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Dicloxacillin

Updated: January 3, 2018.

OVERVIEW

Introduction

Dicloxacillin is an oral, second generation penicillin antibiotic that is used to treat bacterial infections caused by penicillinase-resistant staphylococci. Dicloxacillin has been linked to rare instances of clinically apparent, idiosyncratic liver injury.

Background

Dicloxacillin (dye klox' a sil' in) is a second generation penicillin that is resistant to inactivation by penicillinases and is used to treat infections caused by penicillinase-producing bacteria. Like other penicillins, dicloxacillin is a beta lactam antibiotic that is believed to act by binding to the bacterial enzyme that is responsible for synthesizing peptidoglycans which are necessary for the intregity of the bacterial cell wall. Dicloxacillin was approved for use in the United States in 1968 and is still widely used to treat mild-to-moderate staphylococcal infections. To reduce development of drug resistant bacteria, dicloxacillin is recommended to treat or prevent only those infections that are proven or suspected to be caused by penicillinase-producing susceptible bacteria. Dicloxacillin is available in multiple generic forms as 250 and 500 mg capsules and as a suspension for pediatric use. The typical dose is 125 to 500 mg every 6 hours. Common side effects of dicloxacillin include nausea, diarrhea, stomatitis, skin rash and allergic reactions.

Hepatotoxicity

Dicloxacillin therapy has not been associated with serum enzyme elevations during treatment, but has been linked to rare instances of clinically apparent, cholestatic hepatitis. The typical time to onset is 1 to 6 weeks and the pattern of serum enzyme elevations is usually cholestatic, although cases with a mixed pattern have also been described (Case 1). The injury usually presents with jaundice and pruritus. Fever, rash and eosinophlia can occur, but are not prominent and autoantibodies are rarely detected. A similar pattern of injury occurs more frequently with flucloxacillin (also called floxacillin) and cloxacillin, oral isoxazolyl penicillins similar in structure and activity to dicloxacillin, but never approved for use or available in the United States. Similar cholestatic hepatitis arising 1 to 6 weeks after starting therapy occurs with other penicillins.

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

Mechanism of Injury

The cause of the idiosyncratic, cholestatic hepatitis following dicloxacillin therapy is not known. Allergic manifestations (rash, fever and eosinophilia) are not common and the liver injury is usually not accompanied by

signs or symptoms of penicillin hypersensitivity. However, the rapid recurrence of injury with reexposure suggests a hypersensitivity mechanism, perhaps in response to the beta lactam ring. Injury occurs more frequently in older patients. Too few cases of dicloxacillin hepatotoxicity have been reported to comment on possible HLA associations, such as the link to HLA-B*57:01 which has been made to flucloxacin.

Outcome and Management

In the few cases that have been described, cholestasis has been prolonged, but all patients recovered within 6 to 12 weeks without residual injury. Reexposure appears to be associated with recurrence of injury, often with a shortened latency period. The idiosyncratic liver injury from dicloxacillin has not been linked to acute liver failure, chronic injury or the vanishing bile duct syndrome (although these have been described with flucloxacillin). 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 oxacillin.

References to dicloxacillin-induced liver injury are given in the overview section on Penicillinase-Resistant Penicillins (updated 03 January 2018).

Drug Class: Penicillin (Penicillinase-Resistant)

CASE REPORT

Case 1. Cholestatic hepatitis caused by dicloxacillin.

[Modified from Kleinman MS, Presberg JE. J Clin Gastroenterol 1986; 8: 77-8]

A 56 year old man received a 5 day course of oral dicloxacillin (250 mg four times a day) and 2 weeks later developed gastrointestinal discomfort, followed by fever and then jaundice and itching. He had a history of hepatitis 22 years ago, but no other significant medical history and had no current risk factors for viral hepatitis. He took no other medications, had no allergies and drank little alcohol. On admission, his serum bilirubin was 3.8; that later rose (Table). Eosinophil counts were normal. Tests for acute hepatitis A and B were negative and abdominal ultrasound was normal. After several weeks, he began to improve and laboratory abnormalities returned to normal 14 weeks after he had started the course of antibiotics.

Key Points

Medication:	Dicloxacillin
Pattern:	Mixed (R=2.6)
Severity:	3+ (jaundice and hospitalization)
Latency:	Two to three weeks
Recovery:	Complete in 3 months
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	AST* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
0		Dicloxacillin given for 5 days			
3 weeks	2 weeks	225	218	3.8	Eosinophils=487
4 weeks	3 weeks	325	230	8.0	
5 weeks	4 weeks	50	150	10.3	

Table continued from previous page.

Time After Starting	Time After Stopping	AST* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
7 weeks	6 weeks	45	165	11.8	
8 weeks	7weeks	60		9.8	
9 weeks	8 weeks	110		5.0	
10weeks	9 weeks	80	170	3.2	
12 weeks	11 weeks	70	135	1.8	
13 weeks	12 weeks	65	120	1.1	
14 weeks	13 weeks	38	60	0.5	
Normal Values		**<40**	**<100**	**<1.2**	

* Estimates made from Figure 1.

Comment

The appearance of jaundice and itching 3 weeks after starting a 5 day course of dicloxacillin with a mixed pattern of serum enzyme elevations (later becoming more cholestatic) is fully compatible with dicloxacillin induced liver injury. Recovery was somewhat slow, but was complete by 3 months. Idiosyncratic drug induced liver injury from dicloxacillin is rare and only isolated case reports have been published. More common and with a similar pattern of injury are cases of flucloxacillin (which was approved and used in Australia and Europe, but not in the United States). Flucloxacillin hepatotoxicity is characterized by a latency of 2 to 6 weeks (often arising 1 to 3 weeks after stopping therapy), with a cholestatic or mixed enzyme pattern and recovery in 1 to 3 months. Fatalities and vanishing bile duct syndrome have been reported with flucloxacillin, but not with dicloxacillin despite the similarity of the injury caused, probably because dicloxacillin is just much less likely to lead to hepatic injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Dicloxacillin – Generic

DRUG CLASS

Penicillin (Penicillinase-Resistant)

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Dicloxacillin	3116-76-5	C19-H17-Cl2-N3-O5-S