ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1986, p. 359–361
0066-4804/86/020359-03$02.00/0

Vol. 29, No. 2

Aztreonam Treatment of Gram-Negative Septicemia

DENIS PIERARD,[1]* JOHAN BOELAERT,[2] HERMAN W. VAN LANDUYT,[3] ANNE NAESSENS,[1] LUC HUYGHENS,[4] AND SABINE LAUWERS[1]

Departments of Microbiology[1] and Internal Medicine,[4] Akademisch Ziekenhuis Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium, and Departments of Internal Medicine[2] and Microbiology,[3] Algemeen Ziekenhuis Sint Jan, Ruddershove, 8000 Bruges, Belgium

Received 19 April 1985/Accepted 29 October 1985

Seventy-five aztreonam treatment courses in 74 patients with gram-negative septicemia resulted in 56 clinical cures (75%), 12 partial clinical cures (16%), and 7 clinical failures (9%). Eradication of the original pathogen from the blood was obtained in all patients but two, who had relapses 1 and 4 days, respectively, after treatment. In nine patients (12%) a superinfection was reported. Significant adverse reactions were limited to one transient urticarial rash. Aztreonam may prove to be an effective alternative for the treatment of gram-negative septicemia, but superinfections should be carefully monitored.

Gram-negative septicemia remains a serious condition, especially in patients with underlying disease and impaired host defenses. New molecules such as the monobactams could be an alternative to combination treatment, including aminoglycosides, which are associated with a high risk of toxicity in these patients who are often exposed to other risks of nephro- or ototoxicity. Aztreonam is the first monobactam to be investigated clinically (7, 8). Its activity is only directed against gram-negative aerobic organisms and is comparable to that of broad-spectrum cephalosporins on members of the family *Enterobacteriaceae* and *Pseudomonas aeruginosa* (3–5, 10). We present here the results of an open clinical study of aztreonam therapy in 79 patients with bacteriologically proven septicemia due to gram-negative rods.

A total of 44 patients were hospitalized in the Akademisch Ziekenhuis, Vrije Universiteit Brussel, and 35 were hospitalized in the Algemeen Ziekenhuis Sint Jan, Bruges. The study protocol was approved by the ethical committees of both hospitals, and all patients gave informed consent. Criteria for exclusion were negative pretreatment blood cultures, a history of hypersensitivity to beta-lactam antibiotics, pregnancy or lactation, a neutrophil count lower than 1,000/mm^3, and antibiotic treatment within the previous 72 h (except when the causative organism proved to be resistant to the antibiotic used). Four patients were not assessed because of death unrelated to the infection between days 3 and 5 of aztreonam treatment. An additional patient was not evaluable because aztreonam therapy had to be stopped after the first injection because of a side effect (see below).

The 74 evaluable patients included in this study comprised 40 men and 34 women from 16 to 88 years of age (mean, 65.3 years). One patient was treated for two successive episodes of septicemia. Three patients were in frank shock and three were hypotensive before treatment was started. Many patients were severely debilitated by underlying conditions, with the most frequent being malignant disease (15 patients), diabetes mellitus (12 patients), neurological disorders (11 patients), corticosteroid therapy (5 patients), and major trauma (4 patients). In 15 patients treatment was started within 2 weeks of some surgical procedure. Aztreonam was administered intravenously as a 30-min infusion in 66 of the 75 treatment courses and by intramuscular injection in the remaining 9. The standard dosage regimen used was 2 g every 12 h in Brussels and 1 g every 8 h in Bruges. Two grams every 8 h was administered to three severely ill patients. In seven patients with severe renal insufficiency, the dose was cut by half, and in two patients on maintainance hemodialysis the dosage was 0.25 g every 8 h, supplemented after each dialysis by 0.25 g. The duration of treatment ranged from 5 to 18 days (mean, 9.5 days), and the total dose administered was from 8.25 to 72 g (mean, 31.7 g). In only three patients was another antibiotic administered concomitantly: clindamycin in two patients and flucloxacillin in one patient.

In Table 1 are listed the 82 aerobic gram-negative rods isolated from the blood. Table 2 lists the overall clinical and microbiological results of the treatments. A total of 75 treatment courses in 74 patients resulted in 56 (75%) clinical cures (complete resolution of signs and symptoms of infection), 12 (16%) partial clinical cures (substantial or temporary improvement in signs and symptoms without complete resolution), and 7 (9%) clinical failures (persistence or progression in signs and symptoms of infection). Details on clinical failure are shown in Table 3. Two patients in this group fully responded to treatment after the addition of an aminoglycoside, possibly pointing to a synergistic effect between aminoglycosides and aztreonam, as reported by others (9). Eradication of the original pathogen from the blood during therapy was obtained in all cases, but a relapse occurred in two patients (3%) 1 and 4 days, respectively, after completion of treatment. In two patients rated as having been clinically cured, the original pathogen persisted asymptomatically at the primary site of infection: the urinary tract in one and a duodenal fistula in the other.

We observed nine superinfections (septicemia with an organism that was different from the original isolate), corresponding to 12% of the treatment courses, leading to death in three patients. Superinfections occurred during aztreonam therapy (days 2 to 11) in eight patients and on day 4 posttreatment in one patient. Gram-positive organisms were found in six patients (two *Streptococcus faecalis*, two *Staphylococcus epidermidis*, one *Staphylococcus aureus*, one *Streptococcus pneumoniae*, and one *Bacillus brevis*), *Candida albicans* was found in one patient, and both *C. albicans* and *S. faecalis* were found in one patient; the sole

* Corresponding author.

TABLE 1. Aerobic gram-negative rods isolated from the blood

Species	No.	No. isolated in mixed infections	MIC range (μg/ml)	No. resistant to[a]:					
				Amp	Car	Cfz	Cmn	Ctx	Gen
Escherichia coli	44	3	≤0.03 –2	24	21	12	4	1	3
Klebsiella pneumoniae	14	2	≤0.03–2	14	14	1	1	0	0
Serratia marcescens	6	2	0.25–1	6	6	6	6	0	5
Proteus mirabilis	4[b]	2	≤0.03	1	1	1	0	0	0
Enterobacter cloacae	3	1	0.25–1 0.125–4	1	0	1	1	0	0
Enterobacter agglomerans	1		0.06	1	1	1	0	0	0
Salmonella typhimurium	1	1	0.06	0	0	0	0	0	0
Pseudomonas aeruginosa	6	2	0.25–1 8–16	6	4	6	6	4	4
Pseudomonas fluorescens	1		64	1	1	1	1	1	1
Pseudomonas maltophilia	1	1	128	1	1	1	1	1	1
Acinetobacter antitratus	1		16	1	1	1	1	1	1
Total	82			56	50	31	21	8	15
Percent				68	61	38	26	10	18

[a] Abbreviations Amp, ampicillin; Car, carbenicillin; Cfz, cefazolin; Cmn, cefamandole; Ctx, cefotaxime; Gen, gentamicin.
[b] In one case *S. faecalis* and *B. fragilis* were also isolated.

TABLE 2. Clinical and microbiological outcome of 75 episodes of septicemia in 74 patients

Origin	No.	No. with the following clinical outcome:			No. with the following microbiological outcome:		
		Cure	Partial cure	Failure	Definitive eradication	Superinfection	Relapse
Urinary	38	30	4	4	38	3	
Gastrointestinal	11[a]	6	4	1	11	3	
Pulmonary	9	6	1	2	8	1	1
Catheter-related	4	2	2		4	1	
Soft tissue	3	3			3		
Unknown	10	9	1		9	1	1
Total	75	56	12	7	73	9	2
Percent		75	16	9	97	12	3

[a] Two separate episodes of septicemia occurred in one patient.

superinfection with a gram-negative rod (a susceptible *Escherichia coli* with a different serotype from the first isolate) occurred in a patient with septicemia of abdominal origin. The focus of the superinfection was detected in four cases: a central venous catheter in three patients and the urinary tract in one patient. In addition, *S. faecalis* was isolated from the urine of three patients during aztreonam therapy, leading to a symptomatic urinary tract infection in one patient with

TABLE 3. Details of clinical failures

Sex	Age	Underlying disease	Source of septicemia	Organism	Duration of therapy (days)	Further course of outcome
M	19	Traumatic tetraplegia	Urinary	*E. coli*	14	On day 8, septicemia with *C. albicans*; patient died after 3 weeks of amphotericin B therapy
M	45	Surgery for pancreatic carcinoma	Gastrointestinal	*E. coli*	11	Very severe abdominal pathology; patient died on day 11 of aztreonam therapy
M	73	Polytrauma; lung contusion	Pulmonary	*E. coli*	9	Relapse of septicemia 1 day after interruption of aztreonam therapy (stopped because was not effective); other antibiotics also failed; patient died 12 days later
F	57	Diabetes	Urinary	*E. coli*	7	Cured with cefuroxime
F	24	Diabetic coma, aspiration pneumonia	Pulmonary	*K. pneumoniae*	6	Not improved after addition of gentamicin; cured with cefuroxime-gentamicin
M	23	Surgery for hypospadias	Orchiepididymis	*P. aeruginosa*	11	Cured after addition of amikacin on day 4
F	60	Biliary surgery	Urinary	*S. marcescens*	10	Cured after addition of amikacin on day 7

a bladder catheter. No gram-negative organisms resistant to aztreonam were found during the study period.

A clinically significant adverse reaction was seen in only one patient, the patient developed a generalized transient urticarial rash 30 min after the first 2-g intravenous dose of aztreonam, necessitating discontinuation of the therapy. In all other patients clinical tolerance was excellent. Four patients showed unexplained transient elevations of transaminases, exceeding two to three times their basal levels, without clinical impact. Although nine patients had abnormal liver function tests at the start of aztreonam treatment, no further progression was observed. Local tolerance was excellent; only two patients had phlebitis at the site of intravenous infusion.

We conclude from the results of this study that aztreonam, at a dosage of 1 g every 8 h or 2 g every 12 h, is an effective and safe antibiotic for the treatment of gram-negative septicemia. However, the lack of activity of aztreonam against gram-positive organisms requires some caution; if the possibility of mixed infection exists, it would be prudent to start concomitant treatment with an additional antibiotic. The superinfection or colonization with gram-positive organisms, especially *S. faecalis*, has also been reported by others during aztreonam treatment (1, 2, 6) and should be carefully monitored.

This study was supported by the Squibb Institute for Medical Research.

We acknowledge the assistance of R. Galasse, Squibb Belgium, and R. W. Hodder, Squibb Europe.

LITERATURE CITED

1. **Chandrasekar, P. H., B. R. Smith, J. L. LeFrock, and B. Carr.** 1984. Enterococcal superinfection and colonization with aztreonam therapy. Antimicrob. Agents Chemother. **26**:280–282.
2. **Greenberg, R. N., P. M. Reilly, K. L. Luppen, R. McMillian, M. Bollinger, S. M. Wolk, T. B. Darji, and A. A. Noorani.** 1984. Treatment of serious gram-negative infections with aztreonam. J. Infect. Dis. **150**:623–630.
3. **Neu, H. C., and P. Labthavikul.** 1983. In vitro activity and beta-lactamase stability of a monobactam, SQ 26,917, compared with those of aztreonam and other agents. Antimicrob. Agents Chemother. **24**:227–232.
4. **Percival, A., E. Thomas, C. A. Hart, and P. Karayiannis.** 1981. In vitro activity of monobactam, SQ 26,776, against gram-negative bacteria. J. Antimicrob. Chemother. **8**(Suppl. E):49–55.
5. **Philips, I., A. King, K. Shannon, and C. Warren.** 1981. SQ 26,776: in vitro antibacterial activity and susceptibility to beta-lactamases. J. Antimicrob. Chemother. **8**(Suppl. E):103–110.
6. **Romero-Vivas, J., M. Rodriguez-Creixems, E. Bouza, T. Hellin, A. Guerrero, J. Martinez-Beltran, and M. Garcia de la Torre.** 1985. Evaluation of aztreonam in the treatment of severe bacterial infections. Antimicrob. Agents Chemother. **28**: 222–226.
7. **Sykes, R. B., D. P. Bonner, K. Bush, and N. H. Georgopapadakou.** 1982. Aztreonam (SQ 26,776), a synthetic monobactam specifically active against aerobic gram-negative bacteria. Antimicrob. Agents Chemother. **21**:85–92.
8. **Sykes, R. B., C. M. Cimarusti, D. P. Bonner, K. Bush, D. M. Floyd, N. H. Georgopapadakou, W. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. Rathnum, W. A. Slusarchyk, W. H. Trejo, and J. S. Wells.** 1981. Monocyclic beta-lactam antibiotics produced by bacteria. Nature (London) **291**:489–491.
9. **Van Laethem, Y., M. Husson, and J. Klastersky.** 1984. Serum bactericidal activity of aztreonam, cefoperazone and amikacin, alone or in combination, against *Escherichia coli*, *Klebsiella pneumoniae*, *Serratia marcescens* and *Pseudomonas aerginosa*. Antimicrob. Agents Chemother. **26**:224–227.
10. **Wise, R., J. M. Andrews, and J. Hancox.** 1981. SQ 26,776, a novel beta-lactam: an in-vitro comparison with other antimicrobial agents. J. Antimicrob. Chemother. **8**(Suppl. E):39–47.