U.S. National Library of Medicine
National Center for Biotechnology Information

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-. Amoxicillin. [Updated 2016 Mar 30].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Amoxicillin

Updated: March 30, 2016.

OVERVIEW

Amoxicillin is considered a third generation or aminopenicillin and is one of the most commonly prescribed antibiotics. Amoxicillin and other aminopenicillins have been linked with idiosyncratic liver injury, but only rarely and in isolated case reports.

Background

Amoxicillin (a mox' i sil' in) is an orally available aminopenicillin that has been available in the United States since 1980, for which currently more than 50 million prescriptions are filled yearly. Amoxicillin is used to treat mild to moderate infections caused by susceptible agents, such as (but not limited to) Escherichia coli, Hemophilis influenzae, Listeria monocytogenesis, Neisseria gonorrhoeae, Proteus mirabilis, Salmonella, Shigella, Staphylococcus aureus (non-penicillinase producing), Staphyloccocus epidermidis, and Streptococcus pneumoniae. Amoxicillin is available in multiple generic formulations as tablets or capsules of 250, 500 and 875 mg and is usually given in doses of 250 to 850 mg every 8 hours for 7 to 14 days. Pediatric formulations in liquid suspension and chewable tablets are also available.

Hepatotoxicity

Rare instances of idiosyncratic liver injury have been reported in persons receiving the aminopenicillins including amoxicillin. Cases are characterized by a short latency period of a few days to as long as two weeks. The onset of liver injury can occur after the antibiotic is stopped. The serum enzyme pattern associated with aminopenicillin liver injury has included a hepatocellular pattern with marked elevations in ALT and AST, and minimal elevations in alkaline phosphatase and rapid recovery after withdrawal. In addition, cholestatic forms of hepatic injury with marked alkaline phosphatase elevations (as also seen with penicillin-induced liver injury) have also been described, some of which have been associated with prolonged cholestasis (Case 1). The onset of hepatic injury may be accompanied by signs or symptoms of hypersensitivity such as eosinophilia, rash and arthralgias, and in some cases is accompanied by toxic epidermal necrolysis or Stevens Johnson syndrome.

Likelihood score: B (highly likely but rare cause of clinically apparent liver injury).

Much more common than liver injury from amoxicillin alone is the typically cholestatic hepatitis that occurs after treatment with the combination of amoxicillin and clavulanate. Indeed, this combination is currently the most common cause of idiosyncratic acute liver injury in the United States, Europe and Australia. The injury, however, is usually attributed to the clavulanate rather than amoxicillin. The clinical features are similar but perhaps not completely the same. In cases of liver injury seeming due to amoxicillin, an extra effort should be made to make sure that it was not amoxicillin/clavulanate [Augmentin] that was taken.

Mechanism of Injury

The cause of the liver injury associated with amoxicillin use is probably hypersensitivity or allergy. Recurrence with reexposure is highly likely, but intentional rechallenge has not been described.

Outcome and Management

In the few cases that have been described, the majority of patients have recovered, although recovery has been slow in some cholestatic instances (2 to 6 months). Rare instances of acute liver failure and several cases of vanishing bile duct syndrome have been reported with aminopenicillin induced liver injury. Corticosteroids have often been used to treat the allergic manifestations of penicillin related immunoallergic hepatitis; while corticosteroid therapy may improve fever and rash promptly, their efficacy in ameliorating the accompanying liver disease has not been shown. Instances of recurrence of liver injury with unintentional reexposure to aminopenicillins and recurrence with exposure to cephalosporins have been reported. Patients with aminopenicillin induced hepatitis should avoid reexposure to other penicillins and should take cephalosporins with caution.

References to the hepatotoxicity and safety of amoxicillin are given in the Overview section on the aminopenicillins.

Drug Class: Antiinfective Agents, Aminopenicillins

Other Drugs in the Subclass, Aminopenicillins: Amoxicillin/Clavulanate, Ampicillin, Ampicillin-Sulbactam, Bacampicillin, Pivampicillin

CASE REPORT

Case 1. Cholestatic hepatitis due to amoxicillin therapy.

[Modified from Bolzan H, Spatola J, Castelletto R, Curciarello J. Cholestasis intrahepatica inducida por amoxicilina sola. Gastroenterol Hepatol 2000; 23: 237-9]

A 24 year old woman developed anorexia and weakness followed by dark urine and itching 5 days into a 10 day course of amoxicillin for pharyngitis and fever. Within days of finishing the 10 day course, a friend told her that she looked jaundiced. Ten days after stopping the antibiotic, she sought medical care for continuing jaundice and pruritus. Serum ALT, AST and alkaline phosphatase were only modestly elevated, but total serum bilirubin was 10.5 mg/dL with a direct fraction of 8.0 mg/dL. There was no eosinophilia, rash or fever. Tests for viral hepatitis and autoantibodies were negative. An ultrasound of the liver was normal. Her jaundice deepened, and she underwent endoscopic retrograde pancreato-cholangography (ERCP) which was also normal. A liver biopsy showed intrahepatic cholestasis, mild portal inflammation, but little hepatocellular injury, compatible with a resolving cholestatic hepatitis secondary to a medication. She had taken no other medications, herbals or over-the-counter products and had no previous history of liver disease or alcohol abuse.

Key Points

Medication:	Amoxicillin (1500 mg daily for 10 days)
Pattern:	Cholestatic (R=1.2)
Severity:	3+ (jaundice and hospitalization)
Latency:	Five days
Recovery:	Two months
Other medications:	None

Laboratory Values

Days After Starting	Days After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
		Amoxicillin 1500 mg/day for 10 days for pharyngitis			
20	10	30	314	10.5	AMA, ANA, pANCA negative
28	18	13	383	18.4	US normal
51	41	39	546	23.3	ERCP normal
58	48	13	476	4.0	Liver biopsy
82	72	12	222	0.7	
Normal Values		**<18**	**<240**	**<1.2**	

Comment

A dramatic example of somewhat prolonged cholestatic liver injury starting after a few days of amoxicillin therapy. The short latency, abrupt onset and cholestatic pattern of enzymes and clinical presentation are compatible with penicillin and aminopenicillin induced hepatic injury. Cases such as this are convincing, but extremely rare given the frequency with which amoxicillin is used. Patients with suspected amoxicillin induced liver injury should be questioned carefully about the antibiotic taken, making sure that it was not amoxicillin/clavulanate instead (a much more common cause of cholestatic liver injury). This patient should be cautioned against future exposure to penicillins.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Amoxicillin – Generic, Amoxil®

DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Amoxicillin	26787-78-0	C16-H19-N3-O5-S