



Labetalol

Updated: January 15, 2017.

OVERVIEW

Introduction

Labetalol is an antihypertensive agent with both alpha- and beta-adrenergic receptor blocking activity. Labetalol has been linked to several cases of clinically apparent drug induced liver disease, some of which have been severe and even fatal.

Background

Labetalol (la bayt' a lol) is a unique antihypertensive agent that has both alpha- and beta-adrenergic receptor blocking activity. The beta-blockade is nonselective, acting on both beta-1 and beta-2 adrenergic receptors. Beta-1 adrenergic blockade reduces the heart rate and myocardial contractility by slowing the AV conduction and suppressing automaticity. Beta-2 blockade affects peripheral vascular resistance and can cause bronchospasm and hypoglycemia. The alpha blockade is largely directed at the alpha-1 receptors and leads to relaxation of arterial smooth muscle and vasodilation. Labetalol was approved for use in the United States in 1984 and currently more than 2 million prescriptions are filled yearly. Current indications for labetalol are in the therapy of hypertension alone or in combination with other agents. Parenteral forms of labetalol are indicated for therapy of hypertensive emergencies, severe hypertension and pheochromocytoma. Labetalol is available in tablets of 100, 200 and 300 mg in generic formulations and under the trade name Trandate. Parenteral formulations for intravenous administration are also available. The typical oral dose of labetalol in adults is 100 mg twice daily initially with subsequent dose adjustments based upon clinical response and tolerance to a range of 200 to 1200 mg daily. Common side effects include bradycardia, hypotension, fatigue, dizziness, orthostatic hypotension, depression, memory loss, impotence, weight gain and diarrhea. As with all beta-blockers, sudden withdrawal can trigger rebound hypertension.

Hepatotoxicity

Labetalol therapy has been associated with mild-to-moderate elevations of serum aminotransferase levels in up to 8% of patients, a rate far higher than with other beta-blockers. These elevations, however, are usually transient, not associated with symptoms, and can resolve even with continuation of therapy. Idiosyncratic, clinically apparent liver injury from labetalol is rare, but several instances have been reported as isolated case reports as well as in case series. The liver injury typically arises after 4 to 16 weeks of therapy and the pattern of serum enzyme elevations is usually hepatocellular with an acute hepatitis-like onset and course. Immunoallergic features (rash, fever, eosinophilia) are uncommon as is autoantibody formation. While most cases resolve rapidly once labetalol is stopped, there have been several instances of acute liver failure and death or need for emergency

liver transplantation associated with labetalol use, particularly if there is a delay in its discontinuation. Labetalol is the beta-blocker with the highest apparent risk for causing clinically apparent liver injury.

Likelihood score: C (probable although rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism of labetalol hepatic injury is unknown, but it is believed to be due to metabolic idiosyncratic disposition of the agent, which is known to be extensively metabolized in the liver. There is little evidence for hypersensitivity as the cause of injury but it is likely to be due to an idiosyncratic rather than an intrinsic reaction.

Outcome and Management

Severity ranges from minimal and transient ALT elevations to clinically apparent acute hepatitis with jaundice to acute liver failure and death or need for liver transplantation. No instances of chronic hepatic injury or vanishing bile duct syndrome attributable to labetalol have been reported. Rechallenge is usually followed by recurrence of liver injury and should be avoided. There is little information on whether there is cross reactivity of the liver injury with other beta-blockers and patients who are switched to other agents should be carefully monitored.

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

Drug Class: [Beta-Adrenergic Receptor Antagonists](#)

CASE REPORT

Case 1. Labetalol induced acute liver injury.

[Modified from: Douglas DD, Yang RD, Jensen P, Thiele DL. Fatal labetalol-induced hepatic injury. *Am J Med* 1989; 87: 235-6. [PubMed Citation](#)]

A 63 year old woman developed nausea and dark urine approximately 3 months after starting labetalol (200 mg daily) for hypertension. She had no previous history of liver disease, jaundice, or risk factors for viral hepatitis. She was not taking any other medications and denied alcohol abuse. Laboratory testing showed serum bilirubin of 3.6 mg/dL and serum enzyme elevations typical of acute hepatitis (Table). She was negative for serological markers for hepatitis A and B. No diagnosis was made, and she was given another prescription for labetalol, but evidently stopped taking it on her own. Over the next few weeks she recovered, but was then lost to follow up for at least 6 months. When seen again, she had normal liver tests and was hypertensive. Labetalol was restarted. Two months later she developed anorexia and the following month presented with jaundice and serum bilirubin of 3.1 mg/dL. Labetalol was stopped and she was monitored closely. Tests for viral hepatitis were again negative as were routine autoantibodies. Abdominal ultrasound showed gallstones, but no evidence of biliary obstruction. There was mild ascites. Her liver condition worsened, and she developed progressive hepatic failure and died approximately 6 weeks after stopping labetalol for the second time. Autopsy showed a shrunken liver with extensive multilobular collapse with broad bands of fibrosis.

Key Points

Medication:	Labetalol (200 mg daily)
Pattern:	Hepatocellular (R=23)
Severity:	2+ (initially); 5+ (upon reexposure); fatal
Latency:	3 months

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Recovery:	1 month after initial episode
Other medications:	None

Laboratory Values

Weeks After Starting	Weeks After Stopping	AST* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
0 (pre)	0	11	92	0.3	
12	0	1253	205	3.6	Labetalol stopped
14	2 weeks	247	150	1.5	
16	4 weeks	37	111	0.4	
Patient was lost to follow up for 6 months					
0	0	13	117	0.3	Labetalol restarted
13	0	1007	172	3.1	
16	3	582	283	9.5	
17	4	402	315	11.3	
18	5	303	321	12.0	
19	6	225	266	16.8	Death from liver failure
Normal Values		<40	<110	<1.2	

* Converted from $\mu\text{Kat/L}$ and $\mu\text{mol/L}$.

Comment

This patient developed an acute hepatitis-like clinical picture 3 months after starting labetalol. Despite the lack of a suitable diagnosis, labetalol was not discontinued, although the patient evidently stopped taking it on her own and did not return for further management of her hypertension. When seen 6 months later, labetalol was restarted and a similar clinical syndrome arose 2 to 3 months later, but with a progressive and ultimately fatal course. Labetalol has been implicated in at least a dozen cases of acute liver injury with a predominantly hepatocellular pattern of enzyme elevations, a latency period of 2 to 16 weeks, and fatal outcome or emergency liver transplantation in several instances. In contrast, most cases of clinically apparent liver injury due to other beta-blockers have had a somewhat shorter latency period (2 to 12 weeks) and a milder course and outcome. Acute liver injury has also been described with dilevalol, which is one of the 4 stereoisomers of labetalol that has predominantly beta-adrenergic blocking activity.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Labetalol – Generic, Trandate®

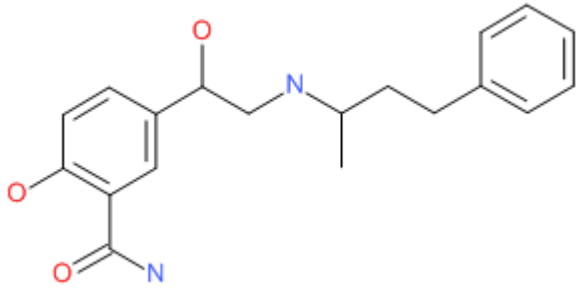
DRUG CLASS

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
Labetalol	36894-69-6	C ₁₉ H ₂₄ N ₂ O ₃	 <p>The chemical structure of Labetalol is shown. It consists of a central benzene ring with a nitro group (-NO₂) at the 3-position and a propyl chain at the 1-position. The propyl chain is attached to a nitrogen atom (N) which is also bonded to a methyl group and a phenyl ring. The nitrogen atom is also bonded to a carbonyl group (-C(=O)-) which is attached to a propyl chain. The carbonyl oxygen is red, and the nitrogen atom is blue.</p>