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Nafcillin

Updated: January 3, 2018.

OVERVIEW

Introduction

Nafcillin is a parenteral, second generation penicillinase-resistant penicillin antibiotic used largely to treat moderate to severe staphylococcal infections. Nafcillin has been linked to rare occurrences of clinically apparent, idiosyncratic liver injury.

Background

Nafcillin (naf 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. Nafcillin was approved for use in the United States in 1970 and is still widely used to treat severe staphylococcal infections. To reduce development of drug-resistant bacteria, nafcillin is recommended to treat or prevent only infections that are proven or suspected to be caused by penicillinase-producing susceptible bacteria. Nafcillin is available in multiple generic forms as solutions or powders for intravenous or intramuscular use in 1 or 2 grams per vial. Oral formulations have been developed and are available in some countries. The recommended dose for parenteral use is 1 to 2 grams every 4 to 6 hours for 5 to 30 days depending upon the type and severity of infection. The oral dose is 500 mg to 1 gram four times daily. Common side effects include nausea, diarrhea, dyspepsia, headache, fatigue, urticaria, skin rash and allergic reactions.

Hepatotoxicity

The serum aminotransferase elevations that appear during high dose intravenous therapy with oxacillin do not appear to occur with high doses of nafcillin, and patients who develop elevated serum aminotransferase levels while on high dose oxacillin can be safety switched to intravenous nafcillin or other penicillin antibiotics. Only rare instances of clinically apparent hepatotoxicity have been linked to use of nafcillin. Typically, the injury has been a cholestatic hepatitis that arises 1 to 6 weeks after starting nafcillin and can be prolonged, but ultimately resolves. Rash, fever and eosinophilia are uncommon but can occur (Case 1). The injury is similar to that described with flucoxacillin and cloxacillin but is far less frequent with nafcillin. Autoantibodies are uncommon.

Mechanism of Injury

The idiosyncratic hepatotoxicity that occurs with nafcillin (and other related penicillins) is sometimes, but not always 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. Too few cases of nafcillin hepatotoxicity 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 cholestatic hepatitis due to nafcillin can be symptomatic and prolonged, but has not been linked to acute, liver failure, chronic or permanent injury, or vanishing bile duct syndrome (although these forms of liver injury have been described with the related antibiotic, flucloxacillin). Recovery can be expected in 4 to 12 weeks. Prednisone has been used to treat the cholestatic liver injury when it is symptomatic and prolonged, but its effects are unclear while its side effects can be serious. Patients with clinically apparent liver injury due to nafcillin should be told to avoid reexposure to the penicillinase-resistant penicillins, including dicloxacillin and oxacillin.

References

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

Drug Class: Penicillin (Penicillinase-Resistant)

CASE REPORT

Case 1. Cholestatic hepatitis caused by nafcillin.

[Modified from: Mazuryk H, Kastenberg D, Rubin R, Muñoz SJ. Cholestatic hepatitis associated with the use of nafcillin. Am J Gastroenterol 1993; 88: 1960-2. PubMed Citation]

An elderly lady with septic arthritis was treated with intravenous nafcillin for 3 weeks and developed skin rash and diarrhea (week 2), followed by jaundice and worsening pruritus (week 3). Nafcillin was stopped and ciprofloxacin begun. She had no previous history of jaundice or risk factors for liver disease. Initial laboratory data revealed a serum bilirubin of 5.7 mg/dL, with marked elevations in alkaline phosphatase and modest elevations in serum aminotransferase levels (Table). She had eosinophilia (21%). Tests for viral hepatitis and autoantibodies were negative. Imaging of the abdomen, liver and biliary tree showed no masses or evidence of obstruction. A liver biopsy was compatible with cholestatic hepatitis caused by a medication. Her recovery was slow and she had persistent jaundice and pruritus. Prednisone (20 mg/day) was started, and she recovered clinically and biochemically over the next few weeks allowing prednisone to be discontinued after a total of only 26 days.

Key Points

Medication:	Nafcillin
Pattern:	Cholestatic (R=0.4)
Severity:	3+ (jaundice and hospitalization)
Latency:	Two to three weeks
Recovery:	Complete in 2 months after a course of prednisone
Other medications:	Cefazolin, possibly others

Laboratory Values

Weeks After Starting	Weeks After Stopping	ALT (U/L)	Alk P* (U/L)	Bilirubin *(mg/dL)	Other
0		Normal	Normal	<1.0	Nafcilllin started
1			Normal	<1.0	
3	0		Normal	1.5	Nafcillin stopped

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Weeks After Starting	Weeks After Stopping	ALT (U/L)	Alk P* (U/L)	Bilirubin *(mg/dL)	Other
4	1		935	5.7	
4.5	1.5	117	1192	9.1	Hospitalized
5	2		1000	11.0	
6	3		1100	13.0	Prednisone started
7	4		350	3.5	
8	5		150	2.0	Prednisone stopped
12	9		Normal	Normal	
Normal Values		**<42**	**<150**	**<1.2**	

* Estimates made from Figure 1.

Comment

The abrupt onset of a cholestatic hepatitis within 3 to 4 weeks of starting nafcillin suggested that the drug was responsible. Liver biopsy confirmed intrahepatic cholestasis compatible with acute drug induced liver disease. While prednisone therapy appeared to have a beneficial effect, most cases of hepatic injury due to penicillinase-resistant penicillins follow a similar course and resolve without prednisone therapy. In this case, the dose and duration of prednisone therapy were kept to a minimum.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Nafcillin – 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
Nafcillin	147-52-4	C21-H22-N2-O5-S