential diagnosis standing out to be common in the case being compared too.

Drug-induced hepatic injury is the most common reason for withdrawal of an approved drug. Knowledge of the commonly implicated agents is therefore important in diagnosis. [10]Causality assessment of ADRs is a method used for estimating the strength of relationship between drug(s) exposure and occurrence of adverse reaction(s).[11] The causality of the ADR seen in this case is assessed using World Health Organization- Uppsala monitoring centre(WHO-UMC) scale, Naranjo scale and Hartwigs severity assessment scale *(Table 2)*. Adverse drug reactions (ADRs) are animportant cause of morbidity, hospitalization and even death. Hence it is crucial to identify ADRs and to develop a causal relationship between the drug and the adverse event. Therefore a standardized assessment for the relationship-likelihood of case reports of suspected ADRs in a structured way, would aid in a reliable reproducible measurement of causality. [12]

CONCLUSION

Health care professionals should be aware of such rare ADRs, to improve quality of life of the patient by providing timely healthcare interventions thereby enhancing pharmacovigilance. By being aware of such rare adverse effects, we can reduce drug errors which aids not only in the reduction of treatment cost for the patients but also provides information to the doctors regarding the adverse effects associated with a particular drug. It allows drug marketing companies to be cautious of such effects and allows post marketing studies to focus more on suchareas.

FINANCIAL SUPPORT AND SPONSORSHIP

Nil

CONFLICTS OF INTEREST

There are no conflicts of interest.

REFERENCES

1. https://reference.medscape.com/drug/lopressor-toprol-xl-metoprolol-342360.
2. Philips C, Paramaguru R, Mahadevan P, Ravindranath J, Augustine P. Metoprolol-induced severe liver injury and successful management with therapeutic plasma exchange. Cureus. 2017 2;9(5).
3. Devarbhavi H. Drug-induced liver injury unique to India. Clinical Liver Disease. 2021;18(3):108.
4. Abboud G, Kaplowitz N. Drug-induced liver injury. Drug safety. 2007;30(4):277-94.
5. Hansen T, Fynne L. Jaundice and liver injury with cholestatic pattern after treatment with Metoprololsuccinat. Ugeskrift for Laeger. 2017 1;179(51).
6. Hagmeyer KO, Stein J. Hepatotoxicity associated with carvedilol. Annals of Pharmacotherapy. 2001;35(11):1364-6.
7. Zubairi MB. Metoprolol-induced liver injury and the hepatoprotective role of vitamin e in rabbits. Asian J Pharm Clin Res. 2019;12(4):145-8.
8. Mitchell NE, Harner W, Laczek J. β-Blocker-Induced Liver Injury: A Class Effect With Incidental Rechallenge. ACG Case Rep J. 2019 Nov 26;6(11):e00273.
9. Mondal S, Das S, Bandyopadhyay S, Datta A, Sardar S, Ghosal PK, Tripathi SK. Hepatotoxicity of atenolol therapy-A report of 2 cases. Journal of Acute Disease. 2013 1;2(3):246-9.
10. Mehta N, Ozick L, Gbadehan E. Drug-induced hepatotoxicity. State University of New-York Medical Journal. 2010 :26(7):51-7.
11. Smyth RL, Peak M, Turner MA, et al. ADRIC: Adverse Drug Reactions In Children a programme of research using mixed methods. NIHR Journals Library, Southampton (UK); 2014. PMID: 25642515.
12. Zaki S. Adverse drug reaction and causality assessment scales. Lung India. 2011 1;28(2):152.

Cite this article : Sneha Joy, Lakshmi R, Sujith Kumar S
Metoprolol Induced Jaundice : A Case Report
Asian J. Pharm. Hea. Sci.. 2022;12(1):2677-2680. DOI : 10.5530/ajphs.2022.12.14