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Ticarcillin-Clavulanate

Updated: December 12, 2013.

OVERVIEW

Introduction

The combination of ticarcillin and clavulanate provides an extended-spectrum penicillin with a beta-lactamase inhibitor and is used to treat serious bacterial infections due to susceptible organisms. Given parenterally, ticarcillin-clavulanate can cause mild transient aminotransferase elevations, and therapy has been linked to instances of acute cholestatic liver disease similar to that described commonly with amoxicillin-clavulanate (Augmentin).

Background

The combination of ticarcillin, a fourth generation penicillin, and clavulanate combines the extended-spectrum of ticarcillin with beta-lactamase inhibitory activity of clavulanic acid. This combination is indicated for serious infections of the lower respiratory tract, urinary tract, bones and joints and skin. The extended-spectrum of ticarcillin makes it an appropriate agent in therapy of Pseudomonas aeruginosa. Ticarcillin also has extended activity against some Enterobacter and Proteus. Ticarcillin is available only in parenteral formulations. The combination of ticarcillin and clavulanate was approved for use in the United States in 1985 and is available generically and under the trade name of Timentin. The combination is provided as 3 grams of ticarcillin with 100 mg of clavulanate which is typically given intravenously every 4 to 6 hours for 5 to 14 days. Common side effects of ticarcillin include nausea, epigastric discomfort, diarrhea, headache, dizziness, rash and hypersensitivity reactions.

Hepatotoxicity

Intravenous therapy with ticarcillin and clavulanate is associated with elevations in serum aminotransferase levels in up to 10% of patients; however, these abnormalities are usually subclinical and self-limited. More important are rare instances of acute cholestatic liver injury arising several days to several weeks after initiation of ticarcillin-clavulanate. This hepatic injury resembles that caused by amoxicillin-clavulanate and is probably caused by the beta-lactamase inhibitor rather than the ticarcillin. However, too few cases have been described in the literature to define the clinical characteristics of the idiosyncratic liver injury.

Mechanism of Injury

The cause of the liver injury associated with the combination of ticarcillin and clavulanate is probably hypersensitivity to the clavulanic acid. However, the possibility exists that some instances of hepatotoxicity following this combination are due to ticarcillin.

Outcome and Management

In the few cases of cholestatic liver injury following therapy with ticarcillin/clavulanate that have been described, resolution occurred rapidly in one patient whereas the second died of an underlying disease before recovery was complete. Cases of fatalities and chronic cholestasis have been described after amoxicillin-clavulanate therapy which is a much more commonly prescribed combination.

Drug Class: Antiinfective Agents, Penicillins (Fourth Generation)

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

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ticarcillin-Clavulanate – Generic, Timentin®

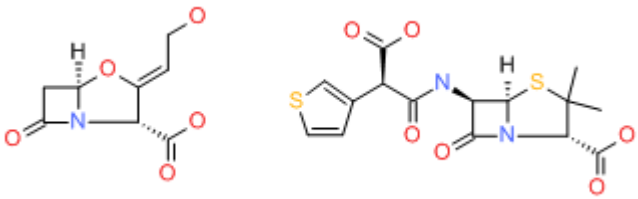
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Ticarcillin-Clavulanic Acid	86482-18-0	C15-H16-N2-O6-S2. C8-H9-N-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 12 December 2013

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.

(Expert review of penicillin induced liver injury mentions that there have been few reports of liver injury due to the extended-spectrum penicillins).

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).

Pines A, Khaja G, Raafat H, Sreedharan KS. Preliminary clinical experience with ticarcillin (BRL 2288) in 101 patients treated for severe respiratory infection. Chemotherapy 1974; 20: 39-44. PubMed PMID: 4210892.

(Early experience in 101 patients with severe infections given im ticarcillin; local pain was common; minimal and transient elevations in ALT occurred in 4 and Alk P in 5 patients).

Parry MF, Neu HC. Comparative study of ticarcillin plus tobramycin versus carbenicillin plus gentamicin for the treatment of serious infections due to gram-negative bacilli. Am J Med 1978; 64: 961-6. PubMed PMID: 247895.

(Comparison of 2 antibiotic combinations in 82 patients with severe gram-negative infections; transient, anicteric ALT elevations [<3 fold increased] occurred in 23% of carbenicillin, but only 3% of ticarcillin treated patients).

Nelson JD, Kusmiesz H, Shelton S, Woodman E. Clinical pharmacology and efficacy of ticarcillin in infants and children. Pediatrics 1978; 61: 858-63. PubMed PMID: 673548.

(Among 98 children given ticarcillin iv or im, 3 had AST elevations to 50-81 U/L without jaundice and all values decreased during continued treatment).

González MA. Comparison of the efficacy and safety of mezlocillin and ticarcillin in the treatment of patients with serious systemic infections. J Antimicrob Chemother 1982; 9 (Suppl A): 229-30. PubMed PMID: 6210671.

(Randomized clinical trial of ticarcillin vs mezlocillin in 34 patients with severe infections; no mention of ALT elevations).

Graft DF, Chesney PJ. Use of ticarcillin following carbenicillin-associated hepatotoxicity. J Pediatr 1982; 100: 497-9. PubMed PMID: 7062188.

(Three patients with cystic fibrosis had elevations of ALT levels [to 54, 320 and 445 U/L] during iv carbenicillin therapy, minimally or not at all during subsequent iv ticarcillin therapy).

Parry MF, Neu HC. The safety and tolerance of mezlocillin. J Antimicrob Chemother 1982; 9 (Suppl A): 273-80. PubMed PMID: 6210679.

(Analysis of 1148 patients given iv mezlocillin for 1-52 days; 3.7% had hypersensitivity reactions, 0.9% elevations in ALT, AST or Alk P, all were reversible and anicteric. In direct comparison, AST elevations occurred in 1.5% of mezlocillin vs 7.4% of ticarcillin recipients).

Ramírez-Ronda CH, Gutiérrez J, Bermúdez RH. Comparative effectiveness, safety and tolerance of mezlocillin and ticarcillin: a prospective randomized trail. J Antimicrob Chemother 1982; 9 (Suppl A): 125-9. *(Randomized clinical trial* comparing mezlocillin [n=21] and ticarcillin [n=20]; no ALT elevations mentioned). PubMed PMID: 6210660.

Reed WP, Palmer DL. Comparison of azlocillin and ticarcillin in the treatment of urinary tract infection. J Antimicrob Chemother 1983; 11 (Suppl B): 189-93. PubMed PMID: 6619028.

(Randomized clinical trial of azlocillin vs ticarcillin in 35 patients with urinary tract infections, both were highly effective; no mention of ALT elevations or hepatic injury).

Jansen W, Schwarz A. Comparative evaluation of netilmicin-ticarcillin and tobramycin-ticarcillin in the treatment of serious systemic infections in elderly patients. Clin Ther 1984; 7: 112-20. PubMed PMID: 6394127.

(Clinical trial in 60 patients with severe infections treated with ticarcillin combined with an aminoglycoside for 4-12 days; 92% efficacy, oto- and nephrotoxicity was attributed to tobramycin, no mention of hepatotoxicity or ALT elevations).

Van der Auwera P, Legrand JC. Ticarcillin-clavulanic acid therapy in severe infections. Drugs Exp Clin Res 1985; 11: 805-13. PubMed PMID: 3836862.

(20 patients with severe infections received iv ticarcillin-clavulanate for 3 to 41 days; ALT elevations occurred in 3, but all were mild and self-limited).

Cone LA, Woodard DR, Stoltzman DS, Byrd RG. Ceftazidime versus tobramycin-ticarcillin in the treatment of pneumonia and bacteremia. Antimicrob Agents Chemother 1985; 28: 33-6. PubMed PMID: 3899005.

(Randomized clinical trial of ceftazidime [n=128] vs tobramycin-ticarcillin [n=131] for severe infections; no mention of ALT elevations).

Mostow SR, O'Brien RF. Safety and effectiveness of ticarcillin plus clavulanate potassium treatment of lower respiratory tract infections. Am J Med 1985; 79: 78-80. PubMed PMID: 4073098.

(Description of 43 patients treated with ticarcillin-clavulanate; no mention of ALT elevations or liver toxicity).

Cox CE. Comparative study of ticarcillin plus clavulanate potassium versus piperacillin in the treatment of hospitalized patients with urinary tract infections. Am J Med 1985; 79: 88-90. PubMed PMID: 4073101.

(Randomized clinical trial in hospitalized patients; 29% of ticarcillin-clavulanate vs 18% piperacillin recipients had laboratory adverse events, mostly ALT elevations, but specific numbers not given).

Gebhart RJ, Duma RJ, Patterson PM. Timentin in the treatment of symptomatic complicated urinary tract infections in adult patients. Am J Med 1985; 79: 101-5. PubMed PMID: 3852637.

(Use of iv ticarcillin-clavulanate in 34 patients with urinary tract infection; adverse events occurred in only one patient, no ALT elevations mentioned).

Pankey GA, Katner HP, Valainis GT, Clarkson MJ, Cortez LM, Dalovisio JR. Overview of bacterial infections of the skin and soft tissue and clinical experience with ticarcillin plus clavulanate potassium in their treatment. Am J Med 1985; 79: 106-15. PubMed PMID: 4073076.

(Trial in patients with severe skin infections found ALT elevations in 3 of 19 [16%] patients on ticarcillin-clavulanate, but none of 12 on cefazolin).

Roselle GA, Bode R, Hamilton B, Bibler M, Sullivan R, Douce R, Staneck JL. Clinical trial of the efficacy and safety of ticarcillin and clavulanic acid. Antimicrob Agents Chemother 1985; 27: 291-6. PubMed PMID: 3888101.

(43 patients given ticarcillin-clavulanate; 88% cure, 25% adverse events, but no mention of ALT elevations or liver injury).

Sanders CV, Marier RL, Aldridge KE, Derks FW, Martin DH. Safety and effectiveness of ticarcillin plus clavulanic acid in the treatment of community-acquired acute pyelonephritis in adult women. Am J Med 1985; 79: 96-100. PubMed PMID: 3907345.

(Use of ticarcillin-clavulanate had poor efficacy in pyelonephritis and 2 of 19 [10%] patients had AST elevations).

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 9 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).

Sweet JM, Jones MP. Intrahepatic cholestasis due to ticarcillin-clavulanate. Am J Gastroenterol 1995; 90: 675-6. PubMed PMID: 7717345.

(60 year old woman with neutropenic sepsis developed jaundice with 2 days of starting ticarcillin-clavulanate and gentamicin with bilirubin rising to 33 mg/dL, ALT 142 U/L, Alk P 355 U/L, improving on stopping antibiotics, but temporary worsening with restarting ticarcillin-clavulanate, then resolving in 1 month; the role of sepsis in causing the jaundice is suggested by the very short latency after starting ticarcillin-clavulanate).

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, no cases were attributed to piperacillin or ticarcillin).