Drug Therapy

Aztreonam

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Aztreonam belongs to the monobactam group of naturally occurring antibiotic compounds characterized by a monocycling ring structure. Aztreonam is the first monobactam that has been approved for use in pediatric medicine by US FDA in the year 1998.

Mechanism of Action

Aztreonam is a bactericidal antibiotic, which interferes with the synthesis of the bacterial cell wall(1), the mechanism being similar to that of penicillins and cephalosporins. It binds preferentially to the Penicillin binding protein-3 (PBP-3) of gram negative bacteria and causes lysis and death. There is poor affinity of Aztreonam for the PBP's of gram positive and anaerobic bacteria, which accounts for its narrow spectrum of activity(2). This drug is stable to hydrolysis by chromosomal or plasmid mediated beta lactamases of gram negative species and does not induce chromosomal beta lactamase production.

Pharmacokinetics

Aztreonam is not absorbed orally. It is distributed in most of the body fluids including bone, blister fluid, bile, bronchial and intestinal secretions. Concentrations in lung, bile, bronchial and intestinal secretions. Concentrations in lung, bile and peritoneal fluid are nearly equal to that of serum(3). It crosses the blood brain barrier and achieves therapeutic levels in the cerebrospinal fluid(1.4 micrograms/ml)(4,5). Aztreonam penetrates into cerebrospinal fluid (CSF) more rapidly in patients with inflamed meninges(6). It is also active across a wide range of pH values, making it a useful adjunct in the treatment of abscesses. After intramuscular injection, absorption is almost complete. Absorption after intraperitoneal administration in patients with peritonitis is 92%. Over a large dosage range, plasma concentrations increase in direct proportion to the dose. Diffusion across the placenta is poor, as is diffusion into breast milk. The serum half life is 2.4 to 5.7 hours for preterm infants during the first week of life. In contrast, the mean half life is 1.7 hours for patients older than one month but younger than 12 years of age. Elimination of Aztreonam is primarily renal, with glomerular filtration and secretion playing equal roles. Sixty to seventy percent of the administered dose is excreted in the urine unchanged(8). In patients with impaired renal function, serum aztreonam concentrations are higher, and the half life is extended(9).

Spectrum of Activity

Aztreonam has excellent activity against major gram negative pathogens like *E. coli*, Klebsiella species, *H. influenzae*, Serratia species and *Pseudomonas aeruginosa*. For Pseudomonas, the minimum bactericidal concentration (MBC) is generally 4-16 times greater than the MIC(1,11). Established susceptibility breakpoints for Aztreonam using agar and broth dilutions are 8 µg/ml or

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less (susceptible), 16 µg/ml (intermediate) and 32 µg/ml or greater (resistant). The majority of Enterobacteriacae, notably *E. coli*, *K. pneumoniae* and Citrobacter species are inhibited by less than 1 µg/ml of Aztreonam(12). Serratia and Enterobacter are less susceptible (MIC_{90} 1 to 4 µg/ml), whereas *H. influenzae* and *N. gonorrhea* are more susceptible (MIC_{90} £0.25 µg/ml). Pseudomonas aerugionosa requires the MIC's in the range of 8 to 12 µg/ml of Aztreonam.

Side Effects

The safety profile of Aztreonam has been well studied. Adverse reactions occur in approximately 7-12% of pediatric patients, but only 2% are serious enough to warrant discontinuation of the drug(13). It is well tolerated with no apparent side effects when given intravenously to newborns(14). The most commonly reported adverse reactions in adults were local, consisting of phlebitis or intramuscular injection site discomfort. In US pediatric clinical trials, neutropenia occurred in 11.3% patients younger than 2 years receiving 30 mg/kg every 6 hrs. AST and ALT elevations to greater than 3 times the upper limit of normal were noted in 15-20% patients aged 2 years and above only when receiving more than 50 mg/kg every 6 hrs. These adverse events were reported with increased severity of illness or increased dose.

Systemic reactions such as mild rash, nausea, vomiting and diarrhea were reported in the same trial. Because Aztreonam has no effect on anaerobic bowel flora, the risk of Clostridium defiicile colitis from Aztreonam monotherapy is low(15). Aztreonam also contains 780 mg of Arginine per gram of antibiotic, and concern has been raised regarding possible side effects such as Arginine induced hypoglycemia(16). A recent study addressing this safety issue indicate that Aztreonam was well tolerated and safe in premature infants when a glucose solution (>5 mg/kg/minute) was concomitantly infused(17).

There have been no reports of ototoxicity or nephrotoxicity associated with Aztreonam, nor have there been severe hematological abnormalities associated with its use. Central nervous system side effects are reported rarely, and these tend to be minimal. Hepatic toxicity with transient elevation of transaminases and alkaline phosphatase, is seen occasionally, but it reverts to normal values on cessation of therapy(18). Aztreonam contains a beta lactam ring and therefore has a potential for cross allergenicity with penicillins and cephalosporins. However studies have shown that fewer than 1% of beta lactam allergic individuals given Aztreonam had a possible hypersensitive reaction. Caution is advised in patients with known immediate type hypersensitivity reaction to penicillins and cephalosporins and therapy should be discontinued at the first sign of allergic reaction(19). Bacterial superinfection with aztreonam monotherapy is unusual, but when present it is usually because of gram positive organisms and fungi.

Therapeutic Uses

Aztrenoam has been used successfully in the treatment of a variety of infections such as bacterimias, urinary tract infections, pelvic and intra abdominal infections and respiratory infections. As Aztreonam's activity is limited to the aerobic gram-negative bacilli, it is often used in combination with other drugs depending on the site of infection.

(*a*) *Urinary tract infections:* There is extensive clinical experience with aztreonam in the treatment of both upper and lower urinary tract infections(20,21). Its efficacy is comparable to that of second generation

cephalosporins and aminoglycosides against common gram negative pathogens. Aztreonam is particularly useful as monotherapy for nosocomial urinary tract infections that are resistant to other agents or in situations where the risk of toxicity from aminoglycosides is high(19). Aztreonam reaches high urinary concentrations and hence can be given in a b.i.d. dosage schedule.

(*b*) *Bacterimia:* Aztreonam has been found to be effective in the treatment of gram negative bacterimia(22). Data from a prospective randomized study of 58 neonates with infection caused by gram-negative bacilli including *Pseudomonas aeruginosa*, suggest that the use of Aztreonam in combination with ampicillin is as efficacious as the standard ampicillin and amikacin regime. A combination of aztreobnam with piperacillin was studied in children with febrile neutropenia and was suggested as first line therapy as it averted aminoglycoside related toxicity(23).

(*c*) *Lower Respiratory Infections:* Aztreonam when used empirically for the treatment of lower respiratory infections should always be combined with agents active against gram positive and anaerobic organisms. It possesses no activity against Mycoplasma, Legionella or Chlamydia. Hence, Aztreonam should not be used if these infections are suspected. Aztreonam readily penetrates bronchial secretions and lung tissue. In nosocomial pneumonias, it can be used in combination with anti pseudomonal penicillins and third generation cephalosporins. Clinical trials show it to be as effective as aminoglycosides(24).

(*d*) *Bone and Joint Infections:* Osteomyelitis and septic arthritis caused by susceptible strains of *E. coli*, Proteus, *Klebsiella serratia* and even Pseudomonas have been treated with Aztreonam(25). Since bone and joint infections often require prolonged therapy, Aztreonam is a viable alternative to aminoglycosides in this setting. In situations, where possibility of gram positive infection also exists, an antistaphyloccal agent should be added.

(*e*) *Central Nervous System:* Aztreonam has been shown to penetrate inflamed meninges, and reach therapeutic levels in the central nervous system. It is bactericidal against many pathogens implicated in gram negative meningitis with good activity against *N. meningitides.*

(*f*) *Gastrointestinal System:* It is effective against Campylobacter, Salmonella and Shigella. With the upsurge of multi drug resistant Shigella and Salmonella, it forms a useful adjunct to therapy of gastro-intestinal organisms(26). In a study comparing the efficacy, safety and cost of cefixime, cefriaxone and aztreonam in the treatment of multidrug resistant Salmonella typhi septicemia in children the authors concluded that ceftriaxone was the most cost-effective on an inpatient basis, because of a more rapid clinical cure, and cefixime was the most effective on an outpatient basis, because of the drug cost. However, aztreonam could be used as second line therapy in cases of cefriaxone failure(27).

(*g*) *Specific situations:* (*a*) ICU setting: Serratia is a common organism causing nosocomial infection due to different portal of entry and studies indicate efficacy of aztreonam in this setting(28). It is effective against *B. cepacia*, *Enterobacter cloacae*, *Acinetobacter calcoaceticus*, the

organisms specific to the intensive set up. However, it needs to be reemphasized, the additional gram positive cover needs to be added as it is ineffective against gram positive organisms. (*b*) Cystic Fibrosis: Apart from *P. aeruginosa* and *S. aureus*, *E. coli*, *H. influenzae*, *K. pneumoniae*, *S. epidermidis*, beta-hemolytic streptococcus, *H. parainfluenzae*, *K. oxytoca*, *E. aerogenes* and *E. aglomerans* are commonly isolated in children with cystic fibrosis against which Aztreonam is efficacious(29). It, however, is not effective against *S. aureus*.

(*h*) *Others:* It is also useful in chronic suppurative otitis media in children where it is as effective as Ceftazidime(30). It has also been proven to be effective in anaerobic abdominal infections caused by mainly *Bacteroides fragilis* where it is used with Clindamycin or Metronidazole(31).

Resistance to Aztreonam

Resistance to Aztreonam and extended spectrum cephalosporins is by extended spectrum beta lactamases (ESBL's). These plasmid mediated beta lactamases co transfer resistance to aminoglycosides and trimethoprim sulfamethoxazole. Fluroquinolone resistance is also frequently associated, resulting in organisms resistant to most broad spectrum antibiotics(32,33). The carbapenems are currently considered as the treatment of choice for these pathogens.

Biological Response Modifications

There is a recent suggestion that antibiotics may act as biological response modifiers. Effect of Aztreonam was studied in BALB/c mice and it was shown that it increased the lymphoproliferative response to specific mitogens evident by the production of IL-2 by splenic cells, suggesting the modulatory effect of Aztreonam on different immune parameters, which is independent of its antimicrobial activity and hence of interest in human therapy(34).

Dosage Form and shelf life

It is available as 0.5g and 1.0 g vials. Once reconstituted it must be used within 48 hours if kept at room temperature or within 7 days if

TABLE I–*Recommended Dosage of Aztreonam*

Postnatal age (days)	Weight (g)	Dose	Route
<7	<2000 g	60 mg/kg every 12 hourly	IV, IM
<7	>2000 g	90 mg/kg every 8 hourly	IV, IM
>7	<2000 g	90 mg/kg every 8 hourly	IV, IM
>7	>2000 g	120 mg/kg every 6 hourly	IV, IM
Children		90-120 mg/kg Every 6-8 hours	IV, IM

IV- Intravenous; IM-Intramuscular;
IV-Infusion should be over 15-30 min in neonates and 3-5 min in children.

refrigerated. The recommended dosage is depicted in *Table 1*.

To summarize, Aztreonam, a monobactam, is unique in its bactericidal activity being limited to gram negative bacilli; combined with an excellent safety profile, being devoid of ototoxicity and nephrotoxicity, making it a useful alternative to aminoglycosides. Currently, it is used as first line drug in complicated urinary tract infections with deranged renal function and in intensive care setting when the causative organisms are susceptible to aztreonam. Aztreonam is active against resistant strains of gram negative bacteria which are often involved in nosocomial infections. It's overuse should be avoided to prevent the upsurge of drug resistant *P. aeruginosa* strains.

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