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Piperacillin-Tazobactam

Updated: January 16, 2014.

OVERVIEW

Introduction

Piperacillin is an extended-spectrum ureidopenicillin which, when combined with the beta-lactamase inhibitor tazobactam, is used to treat moderate-to-severe infectious due to susceptible organisms including lactamase producing penicillin-resistant bacteria. Piperacillin-tazobactam has been linked with idiosyncratic liver injury, but only rarely and as isolated case reports.

Background

Piperacillin-tazobactam is the combination of a fourth generation, extended-spectrum penicillin and a beta-lactamase inhibitor that is used for moderate-to-severe infections caused by susceptible agents, such as (but not limited to) Escherichia coli, many Bacteroides and Klebsiella species, Staphylococcus aureus, and Haemophilus influenzae. The combination of piperacillin with tazobactam provides broad activity against beta-lactamase producing penicillin-resistant bacterial species. This combination was approved for use in the United States in 1985 and is generally reserved for severe infections requiring parenteral therapy. Piperacillin-tazobactam is available in parenteral form for intravenous use in generic forms and under the trade name Zosyn. Recommended doses are 3 to 4.5 grams of piperacillin with 0.375 to 0.5 grams of tazobactam every 6 to 8 hours for 7 to 14 days. Common side effects include headache, dizziness, nausea, diarrhea, constipation, skin rash and hypersensitivity reactions.

Hepatotoxicity

In large clinical trials, ALT elevations were reported in 6% to 15% and bilirubin elevations in 3 to 5% of patients receiving piperacillin-tazobactam, with considerably lower rates in patients receiving comparator antibiotics (such as imipenim-cilastatin) and lower rates reported with piperacillin alone. These abnormalities were reported to resolve quickly with stopping therapy. Rare instances of idiosyncratic liver injury have been reported in persons receiving the piperacillin without tazobactam. This combination does not appear to increase the risk of cholestatic hepatitis that might be caused by piperacillin or other penicillins and is not associated with the common delayed cholestatic hepatitis that it typical of clavulanate combinations with penicillins (amoxicillin or ticarcillin).

Mechanism of Injury

The cause of the liver injury associated with piperacillin use is probably hypersensitivity or allergy. Cases of reoccurrence on reexposure have been reported.

Outcome and Management

In the few cases that have been described, patients have recovered promptly. Patients with piperacillin induced hepatitis should avoid reexposure to other penicillins and should take cephalosporins with caution.

Drug Class: Antiinfective Agents, Penicillins (Fourth Generation)

Other Drugs in the Class: Piperacillin, Ticarcillin, Ticarcillin-Calvulanate

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Piperacillin-Tazobactam – Generic, Zosyn®

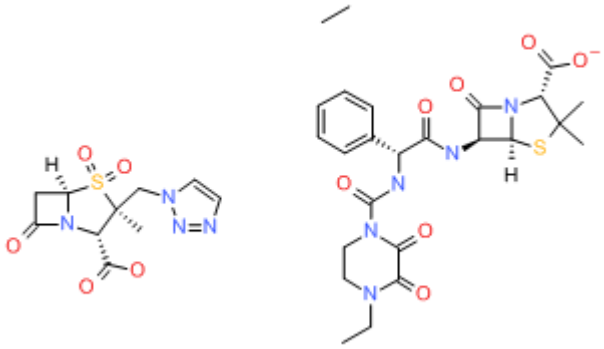
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Piperacillin-Tazobactam	157044-21-8	C23-H27-N5-O7-S. C10-H12-N4-O5-S.Na	

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; piperacillin and ticarcillin are listed as associated with elevations in aminotransferase levels, but without reports of clinically apparent liver injury except with ticarcillin/clavulanate).

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 the extended-spectrum penicillins have rarely been associated with clinically apparent liver injury).

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).

Winston DJ, Murphy W, Young LS, Hewitt WL. Piperacillin therapy for serious bacterial infections. Am J Med 1980; 69: 255-61. PubMed PMID: 6447455.

(Piperacillin was given to 59 patients with severe infections; eosinophilia occurred in 6 and AST elevations in 2, none requiring discontinuation and all resolving with stopping).

Russo J Jr, Russo ME. Comparative review of two new wide-spectrum penicillins: mezlocillin and piperacillin. Clin Pharm 1982; 1: 207-16. PubMed PMID: 6224627.

(Review of two extended-spectrum penicillins, piperacillin is more active than mezlocillin against Pseudomonas, side effect profiles are similar including ALT elevations).

Gooding PG, Clark BJ, Sathe SS. Piperacillin: a review of clinical experience. J Antimicrob Chemother 1982; 9 (Suppl B): 93-9. PubMed PMID: 6460738.

(Review of registration trials including 493 courses of piperacillin, averaging 11 days: 90% cure, 4% hypersensitivity, 6% eosinophilia, 3% transient ALT elevations, 3% bilirubin elevations; one patient developed cholestatic hepatitis that recurred more severely with rechallenge).

Marier RL, Sanders CV, Faro S, et al. Piperacillin v Carbenicillin in the therapy for serious infections. Arch Intern Med 1982; 142: 2000-5. PubMed PMID: 6215008.

(Study of 165 hospitalized patients receiving either piperacillin or carbenicillin for serious infections; 95% vs 88% were cured, but liver test abnormalities occurred in 2% with piperacillin vs 22% with carbenicillin; 4% of patients were withdrawn, but none for jaundice).

Sharifi R, Lee M, Ojeda L. Comparative efficacy of piperacillin versus carbenicillin for complicated urinary tract infections. Urol Int 1984; 39: 345-51. PubMed PMID: 6395464.

(Randomized clinical trial in complicated urinary tract infections for average of 7 days; mild ALT increases in 4% of 24 piperacillin recipients, but 35% [ALT 64-628 U/L, normal <27] of 17 carbenicillin recipients; no patient required early stopping).

Lang R, Lishner M, Ravid M. Adverse reactions to prolonged treatment with high doses of carbenicillin and ureidopenicillins. Rev Infect Dis 1991; 13: 68-72. PubMed PMID: 2017635.

(Retrospective review of 63 patients who received carbenicillin or ureidopenicillins reported high rate of ALT elevations with Mezlocillin [20%] and one cause of jaundice, but none with carbenicillin or piperacillin).

Hargreaves JE, Herchline TE. Severe cholestatic jaundice caused by mezlocillin. Clin Infect Dis 1992; 15: 179-80. PubMed PMID: 1617065.

(Case with onset of jaundice 15 days after starting mezlocillin, vancomycin and gentamicin [bilirubin 10 mg/dL, ALT 100 U/L, Alk P 960 U/L]; values worsened when switched to ampicillin, resolved once antibiotics were stopped).

Ryan J, Dudley FJ. Cholestasis with ticarcillin-potassium clavulanate (Timentin). Med J Aust 1992; 156: 291. PubMed PMID: 1738336.

(75 year old man developed jaundice 31 days after stopping a 10 day course of ticarcillin-clavulanate [bilirubin 8.1 mg/dL, ALT 448 U/L, Alk P 1330 U/L]; died of progressive lymphoma soon thereafter; resembled liver injury associated with amoxicillin-clavulanate).

Kuye O, Teal J, DeVries VG, Morrow CA, Tally FP. Safety profile of piperacillin/ tazobactam in phase I and III clinical studies. J Antimicrob Chemother 1993; 31 (Suppl A): 113-24. PubMed PMID: 8383652.

(Among 845 subjects in phase III studies, ALT elevations occurred in 12.2% and bilirubin elevations in 4.6% with iv piperacillin-tazobactam; higher than reported with comparators imipenim and aminoglycosides).

Wise R. The efficacy and safety of piperacillin/tazobactam in the therapy of bacteraemia. J Antimicrob Chemother 1993; 31 (Suppl A): 97-104. PubMed PMID: 8383659.

(Analysis of 142 patients treated in phase II-III studies found ALT elevations in 12% and bilirubin elevations in 9% of recipients of piperacillin-tazobactam, but no report of clinically apparent liver injury or withdrawal for liver abnormalities).

Arguedas A, Sifuentes-Osornio J, Loaiza C, Herrera M, Corrales JC, Mohs E. An open, multicenter clinical trial of piperacillin/tazobactam in the treatment of pediatric patients with intra-abdominal infections. J Chemother 1996; 8: 130-6. PubMed PMID: 8708744.

(Analysis of 60 children with peritonitis receiving iv piperacillin-tazobactam for 1-15 days; 8% had ALT and 8% Alk P elevations, but all mild and resolving rapidly with stopping).

Quattropani C, Schneider M, Helbling A, Zimmermann A, Krähenbühl S. Cholangiopathy after short-term administration of piperacillin and imipenem/cilastatin. Liver 2001; 21: 213-6. PubMed PMID: 11422785.

(20 year old man received one dose of piperacillin and 3 days of imipenem-cilastatin and developed symptomatic liver disease 2 weeks later[bilirubin 0.9 rising to 4.7 mg/dL, ALT 345- 669 U/L, alk P 201-559 U/L], resolving within 2 months of stopping; unclear whether injury was due to piperacillin or imipenem: Case #1 in piperacillin record).

Dietze MA, Martin P, Schaaf-Lafontaine N. [Clinical case of the month. Cholestatic hepatitis after administration of piperacillin] Rev Med Liege 2002; 57: 571-4. French. PubMed PMID: 12440344.

(58 year old woman developed cholestatic hepatitis 12 days after starting 10 day course of piperacillin, but also 14 after 2 days of amoxicillin-clavulanate [peak bilirubin 15.0 mg/dL, ALT 624 U/L, Alk P 1730 U/L], resovling wihtin 2 months).

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, two cases were attributed to amoxicillin, but no details provided).

Tan JS, Wishnow RM, Talan DA, Duncanson FP, Norden CW. Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized, multicenter study of piperacillin-tazobactam versus ticarcillin-clavulanate. The Piperacillin/Tazobactam Skin and Skin Structure Study Group. Antimicrob Agents Chemother 1993; 37: 1580-6. PubMed PMID: 8215266.

(Among 251 patients treated with either of 2 fourth generation penicillins, overall rates of response and side effects were similar; no mention of ALT levels of hepatic adverse events).

Schoonover LL, Occhipinti DJ, Rodvold KA, Danziger LH. Piperacillin/tazobactam: a new beta-lactam/beta-lactamase inhibitor combination. Ann Pharmacother 1995; 29: 501-14. PubMed PMID: 7655135.

(Review of pharmacology, efficacy and safety of piperacillin-tazobactam; the most common side effects are diarrhea [8%], nausea, headache, pruritus and rash [1%]; laboratory abnormalities occur in <1% of patients, but can include "transient increases in liver function test results"; no other mention of hepatotoxicity).

Dietze MA, Martin P, Schaaf-Lafontaine N. [Clinical case of the month. Cholestatic hepatitis after administration of piperacillin]. Rev Med Liege 2002; 57: 571-4. French. PubMed PMID: 12440344.

(58 year old woman developed cholestatic hepatitis 12 days after starting 10 day course of piperacillin, but also 14 days after finishing a 2 day course of amoxicillin-clavulanate [peak bilirubin 15.0 mg/dL, ALT 624 U/L, Alk P 1730 U/L], resolving within 2 months).