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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-. Oxacillin. [Updated 2018 Jan 3].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Oxacillin

Updated: January 3, 2018.

OVERVIEW

Introduction

Oxacillin is a parenteral, second generation penicillin antibiotic that is used to treat moderate-to-severe, penicillinase-resistant staphylococcal infections. Oxacillin has been linked to rare instances of clinically apparent, idiosyncratic liver injury, but it more commonly causes transient elevations in serum aminotransferases without jaundice.

Background

Oxacillin (ox" a sil' in) is a second generation penicillin that is highly resistant to inactivation by penicillinases and is used to treat moderate-to-severe bacterial infections caused by penicillinase-producing bacteria, particularly staphylococcal infections. Oxacillin was approved for use in the United States in 1989 and is still in common use. Oxacillin is indicated for moderate-to-severe bacterial infections caused by sensitive agents including acute or chronic osteomyelitis and valvular endocarditis. Oxacillin is available in both oral and parenteral preparations in several generic formulations. Parenteral oxacillin is recommended in doses of 250 or 500 mg intramuscularly or intravenously every 4 to 6 hours daily for up to 1 to 8 weeks depending upon the type and severity of infection. Oral oxacillin is recommended in doses of 500 mg every 4 to 6 hours, but is now rarely used. Common side effects include fatigue, anxiety, dizziness, diarrhea, nausea, fever and hypersensitivity reactions.

Hepatotoxicity

Oxacillin has been linked to two forms of hepatotoxicity, first an acute and transient elevation in serum aminotransferase levels occurring with high doses of intravenous therapy; and second, a more prolonged, usually cholestatic, idiosyncratic liver injury that is similar to the hepatotoxicity of other second-generation penicillins such as dicloxacillin, flucloxacillin, and nafcillin.

High doses of intravenous oxacillin are commonly accompanied by elevations in serum ALT in the range of 2 to 20 times the upper limit of normal arising after 1 to 3 weeks of therapy. Alkaline phosphatase levels are only minimally elevated. Fever and nonspecific symptoms of abdominal pain and nausea can occur, but are often absent. Eosinophilia is present in some patients, but rash and arthralgias are uncommon. Serum aminotransferase levels rapidly fall into the normal range (in 1 to 2 weeks) with discontinuation of oxacillin or switch to lower doses, particularly in oral formulations. Jaundice does not occur. There appears to be no cross reactivity of this response with the natural penicillins, clindamycin or even nafcillin. Intravenous carbenicillin can cause a similar syndrome. This hepatotoxicity may be more common in HIV-positive than noninfected individuals.

In addition to the common syndrome of asymptomatic serum aminotransferase elevations during high dose intravenous therapy, oxacillin can also but rarely lead to a more prolonged usually cholestatic hepatitis that appears 1 to 6 weeks after starting therapy and may persist for weeks to months. This form of idiosyncratic liver injury is similar to that described with dicloxacillin and other second generation penicillins. Immunoallergic features of rash, fever and eosinophilia can occur, but are not prominent. Autoantibodies are not found. The liver injury can be prolonged, but generally resolves within 1 to 2 months of onset. Liver biopsy generally shows a cholestatic hepatitis with mixed inflammatory infiltrates.

Mechanism of Injury

The cause of ALT elevations during high dose oxacillin therapy is not known, but may be due to a direct but mild injury to the liver. Fever is common, and eosinophilia and rash can occur. Liver biopsy during these episodes generally shows mild, focal cell injury. The idiosyncratic reaction to oxacillin (and other related penicillins) is rarely accompanied by signs of hypersensitivity or allergy, but has some characteristics that suggest such a mechanism, such as the rapid reappearance of injury with reexposure, and an association with a history of penicillin allergy. Too few cases of oxacillin cholestatic injury have been reported to comment on possible HLA associations, such as the link to HLA-B*5701 which has been made to flucloxacillin.

Outcome and Management

The serum aminotransferase elevations that appear during high dose intravenous therapy with oxacillin are usually benign, asymptomatic and resolve rapidly with stopping therapy or switching to other forms of penicillinase-resistant penicillins. The cholestatic hepatitis that occurs very rarely can be symptomatic and prolonged, but has not been linked to acute, liver failure, chronic or permanent injury, or vanishing bile duct syndrome. Prednisone has been used to treat the cholestatic liver injury, but its effects are unclear while its side effects can be serious. Patients should be told to avoid reexposure to the penicillinase-resistant penicillins, including nafcillin and dicloxacillin.

References to oxacillin induced liver injury are given in the Overview section on Penicillinase-Resistant Penicillins.

Drug Class: Penicillin (Penicillinase-Resistant)

CASE REPORT

Case 1. Elevated aminotransferase levels during intravenous oxacillin therapy.

[Modified from a case in the database of the Drug-Induced Liver Injury Network]

A 52 year old man with multiple medical problems was treated with intravenous oxacillin for suspected osteomyelitis and was found to have elevations in ALT (104 U/L) and AST (82 U/L), with normal alkaline phosphatase and bilirubin levels when tested 7 days later. He had no symptoms that could be attributed to liver injury. Oxacillin was continued, but ALT levels continued to rise. Oxacillin was stopped after 6 weeks. Serum aminotransferase levels promptly fell and were near normal when he was discharged 2 weeks later. This patient also had multiple other medical problems including hypertension, diabetes, chronic hepatitis C, gastrointestinal reflux, chronic obstructive lung disease, depression and chronic radiculopathy for which he took many medications, none of which had been changed recently.

Key Points

Medication:	Oxacillin

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Pattern:	Hepatocellular (ALT elevations only)
Severity:	1+ (aminotransferase elevations without jaundice)
Latency:	One week
Recovery:	Almost complete within 2 weeks of discontinuation
Other medications:	Amlodipine, metoprolol, insulin, lansoprazole, levothyroxine, gabapentin, trimethoprim-sulfamethoxazole, diazepam, cyclobenzaprine, docusate, senna, iron, naproxen

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
- 1 week		16	54	0.7	Admitted with osteomyelitis
0	Oxacillin started: 2 grams iv every 6 hours				
7 days		104	79	0.6	
38 days		108	92	0.7	
40 days		306	98	0.7	
41 days	Oxacillin stopped				
43 days	2 days	318	99	0.7	
46 days	5 days	85			
49 days	9 days	57	85	0.6	
52 daus	12 days	59	80	0.6	
Normal Values		**<40**	**<115**	**<1.2**	

Comment

Oxacillin is well known to cause serum ALT elevations when given in high doses intravenously. The elevations are usually mild to moderate (<20 fold elevated) and appear after 4 to 20 days. Most patients are asymptomatic, but complaints of abdominal discomfort or fever may arise. Alkaline phosphatase and bilirubin levels remain normal. Patients usually tolerate other intravenous antibiotics (including nafcillin) without recurrence and the injury is self-limited, not leading to jaundice or severe liver disease even if oxacillin is continued. The presence of an underlying chronic hepatitis C complicates the interpretation of this case and many of the cases in the literature. However, serum ALT levels were normal before oxacillin was started and returned towards baseline once it was stopped, making it likely that the changes were due to the drug.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Oxacillin – Generic

DRUG CLASS

Penicillin (Penicillinase-Resistant)

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Oxacillin	66-79-5	C19-H19-N3-O5-S