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Aztreonam

Updated: August 2, 2017.

OVERVIEW

Introduction

Aztreonam is a parenterally administered, synthetic monobactam antibiotic that is specifically active against aerobic gram-negative bacilli is resistant to many beta-lactamases. Aztreonam therapy is often accompanied by mild, asymptomatic elevations in serum aminotransferase levels, but it has not been reported to cause clinically apparent liver injury.

Background

Aztreonam (az tree' oh nam) is a monocyclic beta-lactam compound (monobactam) that was originally isolated from Chromobacterium violaceum. It acts by binding to penicillin binding proteins inhibiting cell wall synthesis and decreasing bacterial growth. Aztreonam is active mostly against gram negative organisms and more closely resembles aminoglycosides rather than penicillins. Aztreonam was approved for use in the United States in 1986 and is indicated in the treatment of various moderate-to-severe systemic or skin, intra-abdominal, genitourinary, and respiratory gram-negative infections. Aztreonam is available in generic forms and under the brand name Azactam as a powder or a solution for injection, and under the brand name Cayston as a powder for solution to use in inhalational therapy. The recommended dosage is 0.5 to 2 g by intravenous or intramuscular injection every 8 to 12 hours, typically for 5 to 14 days. The most common side effects of aztreonam are injection site phlebitis, rash and gastrointestinal symptoms.

Hepatotoxicity

Aztreonam has systemic toxicities that are similar to those of other beta lactam antibiotics, but it is unclear whether it can cause hepatic injury similar to that of the penicillins or cephalosporins. Asymptomatic serum aminotransferase elevations are common during high dose, intravenous aztreonam therapy (10% to 38%). The enzyme abnormalities are usually mild-to-moderate, asymptomatic, self-limited and not requiring drug discontinuation. Enzyme elevations occur slightly more commonly during aztreonam therapy than with other comparative antibiotics. Cases of frank liver injury and jaundice attributable to aztreonam must be extremely rare as no individual cases have been reported. For this reason, there is no data regarding the latency or pattern of the injury. Instances of marked aminotransferase elevations within 3 to 5 days of starting aztreonam have been reported, but these cases were without jaundice and resolved rapidly once the drug was stopped.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of injury

Aztreonam has little hepatic metabolism and is excreted rapidly and largely unchanged in the urine, perhaps explaining the lack of hepatotoxicity associated with its use.

Outcome and Management

In the majority of cases, aztreonam induced liver injury appears to be transient, mild and asymptomatic, being marked by serum enzyme elevations only. Full recovery is expected after stopping the medication.

Drug Class: Antiinfective Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Aztreonam – Azactam®

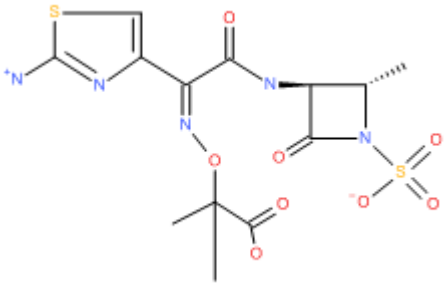
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Aztreonam	78110-38-0	C13-H17-N5-O8-S2	

ANNOTATED BIBLIOGRAPHY

References updated: 02 August 2017

Zimmerman HJ. Hepatic injury from the treatment of infectious and parasitic diseases. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 589-637.

(Expert review of liver injury due to antimicrobial agents published in 1999; aztreonam is not discussed).

Moseley RH. Other beta-lactam antibiotics. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd Edition. Amsterdam: Elsevier, 2013. p. 466. (Expert review of antibiotic induced liver injury mentions that aztreonam and the carbapenems are

associated with a high rate of serum enzyme elevations, but have not been convincingly linked to cases of clinically apparent liver injury).

Petri WA Jr. Penicillins, cephalosporins, and other betalactam 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. 1477-504.

(Textbook of pharmacology and therapeutics).

Swabb EA, Leitz MA, Pilkiewicz FG, Sugerman AA. Pharmacokinetics of the monobactam SQ 26,776 after single intravenous doses in healthy subjects. J Antimicrob Chemother 1981; 8 (Suppl E): 131-40. PubMed PMID: 7199041.

(Controlled pharmacokinetic study in 48 patients; one patient who received aztreonam developed self-limited, asymptomatic elevations in ALT and AST at 72 hours).

Miller LK, Sanchez PL, Berg SW, Kerbs SB, Harrison WO. Effectiveness of aztreonam, a new monobactam antibiotic, against penicillin-resistant gonococci. J Infect Dis 1983; 148: 612. PubMed PMID: 6225808.

(Controlled trial of aztreonam vs spectinomycin in 93 men with gonococcal urethritis; both agents were 100% effective and there were no side effects except for 1 patient with minimally elevatied AST, but normal ALT levels).

Swabb EA, Sugerman AA. Review of single- and multiple-dose pharmacokinetics of the monobactam, aztreonam (SQ 26,776) in healthy subjects. Chemotherapy 1983; 29: 313-21. PubMed PMID: 6684541.

(Among 90 patients receiving aztreonam, 8% developed ALT or AST elevations).

Greenberg RN, Reilly PM, Luppen KL, McMillian R, Bollinger M, Wolk SM, Darji TB. Treatment of serious gram-negative infections with aztreonam. J Infect Dis 1984; 150: 623-30. PubMed PMID: 6541672.

(Aztreonam given to 106 seriously ill patients for 5-50 days; 36% had elevations of AST, all less than 3 times ULN).

Sattler FR, Moyer JE, Schramm M, Lombard JS, Appelbaum PC. Aztreonam compared with gentamicin for treatment of serious urinary tract infections. Lancet 1984; 1: 1315-8. PubMed PMID: 6145024.

(In a controlled trial of aztreonam vs gentamicin in 35 patients, asymptomatic elevations in ALT [3-5 times ULN] elevations occurred in 20% of aztreonam vs 11% of gentamicin recipients).

Hauben M, Adler C. Acute hepatitis, interstitial nephritis, and eosinophilia. Ann Intern Med 1995; 122: 555-6. PubMed PMID: 7872595.

(A patient with HIV developed acute rise in ALT [from 47 to 2374 U/L] and creatinine [from 0.8 to 7.6 mg/dL] and eosinophilia with no mention of jaundice within 4 days of starting vancomycin and aztreonam; values improved after stopping, but were still abnormal 7 days later; patient also received a day of erythromycin).

Hara K, Kobayashi H, Nishiura T, Yura J, Saito A. Clinical studies of aztreonam in Japan. Rev Infect Dis 1985; 7 (Suppl 4): S810-24. (In studies at 86 institutions among 1,447 patients in Japan, aztreonam was effective in 67% of patients; ALT elevations occurred in 4% of patients, but were self-limited and mild in all, and no patient had associated clinical symptoms). PubMed PMID: 3909341.

Newman TJ, Dreslinski GR, Tadros SS. Safety profile of aztreonam in clinical trials. Rev Infect Dis 1985; 7 (Suppl 4): S648-55. PubMed PMID: 2934785.

(Summary of safety and efficacy trials of aztreonam; among 2388 patients receiving multiple doses, 2-3% developed ALT or AST elevations of more than 3 times ULN, but no patient developed ALT elevations and jaundice).

Bosso JA, Black PG, Matsen JM. Efficacy of aztreonam in pulmonary exacerbations of cystic fibrosis. Pediatr Infect Dis J 1987; 6: 393-7. (In open label study of aztreonam in 25 patients with cystic fibrosis, ALT

elevations occurred in 16, but were always asymptomatic and resolved with stopping therapy). PubMed PMID: 3588112.

Bosso JA, Black PG. Controlled trial of aztreonam vs. tobramycin and azlocillin for acute pulmonary exacerbations of cystic fibrosis. Pediatr Infect Dis J 1988; 7: 171-6. (In controlled trial of aztreonam vs tobramycin and azlocillin in 30 children with an acute pulmonary exacerbation of cystic fibrosis, ALT elevations were more common with aztreonam). PubMed PMID: 3128767.

DeMaria A Jr, Treadwell TL, Saunders CA, Porat R, McCabe WR. Randomized clinical trial of aztreonam and aminoglycoside antibiotics in the treatment of serious infections caused by gram-negative bacilli. Antimicrob Agents Chemother 1989; 33: 1137-43. (Among 63 patients treated with aztreonam, 17% had ALT elevations of 2 to 3 fold, one with symptoms, all resolving with stopping therapy). PubMed PMID: 2679368.

Matsen JM, Bosso JA. The use of aztreonam in the cystic fibrosis patient. Pediatr Infect Dis J 1989; 8 (9 Suppl): S117-9; discussion S128-32. (Review of trials of aztreonam [Bosso et al 1987 and 1988] in patients with cystic fibrosis; frequent elevations in ALT levels were most common adverse event and were always asymptomatic and self-limited). PubMed PMID: 2682510.

Sion ML, Pyrpasopoulos M, Nicolaidis P, Papagianni C, Tsurutsoglu G. Efficacy and safety of aztreonam in the treatment of patients with renal failure. Rev Infect Dis 1991; 13 (Suppl 7): S652-4. (In open label study of aztreonam in 39 patients with renal failure and bacterial infection, ALT elevations occurred in 4 patients [10%], but were invariably mild, asymptomatic and resolved rapidly with stopping therapy). PubMed PMID: 2068477.

Oermann CM, Retsch-Bogart GZ, Quittner AL, Gibson RL, McCoy KS, Montgomery AB, Cooper PJ. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. Pediatr Pulmonol 2010; 45: 1121-34. PubMed PMID: 20672296.

(Among 274 children and adults with cystic fibrosis treated with inhaled aztreonam 2 or 3 times daily for up to 18 months, most adverse events were attributed to the underlying disease and "clinically significant changes in vital signs or mean clinical laboratory values were not observed").

Corey GR, Wilcox M, Talbot GH, Friedland HD, Baculik T, Witherell GW, Critchley I, et al. Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 2010; 51: 641-50. PubMed PMID: 20695801.

(Among 1378 patients with complicated skin or soft tissue infections treated with ceftaroline or vancomycin with aztreonam, clinical cure rates were similar as were total and serious adverse event rates overall, ALT or elevations occurring in 2.2% vs 3.6%).

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, none of which was attributed to aztreonam).

Kwon H, Lee SH, Kim SE, Lee JH, Jee YK, Kang HR, Park BJ, et al. Spontaneously reported hepatic adverse drug events in Korea: multicenter study. J Korean Med Sci 2012; 27: 268-73. PubMed PMID: 22379337.

(Summary of 2 years of adverse event reporting in Korea; of 9360 reports, 567 were liver related, but none were attributed to aztreonam).

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; 114: 1419-25. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period none of which were attributed to aztreonam).

Hutchinson D, Barclay M, Prescott WA, Brown J. Inhaled aztreonam lysine: an evidence-based review. Expert Opin Pharmacother 2013; 14: 2115-24. PubMed PMID: 3992352.

(Review of the pharmacology, efficacy and safety of aztreonam lysine used as inhalation therapy in patients with cystic fibrosis; mentions that adverse events are mostly attributable to the underlying lung disease; no mention of ALT elevations or hepatotoxicity).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, none of which were attributed to aztreonam).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 323 cases [36%] were attributed to antibiotics, but none to aztreonam).

Dryden M, Zhang Y, Wilson D, Iaconis JP, Gonzalez J. A Phase III, randomized, controlled, non-inferiority trial of ceftaroline fosamil 600 mg every 8 h versus vancomycin plus aztreonam in patients with complicated skin and soft tissue infection with systemic inflammatory response or underlying comorbidities. J Antimicrob Chemother 2016; 71: 3575-84. PubMed PMID: 27585969.

(Among 761 patients with severe skin and soft tissue infections treated with either ceftaroline or vancomycin and aztreonam, clinical cure rates were similar as were most adverse event rates, serum enzyme elevations arising in 0.8% vs 2.7%, but there were no serious hepatic-related adverse events in the vancomycin-aztreonam group).

Korczowski B, Antadze T, Giorgobiani M, Stryjewski ME, Jandourek A, Smith A, O'Neal T, et al. A multicenter, randomized, observer-blinded, active-controlled study to evaluate the safety and efficacy of ceftaroline versus comparator in pediatric patients with acute bacterial skin and skin structure infection. Pediatr Infect Dis J 2016; 35: e239-47. PubMed PMID: 27164462.

(Among 159 children with acute bacterial skin and skin structure infections treated with intravenous ceftaroline or comparator antibiotics, clinical cure rates were similar as were adverse events including clinical chemistry abnormalities; ALT elevations above 3 times ULN occurred in 1% on ceftaroline and 2% on comparator agents [1 patient in each group]).