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Evaluation of Aztreonam in the Treatment of Severe Bacterial Infections

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We investigated the clinical efficacy and safety of aztreonam in the treatment of 50 episodes of infection in 46 adult patients. The clinical condition of patients at the beginning of treatment was critical or poor in 28 of the episodes of infection. Episodes treated were 39 urinary tract infections (12 of them with concomitant bacteremia), 2 soft tissue infections, 8 patients with osteomyelitis (1 with concomitant bacteremia), and one episode of pneumonia. Significant isolated microorganisms were aerobic or facultative gram-negative rods and were responsible for the following episodes of infection (number of episodes): members of the family *Enterobacteriaceae* (49), *Pseudomonas aeruginosa* (5), and *Haemophilus influenzae* (1). The overall rate of clinical response to aztreonam was 94% of the treated episodes. Colonization or superinfection or both occurred in 29 episodes, but only 8 episodes required antimicrobial therapy. Aztreonam seems to be an effective single agent therapy for many bacterial infections. Colonization and superinfection by *Candida* sp., *Streptococcus faecalis* or *Staphylococcus aureus* must be monitored.

Aztreonam (AZT) is a member of a new class of monocyclic synthetic β-lactam agents with in vitro activity against the vast majority of gram-negative bacteria, including members of the family *Enterobacteriaceae* and most isolates of *Pseudomonas aeruginosa*. The compound is inactive against aerobic, gram-positive and anaerobic bacteria. It is likely that this selective spectrum of action causes minimal disturbance of normal human fecal flora, thus decreasing the risk of overgrowth of enterococci and other resistant strains (12, 15, 21, 23, 34, 35).

High levels of AZT in serum can be obtained with a 1-g parenteral dose, protein binding is about 56%, and the terminal half life in serum is 1.7 h. AZT is not metabolized in the body, renal excretion occurs by glomerular filtration, and about 65% of the antibiotic is recovered unchanged from the urine (18, 29, 31–33).

With these considerations in mind, we evaluated the clinical efficiency, tolerance, and toxicity of AZT in the treatment of 46 patients with 50 episodes of severe bacterial infections.

MATERIALS AND METHODS

Patients. Forty-six hospitalized patients were selected for the study. All had clear symptoms and signs of infection and microorganisms supposedly responsible for the infection had been identified within the previous 48 h.

We considered as urinary tract infection (UTI) the isolation of significant bacteriuria ($>10^5$ CFU/ml) in the presence of related clinical symptoms. Our single case with respiratory tract infection was a patient with pneumonia defined by the presence of fever and pulmonary infiltrates and the isolation of a single pathogen from an endotracheal aspiration. Our diagnoses of osteomyelitis were supported by the presence of concomitant bacteremia in one case, with the isolation of the responsible microorganisms during surgical procedures in six patients and direct isolation from an open wound with bone exposure in the remaining patient. Patients included in the category of soft tissue infections were documented by the isolation of microorganisms by needle aspiration of an abscess in one case and by the isolation of the responsible microorganism during the surgical procedure in the second patient.

Twenty-five patients were males and twenty-one were females. Of the 46 patients, 4 received two separate courses of AZT therapy bringing the total number of episodes of infection treated to 50.

Patients who received other antibiotics before AZT treatment were admitted to the study only if there was evidence of in vitro resistance of the microorganisms to the initial antibiotics, or if after at least 3 days of therapy, there was clinical evidence of a response failure to such medications. Eleven of our admitted patients had received prior antimicrobial therapy. In nine of them isolated microorganisms were found to be resistant to the administered drugs. In the remaining two patients (both with chronic osteomyelitis) evidence of clinical failure to respond was obvious.

Permission for the study was obtained from the National Health Authorities and the Human Rights and Clinical Trial Committees of the Hospital. Signed consent from patients or relatives was obtained.

Microbiologic studies. Clinical specimens taken before, after, and regularly throughout therapy were sent to the Microbiology Laboratory of Centro Especial "Ramón y Cajal", in which bacterial isolates were identified by standard criteria (14). MICs of aerobic and facultative microorganisms were routinely performed by a standard agar dilution technique, with a final inoculum of 10^4 CFU (5).

Antibiotics. AZT used in this study was provided by Squibb Institute for Medical Research as a dry, water-soluble powder in 1- or 2-g vials, for parenteral use. Immediately before use, it was reconstituted according to manufacturers recommendations. For intravenous use it was further diluted in 50 ml of 5% glucose in water, or normal saline, and slowly infused over a period varying from 15 to 30 min. AZT was administered in amounts varying from 1.5 to 8 g per day in three injections every 8 h.

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Other antibiotics were administered only during three courses of therapy. The treatments were as follows: one patient with soft tissue infection caused by *Serratia marcescens* and anaerobes also received clindamycin, one patient with osteomyelitis by *P. aeruginosa* and anaerobic cocci also received penicillin, and a patient with osteomyelitis caused by *P. aeruginosa* and *Staphylococcus aureus* also received cloxacillin.

AZT levels in serum were obtained at least once in every patient and, with exceptions, on a once a week basis. Blood for peak values was obtained 15 min after completion of intravenous infusion and after 60 min of an intramuscular injection. Valley levels were obtained immediately before a new injection. Serum was stored at −70°C until assay procedures were carried out. Levels were measured by the agar-well bacteriologic method (38) using *Escherichia coli* ATCC 25922 as the assay organism. Oxoid agar number 2 was the culture medium used.

Evaluation of patients. In agreement with the methods of McCabe and Jackson, patients were classified according to their underlying conditions as having rapidly fatal, ultimately fatal, or nonfatal diseases (16). At the commencement of AZT therapy, the patient's condition was graded as critical (condition rapidly deteriorating with death in a short period of time not unlikely), poor (condition deteriorating with death possible but not imminent), fair (condition deteriorating but death not likely), or good (condition stable) as described elsewhere (37).

Patients were examined daily by one of the authors of this study.

Laboratory studies, including a complete blood count, urinalysis, Coombs test, and blood biochemistry (SMAC 24; Technicon Co.), were made before and after therapy and at least once a week during therapy to monitor patients for evidence of hematologic, renal, or hepatic toxicity.

Patients were considered cured when a complete resolution of symptoms and signs of infection and eradication of causative organisms during and after therapy were achieved. Patients were considered improved when symptoms and signs of infection disappeared or decreased but the causative organism persisted or reappeared after therapy was discontinued, or when symptoms and signs of infection disappeared or decreased but surgery (drainage of abscess, cholecystectomy, removal of infected prosthesis, etc.) were required for cure of infection. Patients were classified as failures when symptoms and signs of infection persisted unchanged and no bacteriological response was found. We also included as failures the presence of adverse reactions leading to termination of therapy.

All patients were followed up for at least 1 month after AZT therapy was discontinued. Patients with osteomyelitis were followed up for a minimum period of 3 months.

We classified colonization as the isolation of microorganisms from clinical material during or after therapy that were not present in the original clinical specimens. We used the term superinfection to describe the presence of such isolates in a setting consisting of infection and not attributable to other causes.

RESULTS

Patients. From May 1983 to May 1984, 46 patients received 50 courses of therapy. Their ages varied from 12 to 88 years (mean ± standard deviation [SD], 60.9 ± 21.0). The underlying diseases of the patients were as follows (number of episodes): urinary tract disease (30), heart disease or high blood pressure or both (11), diabetes mellitus (6), automobile accidents (6), chronic obstructive pulmonary diseases (5), malignancy (4), and miscellaneous diseases (12). In 23 patients more than one underlying disease was present. Twenty-one patients had ultimately fatal diseases, and the remaining 25 patients had nonfatal diseases. The clinical condition at the beginning of treatment was considered critical or poor in 28 episodes and fair or stable in the remaining 22 episodes.

Infections. Of the 50 episodes of infection, 39 were treated for UTI. Twelve episodes of UTI had concomitant bacteremia. Two patients had extensive and severe soft tissue infections. Eight other patients had severe osteomyelitis caused by gram-negative rods. Finally, one patient had gram-negative pneumonia caused by Haemophilus influenzae (Table 1). Thirteen of our patients had concomitant bacteremia. The portal of entry in 12 patients was the urinary tract and in the remaining patient it was vertebral osteomyelitis. The responsible microorganism on eight occasions was *E. coli*, on four occasions it was other members of the family *Enterobacteriaceae*, and on one occasion it was *P. aeruginosa*. In all cases treatment with AZT lead to sterilization of blood cultures.

Microorganisms. The significant microorganisms isolated are summarized in Table 1. A total of 58 isolates were identified in 50 episodes of infection. Forty-two of these episodes were caused by a single microorganism. In the remaining eight episodes a polymicrobial etiology was documented. All isolated significant aerobic or facultative gram-negative microorganisms had AZT MICs ≤8 mg/liter.

Antibiotic treatment. Total amounts of AZT administered per patient varied from 12 to 292 g (mean ± SD, 65.6 ± 79.6). The duration of therapy ranged from 7 to 44 days (mean ± SD, 17.08 ± 11.41).

Daily dosages of AZT administered per patient varied according to the infection. Patients with osteomyelitis were treated with doses varying from 6 to 7.5 g per day. Patients with UTI received daily dosages ranging from 1.5 to 6 g per day (mean ± SD, 2.5 ± 1.23). The patients with soft tissue infections received doses varying from 2 to 3 g per day. Mean peak levels of AZT in serum in each patient ranged from 38.6 to 170 mg/liter (mean ± SD, 93.7 ± 38.8), and mean serum valleys varied from 0.2 to 40 mg/liter (mean ± SD, 10.7 ± 10.7).

Response to treatment. By using the criteria described previously, a clinical cure occurred in 29 of 50 episodes, and there was a clear improvement in 18 other episodes. Patients defined as improved can be further detailed as follows. Twelve patients had either UTI (11 patients) or soft tissue infections. According to our definitions three patients remained totally cured but required surgery. In the remaining nine patients the original pathogens were again isolated from the urine within an 8-week period but without clinical symptoms. Six patients with osteomyelitis were included in the improved group. Three patients remained asymptomatic with clinical and microbiological cure after the combined surgical and medical treatment received for osteomyelitis. The remaining three patients with osteomyelitis relapsed in periods varying from 3 weeks to 6 months after the course of AZT therapy. In this last group, osteomyelitis in two patients was due to *Pseudomonas aeruginosa* and the other one was caused by *Proteus mirabilis*.

Three episodes of infection failed to respond to AZT. On two occasions the failure occurred in patients with UTIs. One of the patients had *E. coli* and vesico-uretheral reflux, and the other patient was an elderly diabetic male with infection caused by *Serratia marcescens* and *Proteus mirabilis*. A third patient had posttraumatic osteomyelitis

TABLE 1. Infections, isolates, and evolution

Infection[a]	Isolates	No. of infections	No. cured	No. improved	No. of failures
UTI	*Escherichia coli*	24	17	6	1
	Serratia marcescens	4	3	1	0
	Klebsiella pneumoniae	3	2	1	0
	Proteus mirabilis	3	2	1	0
	Serratia marcescens + *Paroteus mirabilis*	2	0	1	1
	Enterobacter sp.	1	1	0	0
	Pseudomonas aeruginosa	1	1	0	0
	Klebsiella ozenae	1	0	1	0
Osteomyelitis	*Pseudomonas aeruginosa*	1	0	0	1
	Serratia marcescens	1	0	1	0
	Proteus mirabilis	1	0	1	0
	Pseudomona aeruginosa + *Escherichia coli*	1	0	1	0
	Pseudomonas aeruginosa + *Staphylococcus aureus*	1	0	1	0
	Pseudomonas aeruginosa + anaerobes	1	0	1	0
	Serratia marcescens + *Citrobacter* sp.	1	0	1	0
	Escherichia coli	1	1	0	0
Pneumonia	*Haemophilus influenzae*	1	1	0	0
Soft tissue	*Proteus mirabilis* + *Proteus vulgaris*	1	1	0	0
	Serratia marcescens + anaerobes	1	0	1	0
Total		50	29	18	3

[a] There were 35 patients with UTI, including 39 episodes and 12 cases of bacteremia. There were eight patients with osteomylitis, including eight episodes and one case of bacteremia. There was one patient with pneumonia. There were two patients with soft tissue infections.

caused by *Pseudomonas aeruginosa*, and therapy was discontinued after 7 days of treatment due to one episode of anaphylactic shock. On all three occasions the pathogens isolated after AZT therapy continued to be susceptible to AZT. The total rate of clinical response was 47 of 50 evaluable episodes (94%).

Surgery was necessary as part of therapy in 10 of 50 instances of infection. It was used as debridement of wound infections or curettage for osteomyelitis or urological surgery.

From the microbiological point of view AZT succeeded in the eradication of original pathogens in 34 of the 50 episodes. In 16 episodes of infection (including relapses of UTIs), AZT failed to eradicate one of the original pathogens. All of these follow-up isolates remained susceptible to AZT.

Adverse effects. Local tolerance to AZT was excellent, and in no case was it necessary to discontinue the drug due to local intolerance. Elevation of transaminases to values double or higher than that of the upper limit of normality, not explained by other reasons, were observed in five patients. The maximum value of serum glutamic oxalacetic transaminase and serum glutamic pyruvate transaminase elevations ranged from 106 to 268 for serum glutamic pyruvate transaminase (mean ± SD, 165.4 ± 56.1) and from 57 to 230 for serum glutamic oxalacetic transaminase (mean ± SD, 122.6 ± 67.9), and we think that this modest increase may be considered standard (2, 11, 17, 36). Two patients developed rapidly reversible leukopenia at the end of the course of therapy, and the minimum values reached by the leukocyte count and the total amount of neutropenia were 2,000/μl and 2,900/μl, with 260 and 493 polymorphonuclear leukocytes per μl, respectively. The second patient was simultaneously receiving cloxacillin because of a polymicrobial osteomyelitis caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus*. In both cases leukopenia occurred after the fourth week of antimicrobial therapy. One patient developed a positive Coombs test without any signs of hemolytic anemia on two separate occasions. In the same patient, a severe episode of shock, rash, and eosinophilia occurred, and AZT therapy was discontinued.

Colonization or superinfection or both occurred in 29 of the 50 episodes of infection. Colonization, as previously described, occurred in 21 of the episodes (14 by *Streptococcus faecalis*, 5 by *Staphylococcus aureus*, and 2 by *Candida albicans*). The 14 colonizations by *Streptococcus faecalis* occurred in the urine. Of the five colonizations by *Staphylococcus aureus*, four occurred in the urine and one occurred in a fistulous tract. The two colonizations by *C. albicans* occurred in the urine and the trachea. The remaining eight episodes were superinfections. In five episodes it was UTI caused by *Streptococcus faecalis* (bacteriuria plus obstructive uropathy which required ampicillin therapy). Two patients had *Staphylococcus aureus* superinfections, with one patient having bacteremia and the other having purulent conjunctivitis. The patient with *Staphylococcus aureus* bacteremia received a 14-day course of vancomycin therapy and was cured. In the remaining patient, *C. albicans* was obtained from an abscess by aspiration after AZT therapy. Additional information regarding these patients is included in Table 2.

DISCUSSION

AZT, is a member of a new class of monocyclic synthetic β-lactam agents with in vitro activity against the vast majority of gram-negative bacteria, including members of the family *Enterobacteriaceae* and most isolates of *Pseudomonas aeruginosa*. The compound is inactive against aerobic gram-positive and anaerobic bacteria, has a high affinity for essential PBP 3 of gram-negative bacilli, and is stable to a wide range of β-lactamases (1, 4, 7, 15, 19, 21, 23, 35).

Due to its spectrum of activity, its low systemic and local toxicity, the convenient pharmacokinetics, and the very low immunological cross-reactivity with other β-lactam antibiotics, AZT may be especially useful as an alternative to the more toxic aminoglycosides in many clinical settings (13, 18, 29, 33).

Results of some previously published studies suggest a high degree of clinical efficacy of AZT in the treatment of several human bacterial infections (6, 9, 19, 20, 22, 24–28).

Our patients were appropriate for the evaluation of this

TABLE 2. Superinfections

Underlying disease	Infection	Primary microorganism	New microorganism	Infection	Treatment	Evolution[a]
Vesicocutaneous	UTI	*Enterobacter* sp.	*Streptococcus faecalis*	UTI	Ampicillin	C
Prostatic adenoma	UTI	*Serratia marcescens* *Proteus mirabilis*	*Streptococcus faecalis*	UTI	Ampicillin	F
Uterine prolapse	UTI	*Escherichia coli*	*Streptococcus faecalis*	UTI	Ampicillin	C
Leukopathy	Soft tissue	*Proteus mirabilis* *Proteus vulgaris*	*Calbicans*	UTI		C
Multiple sclerosis	UTI	*Proteus* sp.	*Staphylococcus aureus*	Bacteremia	Vancomycin	C
Prostatic adenoma	UTI	*Klebsiella ozenae*	*Streptococcus faecalis* *Staphylococcus aureus*	UTI Conjunctivitis	Ampicillin	I
Multiple sclerosis	UTI	*Pseudomonas aeruginosa*	*Streptococcus faecalis*	UTI	Amoxycillin	C

[a] Abbreviations: C, cured; I, improved; F, failure.

new compound. Practically all had severe infections and were in a serious clinical condition at the beginning of therapy. They were all managed in the absence of concomitant aminoglycoside therapy, and the overall rate of clinical response was excellent (94%) and compares well with results obtained in similar situations with aminoglycosides, wide-spectrum penicillins, or expanded-spectrum cephalosporins (3, 28, 30, 37, 39, 40).

Colonization and superinfection has been reported previously in patients treated with this antibiotic (6, 8, 10, 20, 22, 26) and all broad-spectrum antibiotics. Particularly, expanded-spectrum cephalosporins tend to select microorganisms such as *Streptococcus faecalis* and *C. albicans*, and we and others have described colonizations and superinfections caused by such pathogens (2, 38, 41). The reduced spectrum of in vitro activity of AZT raises hopes for the decrease or disappearance of such adverse effects. However, we found a high rate of colonization and superinfection, probably because of the selection pressure of AZT on the gram-negative aerobic and facultative flora that obviously depends on the type of infections and underlying conditions of the patients, the doses of AZT administered, and the duration of therapy.

In summary, in our experience, AZT proved to be a clinically effective antibiotic when used as a single agent therapy for the treatment of severe bacterial infections caused by susceptible microorganisms.

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