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Penicillins (1st Generation)

Updated: January 16, 2014.

OVERVIEW

The natural or "first generation" penicillins are bactericidal antibiotics naturally derived from the mold, Penicillium chrysogenum. Their basic structure includes a thiazolidine ring connected to a beta-lactam ring with a variable side chain. Penicillins bind to bacterial proteins and inhibit synthesis of the bacterial cell wall, causing cell lysis particularly in rapidly growing organisms. Bacterial resistance to penicillin is usually mediated by beta-lactamase, an enzyme which destroys the beta-lactam ring of penicillin, rendering it inactive. Penicillin was introduced into medicine in the 1940's and ushered in the modern era of antibiotic therapy, ending the dominance of many diseases that had been major causes of morbidity and mortality. At present, several first generation penicillins are available in the United States: the benzathine, potassium, procaine and sodium salts of penicillin G and the orally available penicillin V potassium. These agents are discussed together as they are rare causes of hepatotoxicity and can be considered similar enough to be grouped together.

Other drugs within this class:

Penicillin G

Penicillin G Benzathine

Penicillin V

CHEMICAL FORMULAS AND STRUCTURES

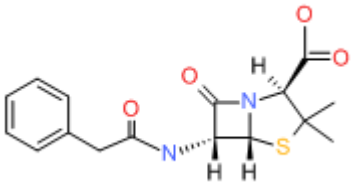
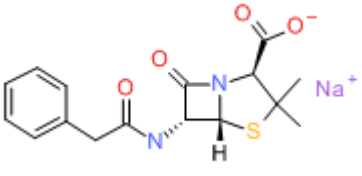
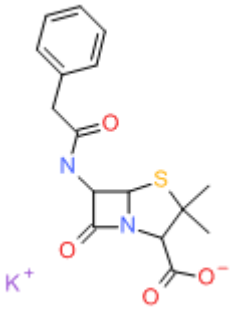
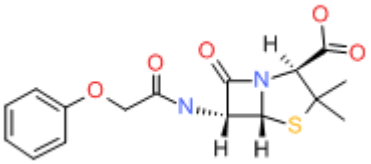
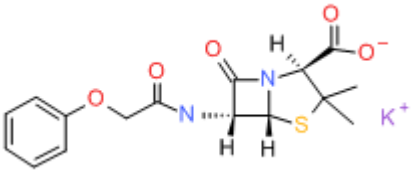
DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Penicillin G (Benzylpenicillin)	61-33-6	C16-H18-N2-O4-S	
Penicillin G Sodium	69-57-8	C16-H18-N2-O4-S	

Table continued from previous page.

Penicillin G Potassium	113-98-4	C16-H18-N2-O4-S.K	
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	

ANNOTATED BIBLIOGRAPHY

References updated: 16 January 2014

Zimmerman HJ. Penicillins. In, Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. 2nd Ed. Philadelphia: Lippincott, 1999. p. 595-6.

(Expert review of penicillins and liver injury published in 1999; liver injury from penicillin is rare and usually associated with allergic reactions).

Moseley RH. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 463-82.

(Review of hepatotoxicity of antibiotics mentions that liver injury from the natural penicillins is rare, with both hepatocellular and cholestatic patterns being described).

Petri WA Jr. Penicillins, cephalosporins, and other β-lactam antibiotics. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1477-1504.

(Textbook of pharmacology and therapeutics).

Howells L, Kerns JDO. Hepatitis after penicillin injection. Lancet 1946; 1: 51-2.

(Outbreak of hepatitis after penicillin injections at venereal disease centers, arising 62 to 157 days afterwards with jaundice lasting 10-44 days; "As a routine each syringe is used for about 5 patients, the syringe being boiled frequently, but not necesarily between each case"; an unfortunate example of iatrogenic spread of hepatitis B).

Rabinovitch J, Snitkoff M. Acute exfoliative dermatitis and death following penicillin therapy. JAMA 1948; 138: 496-8. PubMed PMID: 18884886.

(72 year old woman developed generalized pruritus 7 days after completing an 11 day course of penicillin with fever, confluent exfolative rash, progressive abdominal pain, pneumonia, jaundice, coma and death; difficult to say whether jaundice was due to penicillin reaction vs vascular collapse and sepsis).

Felder SL, Felder L. Unusual reaction to penicillin. J Am Med Assoc 1950; 143: 361-2. PubMed PMID: 15415270.

(53 year old man developed rash 10 days after starting intramuscular procaine penicillin with fever, giant urticaria, lymphadenopathy and Alk P 3 times ULN, but no jaundice, resolving within 2 weeks of stopping with conservative therapy using epinephrine and antihistamines).

Waugh D. Myocarditis, arteritis, and focal hepatic, splenic, and renal granulomas apparently due to penicillin sensitivity. Am J Pathol 1952; 28: 437-47. PubMed PMID: 14923834.

(60 year old man with multiple medical problems developed fever, eosinophilia and rash within hours of a penicillin injection requiring corticosteroids; sudden unexplained death 13 days later allowed for autopsy that showed interstitial myocarditis and arteritis with granulomas in liver, kidney and spleen, but no hepatitis or cholestasis).

Murphy ES, Mireles M. Shock, liver necrosis, and death after penicillin injection. Arch Pathol 1962; 73: 355-62. PubMed PMID: 14477414.

(66 year old woman with known penicillin allergy, given penicillin after surgery developed anaphylaxis with shock and diffuse bleeding, developing jaundice and dying several days later; autopsy showed centrolobular necrosis; unclear whether jaundice due to penicillin hepatotoxicity or ischemic liver injury, the autopsy favoring the later).

Vardivia-Barriga V, Feldman A, Orellana J. Generalized hypersensitivity with hepatitis and jaundice after the use of penicillin and streptomycin. Gastroenterology 1963; 45: 114-7. PubMed PMID: 14046304.

(25 year old woman had acute allergic reaction after a injection of penicillin and streptomycin becoming jaundiced within 2 days; other diagnoses could not be excluded in this early case).

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 PMID: 4873914.

(19 year old man developed fever, nausea and abdominal pain a few hours after a single dose of oral penicillin with jaundice arising 2 days later with prolonged course, many in vitro assays for penicillin allergy and three liver biopsies done; clearly not "lupoid" hepatitis, but reasonably convincing case of drug induced prolonged cholestasis and possibly vanishing bile duct syndrome: Case 2).

Knirsch AK, Gralla EJ. Abnormal serum transaminase levels after parenteral ampicillin and carbenicillin administration. N Engl J Med 1970; 282: 1081-2. PubMed PMID: 5438429.

(Elevations in AST and CPK but not ALT after intramuscular injections of ampicillin and carbenicillin, not with cephalosporins or saline; thus representing muscle, not liver injury).

Goldstein LI, Ishak KG. Hepatic injury associated with penicillin therapy. Arch Pathol 1974; 98: 114-7. PubMed PMID: 4366005.

(Often cited paper describes 42 year old man who developed fever, arthralgias and mild alkaline phosphatase elevations [3 times ULN] with normal bilirubin [0.7 mg/dL] and ALT [40 U/L] 8 days after starting penicillin; a liver biopsy showed lobular unrest and mild hepatocyte injury).

McArthur JE, Dyment PG. Stevens-Johnson syndrome with hepatitis following therapy with ampicillin and cephalexin. N Z Med J 1975; 81: 390-2. PubMed PMID: 1057088.

(Stevens-Johnson syndrome in a 9 month old child given ampicillin [rash] and cephalexin, found to have a hepatocellular injury with bilirubin of 13 mg/dL, resolving on prednisone).

Beeley L, Gourevitch A, Kendall MJ. Jaundice after oral penicillin. Lancet 1976; 2: 1297. PubMed PMID: 63763.

(Letter describing 36 year old woman who developed fever, rash and prostration after 48 hours of penicillin V [250 mg four times a day] with bilirubin 6.1 mg/dL, AST 62 U/L, alkaline phosphatase 40 U/L, resolving within 3 weeks).

Paine TF Jr. Updating the side effects of the penicillins. Zhonghua Min Guo Wei Sheng Wu Xue Za Zhi 1978; 11: 104-9. PubMed PMID: 581569.

(Review article mentions liver injury with high dose intravenous penicillins).

Williams CN, Malatjalian DA. Severe penicillin-induced cholestasis in a 91-year-old woman. Dig Dis Sci 1981; 26: 470-3. PubMed PMID: 7249889.

(91 year old woman received cloxacillin for 9 days followed by penicillin G for 5 days, developing symptoms by day 3 with subsequent cholestatic hepatitis, cloxacillin being the more likely culprit).

Roberts J, Bianco MM, Fine J. Fatal anaphylactic reaction to oral penicillin: report of case. J Am Dent Assoc 1985; 110: 505-6. PubMed PMID: 3923075.

(30 year old woman developed anaphylaxis and cardiopulmonary arrest within few minutes of single dose of Pen V; attempts at resuscitation failed; no mention of liver injury. Penicillin accounts for 75% of anaphylactic deaths, 400-800/year, and anaphylaxis incidence is 1-4/1000 exposures).

Friis H, Andreasen PB. Drug-induced hepatic injury: an analysis of 1100 cases reported to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. J Intern Med 1992; 232: 133-8. PubMed PMID: 1506809.

(Adverse drug reaction reports in Denmark between 1978 and 1987; no mention of penicillins).

Oñate J, Montejo M, Aguirrebengoa K, Ruiz-Irastorza G, González de Zárate P, Aguirre C. Hepatotoxicity associated with penicillin V therapy. Clin Infect Dis 1995; 20: 474-5. PubMed PMID: 7742464.

(67 year old woman with actinomycosis was given penicillin G and then penicillin V; 10 days after starting she developed abdominal pain and at 15 days had abnormal liver tests [bilirubin 1.3 mg/dL, ALT 3073 U/L, Alk P normal], resolving after being switched to erythromycin).

Pillans PI. Drug associated hepatic reactions in New Zealand: 21 years experience. N Z Med J 1996; 109: 315-9. PubMed PMID: 8816722.

(Adverse drug reaction reports in identified 943 cases of liver injury over 21 year period in New Zealand; no mention of penicillin).

Bauer TM, Bircher AJ. Drug-induced hepatocellular liver injury due to benzylpenicillin with evidence of lymphocyte sensitization. J Hepatol 1997; 26: 429-32. PubMed PMID: 9059967.

(54 year old man with osteomyelitis was started on benzylpenicillin [5 MU intravenously every 6 hours] and after 21 days developed eosinophilia and elevated liver tests [bilirubin 0.5 mg/dL, ALT 423 U/L, Alk P 101 U/L], resolving with stopping penicillin; on follow up he had positive lymphocyte stimulation test to benzylpenicillin, negative to amoxicillin and cephalosporin).

Perman E. [A severe adverse effect of penicillin on the liver. Drug insurance covered the compensation] Lakartidningen 1998; 95: 3536. Swedish. PubMed PMID: 9742846.

(Two cases of jaundice due to flucoxacillin).

Andrade RJ, Guilarte J, Salmerón FJ, Lucena MI, Bellot V. Benzylpenicillin-induced prolonged cholestasis. Ann Pharmacother 2001; 35: 783-4. PubMed PMID: 11409000.

(28 year old woman with Streptococcal pharyngitis was given a single intramuscular injection of benzylpenicillin and developed abdominal pain, fever and jaundice 5 days later [bilirubin 7.6 mg/dL, ALT 357 U/L, Alk P 844 U/L, 1% eosinophils]; jaundice resolved rapidly, but liver enzymes were elevated for 18 months).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-101. PubMed PMID: 16165719.

(Survey of all cases of drug induced liver injury with fatal outcome from Swedish Adverse Drug Reporting system from 1966-2002; one case was attributed to Penicillin V, but no details given).

Andrade RJ, Lucena MI, Kaplowitz N, Garcia-Munoz B, Borraz Y, Pachkoria K, Carcia-Cortes M, et al. Outcome of acute idiosyncratic drug-induced liver injury: Long-term follow-up in a hepatotoxicity registry. Hepatology 2006; 44: 1581-8. PubMed PMID: 17133470.

(Clinical description of 28 patients with "chronic" outcome of drug induced liver injury included one case attributed to amoxicillin with jaundice 5 days after a 1 day course with severe hypersensitivity; 6 months later, only GGT was elevated ~1.4 fold).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, antimicrobials accounted for 45% of cases with 23 single agent cases due to amoxicillin/clavulanate, 13 nitrofurantoin, 10 fluoroquinolones, 9 macrolides, 9 sulfonamides, 5 cephalosporins, 3 oxacillin, 2 doxycycline, 2 amoxicillin, and one each for gentamicin, imipenem, and clindamycin, but none from first generation penicillins).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury including 66 due to antimicrobial agents, but only two due to amoxicillin and none attributed to natural penicillins).

Leitner JM, Graninger W, Thalhammer F. Hepatotoxicity of antibacterials: pathomechanisms and clinical data. Infection 2010; J38: 3-11. PubMed PMID: 20107858.

(Review of mechanisms of liver injury due to antibacterial agents; first generation penicillins are not discussed).

Ferrajolo C, Capuano A, Verhamme KMC, Schuemie M, Rossi F, Stricker BH, Sturkenboom CJM. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. BJCP 2010; 70: 721-8. PubMed PMID: 21039766.

(Among 624,673 adverse drug reports in children in a worldwide pharmacovigilance database, 6595 [1%] were for hepatic injury and antibacterials accounted for 11%, those with the highest adjusted odds ratios being aztreonam, erythromycin, ceftiaxone and minocycline; no mention of penicillins).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. (In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, including 15 due to amoxicillin/clavulanate, 1 from dicloxacillin [2nd generation] and 1 from phenoxymethylpenicillin [1st generation], the latter two cases being anicteric). PubMed PMID: 23419359.