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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Metoprolol. [Updated 2017 Jan 15].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Metoprolol

Updated: January 15, 2017.

OVERVIEW

Introduction

Metoprolol is a cardioselective beta-blocker that is widely used in the treatment of hypertension and angina pectoris. Metoprolol has been linked to rare cases of drug induced liver injury.

Background

Metoprolol (met" oh proe' lol) is considered a "selective" beta-adrenergic receptor blocker in that it has potent activity against beta-1 adrenergic receptors which are found in cardiac muscle, but has little or no activity against beta-2 adrenergic receptors found on bronchial and vascular smooth muscle. Metoprolol was approved for use in the United States in 1978 and is still widely used in the therapy of hypertension and angina pectoris, with more than 27 million prescriptions filled yearly. Metoprolol is also used to reduce the risk of cardiovascular mortality after acute myocardial infarction. Metoprolol is available in standard 50 and 100 mg tablets as well as 25, 50, 100 and 200 mg extended release tablets in generic forms as well as under the trade name of Lopressor and Toprol XL, and as a fixed combination with a hydrochlorothiazide as Lopressor HCT and Dutoprolol. Parenteral formulations for intravenous use are also available. The usual initial oral dose of metoprolol in adults is 100 mg daily in one or two divided doses daily, with subsequent adjustment based upon clinical response and tolerance, the usual maintenance dosage being 100 to 400 mg daily. The entended release forms are given in doses of 25 to 100 mg once daily. Common side effects include bradycardia, hypotension, fatigue, dizziness, depression, insomnia, memory loss and impotence. Beta-blockers are contraindicated in patients with asthma, bradycardia and heart failure and should be used cautiously in the elderly and in patients with diabetes. As with all beta-blockers, sudden withdrawal can trigger rebound hypertension.

Hepatotoxicity

Metoprolol therapy has been associated with a low rate of mild-to-moderate elevations of serum aminotransferase levels which are usually asymptomatic and transient and resolve even with continuation of therapy. A few instances of clinically apparent, acute liver injury attributable to metoprolol have been reported. In view of its wide scale use, metoprolol induced liver injury is exceedingly rare. The typical liver injury associated with beta-blockers has a latency to onset of 2 to 12 weeks and a hepatocellular pattern of liver enzyme. Symptoms of hypersensitivity (rash, fever, eosinophilia) and autoantibody formation have not been reported. Reported cases due to metoprolol have included cases of acute liver failure, but ultimately all were self-limiting and resolved fairly rapidly once once drug was stopped.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of drug induced liver injury from metoprolol is not known. The agent is metabolized in the liver via the cytochrome P450 (largely CYP 2D6). The rare instances of liver injury due to beta-blockers are likely to be idiosyncratic.

Outcome and Management

The severity of liver injury due to metoprolol ranges from mild serum aminotransferase elevations to mild acute hepatitis with jaundice. In large case series of acute liver failure due to medications, metoprolol has not been listed as a cause. Rechallenge has been reported to result in recurrence of injury and should be avoided. There is little information about cross reactivity among the beta-blockers to hepatic injury. Switching to another beta-blocker after metoprolol related acute liver injury should be done with caution and prospective monitoring.

References to the safety and potential hepatotoxicity of metoprolol are provided in the overview on Beta-Adrenergic Receptor Antagonists, last updated in June 2019.

Drug Class: Beta-Adrenergic Receptor Antagonists

CASE REPORT

Case 1. Metoprolol induced acute liver injury.

[Modified from: Larrey D, Henrion J, Heller F, Babany G, Degott C, Pessayre D, Benhamou JP. Metoprolol-induced hepatitis: rechallenge and drug oxidation phenotyping. Ann Intern Med 1988; 108:67-8. PubMed Citation]

A 56 year old woman developed fatigue and abdominal pains 2 weeks after starting metoprolol (50 mg daily) for migraine headaches. She had no previous history of liver disease, jaundice, alcohol abuse or risk factors for viral hepatitis. She had been treated with doxycycline, aspirin and a cough suppressant two weeks earlier for an acute bronchitis. She had no jaundice, fever or rash. Laboratory testing showed marked elevations in serum aminotransferase with minimal increase in alkaline phosphatase levels and normal serum bilirubin (Table). All liver tests had been normal in the past. Tests for hepatitis A and B and for autoantibodies were negative. An abdominal ultrasound was normal. A liver biopsy showed moderate steatosis and occasional ballooned hepatocyte without inflammation or fibrosis. Metoprolol was discontinued and she rapidly improved symptomatically. Within 3 weeks, liver tests were normal. Rechallenge led to a recurrence of liver injury.

Key Points

Medication:	Metoprolol (200 mg daily)
Pattern:	Hepatocellular (R=19)
Severity:	1+ (enzyme elevations and symptoms without jaundice)
Latency:	3 weeks
Recovery:	3 weeks
Other medications:	Doxycycline, aspirin and cough suppressant 3 weeks previously

Laboratory Values

Time After Starting	Weeks After Stopping	ALT* (U/L)	Alk P* (U/L)	GGT* (mg/dL)	Other
Pre		26	72	20	

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Time After Starting	Weeks After Stopping	ALT* (U/L)	Alk P* (U/L)	GGT* (mg/dL)	Other
Metoprolol (50 mg daily) given for 3 weeks					
3 weeks	0	1140	168	244	Bilirubin 0.7 mg/dL
	2 days	409	132	154	
4 weeks	5 days	171	108	110	
6 weeks	3 weeks	34	84	34	
Metoprolol (50 mg daily) restarted for 5 days					
5 days	0	66	144	Not done	
7 weeks	6 weeks	24	126	26	
Normal Values		**<40**	**<110**	**<50**	

* Converted from µKat/L.

Comment

This patient developed an anicteric acute hepatitis-like clinical picture three weeks after starting metoprolol. A history of exposure to doxycycline raised the issue of whether the acute injury was due to metoprolol or to a delayed reaction to doxycycline, and a rechallenge was performed a few weeks after recovery. Within a week, serum ALT and alkaline phosphatase levels had increased and metoprolol was stopped. The short latency period, mild acute hepatocellular injury and rapid recovery are typical of the liver injury reported with beta-blockers.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Metoprolol – Generic, Lopressor®, Toprol®

DRUG CLASS

Beta-Adrenergic Receptor Antagonists

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Metoprolol	51384-51-1	C15-H25-N-O3