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Penicillin G and V

Updated: January 16, 2014.

OVERVIEW

Introduction

Penicillin G and V are first generation penicillins that are used widely to treat infections due to susceptible organisms and have been linked rarely and only weakly with idiosyncratic liver injury.

Background

Penicillin G benzathine, potassium, procaine and sodium are currently available in the United States in parenteral formulations for intravenous or intramuscular use. Penicillin V potassium (also called phenoxymethyl penicillin) is a more acid stable and can be administered orally. Both Penicillin G and V are available in multiple generic formulations. The natural penicillins are indicated as therapy for mild-to-severe infections caused by susceptible organisms including (but not limited to) streptococcal infections and pneumonia, enterococcal and non-enterococcal endocarditis, diphtheria, anthrax, bacterial meningitis, Lyme disease, gonorrhea, syphilis, actinomycosis, botulism and others. The first generation penicillins are susceptible to inactivation by beta-lactamase, and resistance is relatively common. The usual doses of intravenous penicillin G are 300,000 to 4 million units every 6 to 8 hours. Benzathine penicillin G is given in a one time dose of 2.4 million units intramuscularly as therapy of primary or secondary syphilis, and as three weekly doses for syphilis of longer duration; it is also used as prophylaxis against rheumatic fever. Penicillin V is available in tablets of 250 and 500 mg and is usually given in doses of 250 to 500 mg every 6 to 8 hours for 7 to 20 days. It is also available as an oral solution. Side effects of penicillin G and V include nausea, diarrhea, gastrointestinal upset, headache, dizziness, rash and hypersensitivity reactions.

Hepatotoxicity

Rare instances of idiosyncratic liver injury have been reported in persons receiving the first generation penicillins. Many case reports predated availability of serologic testing for viral hepatitis and many described patients with multiple reasons for having liver disease (such as sepsis) and who were receiving other potentially hepatotoxic agents. Three distinct forms of liver injury can occur with the first generation penicillins: (1) transient, asymptomatic elevations in serum aminotransferase levels with prolonged high doses of parenteral penicillin, (2) minor liver injury associated with severe hypersensitivity reactions, and (3) idiosyncratic, delayed cholestatic hepatitis. These three forms of injury probably occur with all forms of penicillin, some being more common with one form of penicillin than another.

High doses of intravenous and intramusclar penicillin can be associated with serum aminotransferase elevations that are usually asymptomatic and resolve rapidly with stopping therapy or switching to another antibiotic (Case 1). Jaundice and elevations in alkaline phosphatase are usually absent or mild. This type of hepatotoxicity is most

common with oxacillin and carbenicillin, but can occur with parenteral forms of the first generation penicillins as well.

Patients with severe hypersensitivity reactions to penicillin, such as Stevens-Johnson syndrome or anaphylaxis, may have an accompanying liver injury and jaundice, but it is not clear whether this represents true penicillin hepatotoxicity or a complication of hyperthermia, shock and generalized immune reactivity. Generalized allergic reactions to penicillin may be accompanied by granulomas in the liver, spleen and kidney, but are usually without evidence of specific hepatitis injury. Virtually all of the penicillins are associated with hypersensitivity reactions, but liver injury is usually overshadowed by the allergic complications (rash, fever, anaphylaxis).

Finally, isolated case reports have shown that the first generation penicillins can cause a delayed cholestatic hepatitis. Symptoms of nausea, abdominal discomfort, jaundice and pruritus generally arise 1 to 4 weeks after starting therapy, and often a few days or weeks after completing a course. The serum enzyme pattern is usually cholestatic, but may be hepatocellular if tested soon after onset. Immunoallergic features are common, but autoantibody formation is rare. Most cases are mild-to-moderate in severity and resolve rapidly (Case 2). This delayed form of idiosyncratic cholestatic hepatitis is typical of many penicillins, varying in frequency with the specific form. Idiosyncratic, cholestatic hepatitis is quite rare with the natural penicillins, more common with certain broad spectrum penicillins (cloxacillin, flucloxacillin) and is most common with amoxicillin with clavulanic acid.

Mechanism of Injury

The cause of the idiosyncratic, cholestatic liver injury associated with penicillin is probably hypersensitivity or allergy. No cases of rechallenge or reexposure have been reported. The serum aminotransferase elevations that occur with high doses of parenteral penicillin are likely due to direct hepatotoxicity.

Outcome and Management

The asymptomatic rise in serum aminotransferase levels that occurs with high dose penicillin therapy usually resolves rapidly once penicillin is stopped. These patients may tolerate another form of penicillin without recurrence. In the few cases of cholestatic hepatitis that have been described with the first generation penicillins, patients have recovered although recovery was slow in some instances (2 to 6 months). Fatal cases of penicillin associated liver injury have been described, but usually in association with severe allergic reactions such as Stevens-Johnson syndrome in which shock and ischemic hepatitis may have contributed to the outcome. Patients with idiosyncratic liver injury attributed to penicillin should not be reexposed to other penicillins.

References

References to hepatotoxicity of penicillin G and V are provided in the Overview of the First Generation Penicillins.

Drug Class: Antiinfective Agents, Penicillins (First Generation)

CASE REPORTS

Case 1. Serum aminotransferase elevations attributed to penicillin therapy.

[Modified from: Bauer TM, Bircher AJ. Drug-induced hepatocellular liver injury due to benzylpenicillin with evidence of lymphocyte sensitization. J Hepatol 1997; 26: 429-32. PubMed Citation}

A 54 year old man with pyogenic vertebral spondylitis developed rising serum aminotransferase levels approximately 3 weeks after starting a course of high dose intravenous benzylpenicillin. On admission, and before starting penicillin, he was febrile and complained of fatigue and low back pain. He had no history of alcohol abuse or previous allergic reactions to medications or liver disease. Serum ALT was elevated (Table), but levels fell into the normal range as the infection came under control with antibiotic therapy. After 4 weeks of penicillin therapy, serum ALT levels were found to be elevated in association with marked eosinophilia, but the patient had no symptoms of liver disease and was not jaundiced. Penicillin was continued for another two weeks, but when ALT levels continued to rise antibiotic therapy was changed to a cephalosporin. Serum aminotransferase levels and eosinophilia promptly resolved. Tests for hepatitis A, B and C were negative as were autoantibodies. The patient received several other medications and underwent minor surgery under propofol and alfentanil anesthesia a few days before the onset of the marked ALT elevations. In follow up, he recovered from the infection and had normal liver tests and repeat viral serology was negative.

Key Points

Medication:	Penicillin G benzathine (5 MU iv every 6 hours)
Pattern:	Hepatocellular (no alkaline phosphatase elevations)
Severity:	1+ (serum enzyme elevations without jaundice)
Latency:	3 weeks
Recovery:	Somewhat more than 3 weeks
Other medications:	Ibuprofen, ranitidine, low molecular weight heparin, chloral hydrate, diazepam and, on day 21, propofol and alfentanil anesthesia.

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P (U/L)	Bilirubin (mg/dL)**	Other
Pre	Pre	106	159	0.6	0.2% eosinophils
Benzylpenicillin (5 MU iv q 6 hr) started for Streptococcal pyogenic vertebral spondylitis					
5 days		40			
11 days		30	Normal		
17 days		25			
21 days		25			
General anesthesia with propofol and alfentanil for minor surgery (~ day 26)					
29 days		423	101	0.5	13% eosinophils
32 days		570			
35 days		610			
40 days	0	680			Penicillin stopped and Ceftriaxone started
45 days	4 days	600			
48 days	7 days	400			
56 days	15 days	230			
2 months	1 month	160			
Normal Values		**<37**	**<109**	**<1.2**	

*Estimates made from Figure 1. **Bilirubin converted from μmol (1 mg/dL = 17.1 μmol/L).

Comment

The asymptomatic rise in serum aminotransferase levels after 4 weeks of high dose penicillin therapy and their fall once it was stopped is suggestive of penicillin induced direct hepatic injury. The onset and pattern of hepatic injury resembled the common hepatotoxicity of oxacillin with asymptomatic rises in aminotransferases that decrease rapidly when stopped and are often associated with eosinophilia. In the current case, other diagnoses could not be completely ruled out such as drug induced liver disease from other medications (low molecular weight heparin) or an underlying condition that led to the baseline, pre-penicillin ALT elevations.

Case 2. Cholestatic hepatitis attributed to penicillin therapy.

[Modified from: Girard JP, Haenni B, Bergoz R, Kapanci Y, Cruchaud A. Lupoid hepatitis following administration of penicillin. Case report and immunological studies. Helv Med Acta 1967; 34: 23-35. PubMed Citation]

A 19 year old man took one tablet of penicillin for a sore throat and developed headache and nausea followed over the next two days by fever and jaundice. He had received two injections of Penicillin G one month previously without incident. He denied previous history of liver disease or penicillin allergy and had no risk factors for viral hepatitis. On admission to the hospital, he was febrile, jaundiced and had a generalized skin rash. He had tender hepatomegaly and splenic enlargement as well as cervical adenopathy. Blood tests showed elevations in serum bilirubin, but mild increases in serum enzymes. He recovered rapidly from the symptoms of fever and prostation, but remained jaundiced for several months. Three liver biopsies were performed; the initial biopsy showed cholestasis with moderate lymphocyte and eosinophil infiltrations; the follow up biopsies showed gradual improvement. During follow up, his serum bilirubin levels were intermittently elevated and alkaline phosphatase levels were minimally increased, but he was asymptomatic, afebrile and had normal ALT levels.

Key Points

Medication:	Oral penicillin (200,000 U)
Pattern:	Mixed (R=2.1)
Severity:	3+ (jaundice and hospitalization)
Latency:	2 days
Recovery:	More than 3 months
Other medications:	None mentioned

Laboratory Values

Time After Starting	Time After Stopping	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Took a single table of penicillin for sore throat					
4 days	3 days	96	105	7.3	Fever to 40 deg C
8 days	7 days	48	82	3.6	
25 days	24 days	31	51	3.1	
2 months	2 months	17	58	1.9	
3 months	3 months	9	56	0.8	
5 months	5 months	9	69	0.6	
11 months	11 months	9	68	1.9	
Normal Values		**1-17**	**10-40**	**<1.2**	

Comment

A dramatic example of immunoallergic, cholestatic hepatitis arising within days of taking a single dose of penicillin. The pattern of serum enzyme elevations and liver histology was fully supportive of a drug induced liver injury and there was no evidence of other forms of liver disease (although no imaging of the gallbladder was mentioned). The onset with fever and rash suggests hypersensitivity and are typical if not universal with penicillin associated acute liver injury. The short latency (4 days) is typical of cases with reexposure to the responsible agent; with first exposure, the latency is typically 2 to 4 weeks.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Various Generic

DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

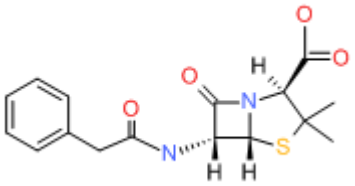
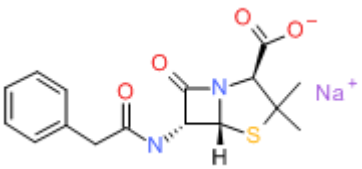
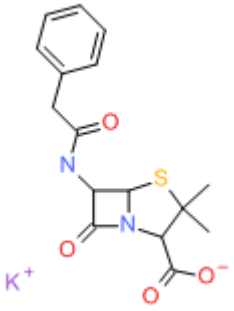
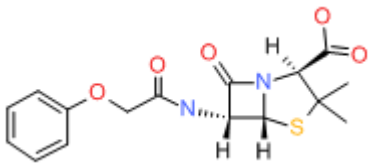
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Penicillin G (Benzylpenicillin)	61-33-6	C16-H18-N2-O4-S	
Penicillin G Sodium	69-57-8	C16-H18-N2-O4-S	
Penicillin G Potassium	113-98-4	C16-H18-N2-O4-S.K	

Table continued from previous page.

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Penicillin V	87-08-1	C16-H18-N2-O5-S	
Penicillin V Potassium	132-98-9	C16-H17-K-N2-O5-S C16-H17-N2-O5-S.K C16-H18-N2-O5-S.K