

Aztreonam in cystic fibrosis

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Aztreonam is the only clinically available member of a unique class of beta-lactam antibiotics called 'monobactams'. As such, it is structurally related to the other beta-lactams: penicillins, cephalosporins, and carbapenems (e.g. imipenem, meropenem).

Its spectrum of activity is specific to Gram negative organisms, including *Haemophilus influenzae* and *Pseudomonas aeruginosa*. Recent reports from the United States suggest over 88% of strains of *P. aeruginosa* from cystic fibrosis (CF) patients are susceptible to aztreonam (Shawar *et al* 1999). Activity against *Burkholderia cepacia complex* is variable but activity against *Stenotrophomonas maltophilia* and *Alcaligenes xylosoxidans* is generally poor. It has no anti-Gram positive activity and therefore has no role in the treatment of *Staphylococcus aureus* (including MRSA) or *Streptococcus pneumoniae*.

Pharmacokinetic studies in adult patients without CF indicate that a dose of 2g gives levels of aztreonam in lung tissue above the minimum inhibitory concentration (MIC) of susceptible strains of *P. aeruginosa* for at least three hours. Further studies in children with CF indicate that a dosage of 200mg/kg/day in four divided doses would be predicted to maintain serum concentrations above the MIC of *P. aeruginosa* for the majority of the dosing interval (Reed *et al*, 1986).

There have been trials assessing the efficacy of aztreonam in treating pulmonary exacerbations in cystic fibrosis but they are somewhat limited.

1. A non-comparative study was reported whereby 25 evaluable patients received 200mg/kg/day aztreonam in four divided doses (Bosso *et al*, 1987). Of 57 isolates of *P. aeruginosa* collected pre-therapy, 48 (84%) were aztreonam-susceptible in vitro, as were 11 (61%) of 18 after therapy. *P. aeruginosa* colony counts were reduced by 3 log₁₀ or more in 15 patients. Clinical scores and white cell counts were significantly improved (p < 0.05).

2. A randomised, controlled trial of aztreonam monotherapy versus tobramycin plus azlocillin was reported in 30 patients (Bosso & Black, 1988). There were 15 patients randomised to each arm. Patients in both groups responded to therapy and there were no significant differences in terms of pulmonary function tests, clinical scores, white cell counts or quantitative bacteriology of sputum.

3. A randomised, controlled trial of aztreonam plus amikacin versus ceftazidime plus amikacin was reported for 56 exacerbations in 42 patients (Schaad *et al*, 1989). The aztreonam dose used was 300mg/kg/day; maximum daily dose 12g. Both regimens were well tolerated and resulted in similar improvements in clinical, bacteriologic, radiologic and laboratory findings, and pulmonary function.

4. A randomised, double-blind comparison of ceftazidime and aztreonam monotherapy was performed in 22 adults with CF (Salh *et al*, 1992). Twenty two treatment courses were evaluable. Both agents demonstrated significant improvement in FEV₁ (aztreonam p < 0.01; ceftazidime p < 0.05) and decline in sputum weight at two weeks.

Aztreonam is generally well tolerated. Commonly reported problems include transient, reversible rises in liver enzymes during therapy. As it is a beta-lactam antibiotic there is the possibility of beta-lactam allergy, ranging from rashes to anaphylaxis. However, the incidence of allergic phenomena with aztreonam is reported to be less than for many other beta-lactams. Koch *et al* (1991) reported an evaluation of 2,793 courses of treatment involving beta-lactams in 121 CF patients. The rates of allergic reactions were 51% of patients for piperacillin, 21% azlocillin, 13% ceftazidime, 6.5% aztreonam and 4% for imipenem. CF patients with severe hypersensitivity reactions to other beta-lactams have successfully tolerated courses of aztreonam. Jensen *et al* (1991) gave 56 courses of aztreonam to 15 patients with known severe beta-lactam allergy. No episodes of anaphylaxis were reported and in only two patients the aztreonam was discontinued because of drug-associated fever. Moss *et al* (1991) treated 18 patients with known beta-lactam allergy with aztreonam. Only one suffered from bronchospasm. The others successfully completed therapy. However, two of these subsequently suffered

anaphylactic reactions to aztreonam on re-exposure.

Summary

- Active against *H. influenzae* and aztreonam-susceptible strains of *P. aeruginosa*
- Results of small trials suggest equivalence to other anti-pseudomonal beta-lactams (e.g. ceftazidime, azlocillin) in treating pulmonary exacerbations of CF
- Transient, reversible rises in liver function tests are common during therapy
- Less likely to trigger allergic reactions than most other beta-lactams. Often tolerated by patients known to have hypersensitivity reaction to penicillins and cephalosporins.

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