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Pharmacokinetics of aztreonam in critically ill surgical patients

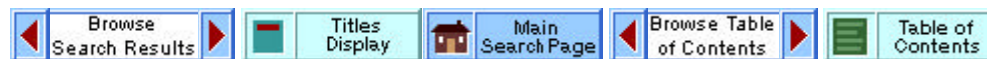
[Report]

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Outline

- [Abstract](#)
- [Methods](#)
 - [Assay of aztreonam.](#)
 - [Pharmacokinetic analysis.](#)
- [Results](#)
- [Discussion](#)
- [Conclusion](#)
- [REFERENCES](#)

Graphics

- [Table 1](#)
- [Table 2](#)
- [Table 3](#)

Abstract

The pharmacokinetics of aztreonam in critically ill surgical patients with serious gram-negative infections were studied.

Blood samples were taken before and at 30 minutes, 2.5 hours, and 5 hours after a dose of aztreonam 2 g i.v. every six hours. All patients had received at least two aztreonam doses before the dosage interval being studied. Aztreonam concentrations were measured by high-performance liquid chromatography. Aztreonam's pharmacokinetics, the severity of illness, and patient

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Pharmacokinetics of aztre...

outcomes were examined.

A total of 28 patients with 111 serum aztreonam concentrations were included in the analysis. The patients were young (mean age, 35 years) and predominantly male. The mean APACHE II score was 19.3, and 22 patients had sepsis. Four patients died. The mean volume of distribution (V) of 0.35 L/kg was nearly twice the previously reported steady-state value for healthy volunteers (0.18 L/kg) and was highly variable. A slightly higher than normal mean V , 0.22 L/kg, was seen in a subset of six patients whose infection occurred earlier in their intensive care and who had lower APACHE II scores. While with some antibiotics the elevated V would imply difficulty in achieving therapeutic drug levels, 99 (89%) of the 111 concentrations were at or above the in vitro susceptibility breakpoint of 8 micro gram/mL.

Despite observations of markedly increased and highly variable V in critically ill surgical patients, a standard dosage of aztreonam was usually sufficient to maintain adequate serum drug levels.

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Aztreonam is used in the therapy of serious gram-negative infections. [1,2] Critically ill surgical patients with serious infections frequently have an altered volume of distribution (V) for antibiotics they receive. [3-6] This has great clinical significance for the dosing of aminoglycosides, as adjusted regimens are required in order to attain therapeutic serum drug levels. [3-6]

Current dosage guidelines for aztreonam (1-2 g every six to eight hours) are derived from pharmacokinetic studies in healthy volunteers. These studies suggest a steady-state V of 0.18 L/kg and a serum half-life ($t_{1/2}$) of 1.7 hours. [1] Winslade et al. [7] studied 21 patients (mean age, 68 years) with abdominal sepsis and a high frequency of underlying disorders, such as malnutrition and cardiopulmonary disease. The aztreonam V in this group averaged 0.28 L/kg. Among victims of penetrating abdominal trauma, Fabian et al. [8] reported a significantly lower rate of infectious complications in recipients of aztreonam and clindamycin (3%) than in those given gentamicin and clindamycin (19%) and speculated that advantages associated with aztreonam's pharmacokinetics may have been responsible. This same group studied the drug's pharmacokinetics after fluid resuscitation from traumatic shock in pigs and found a decreased V at steady state that varied during the five-day postresuscitation period. [9] In both reports, the authors cited the importance of studying aztreonam's pharmacokinetics further in critically ill patients. While the hazards of underdosing drugs like aminoglycosides in critically ill patients with serious infections are well described, the need for alternative dosage regimens in such patients receiving aztreonam has not been adequately explored to date.

The purpose of this study was to determine if the altered pharmacokinetics seen in critically ill surgical patients receiving aztreonam (2 g every six hours) for serious gram-negative infections require dosage adjustments to achieve recommended serum drug levels.

Methods

This prospective study took place in the surgical intensive care unit (SICU) of Los Angeles County + University of Southern California Medical Center, a large, urban, level I trauma center, and was approved by the institutional review board. Informed consent was obtained from all subjects.

We analyzed the following clinical variables in critically ill surgical patients treated with aztreonam for gram-negative infections between January and May 1995: pharmacokinetics (V [in liters per kilogram of

actual body weight] and $t_{1/2}$); severity of illness (APACHE II score, presence of sepsis, length of stay in the SICU); and outcome (resolution of signs and symptoms of infection, mortality). Patients were judged to have sepsis (a systemic inflammatory response to infection) if they had a documented gram-negative infection plus two of the following signs: body temperature of > 38 or < 36 degrees Celsius, heart rate of > 90 beats/min, respiratory rate of > 20 breaths/min, and white blood cell count of $> 12,000$ or $< 4,000$ cu mm (or $> 10\%$ band neutrophils). [10] Patients with clinically significant renal dysfunction (serum creatinine concentration, > 1.9 mg/dL) were excluded.

All patients received aztreonam 2 g i.v. every six hours by infusion pump over 30 minutes. Blood was sampled before a dose (trough) and at 30 minutes, 2.5 hours, and 5 hours after drug infusion. All patients had received at least two doses before the interval being studied. The desired concentration of aztreonam was defined as greater or equal to 8 micro gram/mL, the in vitro susceptibility breakpoint established by the National Committee for Clinical Laboratory Standards. [11] This is the assumption used when mean inhibitory concentrations are referred to and organisms are reported to be resistant or susceptible to aztreonam.

Assay of aztreonam. [↑](#)

Serum aztreonam concentrations were determined by a high-performance liquid chromatographic (HPLC) procedure adapted from the method of Jehl et al. [12] Analytical-grade aztreonam was obtained from the United States Pharmacopeial Convention (Rockville, MD, lot 04620F). The HPLC system consisted of a Hitachi model 6200 pump, an L-4200 ultraviolet-visible light detector, and a D-2500 Chromato-Integrator (Hitachi, Kyoto, Japan). Samples were injected into an Adsorbosphere C_{18} column (4.6 x 25 mm, 5-micro meter particle size) (Alltech Associates Inc., Deerfield, IL) by an AS-2000 autosampler (Hitachi).

Chromatography was performed at ambient room temperature. The mobile phase was 5 mM ammonium phosphate and 2 mM tetrabutylammonium hydroxide buffer adjusted to pH 2.6:acetonitrile (26:74, v/v); the flow rate was at 1.2 mL/min. Serum samples were obtained at the stated intervals and stored at -70 degrees Celsius until batch analysis. Serum was denatured by mixing equal volumes (1.0 mL) of acetonitrile and serum in a glass test tube and gently shaking for 15 minutes. The resulting mixture was centrifuged (4000 rpm) for 15 minutes. The supernatant was transferred with a glass pipette to a fresh glass test tube, and 6 mL of methylene chloride was added. The mixture was gently shaken for 15 minutes and then centrifuged (4000 rpm) for 15 minutes. The aqueous layer was pipetted off and passed through 0.2-micro meter nylon filters. Fifty-microliter volumes of the filtrate were injected into the column. The column eluent was monitored for ultraviolet light absorption at a wavelength of 32 nm. The peak areas were plotted against concentration as a calibration curve.

Aztreonam standard solutions were created daily because of poor stability of the drug in serum at refrigerator temperatures. A stock solution of aztreonam (2000 micro gram/mL in distilled water) was added to serum, yielding standards with drug concentrations ranging from 5 to 200 micro gram/mL. The intraday and interday coefficients of variation were 14.2% and 4.3%, respectively. The calibration curves were linear ($r, > 0.98$). The retention time for aztreonam was approximately seven minutes. Samples with concentrations exceeding that in the standard solution with the maximum concentration were diluted with distilled water, and the injection was repeated. The lower limit of detection was 5 micro gram/mL.

Pharmacokinetic analysis. [↑](#)

Data were analyzed with noncompartmental modeling by using the LAGRAN computer program [13] and the reverse-superposition method of Bauer and Gibaldi. [14] For each patient, terminal $t_{1/2}$, area under the

concentration-versus-time curve, total drug clearance, and steady-state V were calculated.

Results [↑](#)

Thirty patients receiving aztreonam for gram-negative infections were studied. Protocol violations regarding the sampling times occurred for two patients, making all their concentration data uninterpretable; these patients were excluded from evaluation. Because of the large proportion of trauma victims in the study (24 of 28 patients), the demographic data reflect a young, predominantly male population ([Table 1](#)). Blood samples were drawn an average of 7.5 days (range, 1-26 days) after admission to the SICU. Twenty-six of the 28 patients were admitted directly to the SICU from the operating room, and the remaining two patients were blunt-trauma victims transferred from the admitting area. While 27 patients had the four samples drawn at the predetermined times, one sampling was missed for one patient, leaving 111 serum aztreonam concentrations for analysis.

Characteristic	Value
No. pts. (M/F)	28 (25/3)
Mean \pm S.D. age in yr (range)	35.4 \pm 18.3 (14-80)
Underlying illness (no. pts.)	
Penetrating trauma	12
Blunt trauma	12
Necrotizing fasciitis	2
Small-bowel obstruction	
with gangrene	1
Colon neoplasm	1
Mean \pm S.D. APACHE II score (range)	19.3 \pm 7.0 (5-32)
No. (%) pts. with sepsis	22 (79)
Source of infection (no. pts.)	
Peritoneum	12
Sputum	10
Urine	1
Wound	1
No. pts. (%) with resolution of infection	24 (86)
No. (%) deaths	4 (14)

Table 1. Demographic Characteristics of Study Patients

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A majority of the patients (22 of 28, or 79%) met the criteria for sepsis, and 24 sources of infection (predominantly the peritoneal cavity and sputum) were identified in these 22 patients ([Table 1](#)). Four patients died; their APACHE II scores were 23, 30, 32, and 33. Three of these patients were young males who sustained major visceral or vascular injuries after gunshot wounds to the abdomen and developed postoperative pneumonia, adult respiratory distress syndrome, and multiple-organ-system failure. The fourth death occurred in a 61-year-old man who had necrotizing fasciitis after right hemicolectomy for a gangrenous colon. No patient had adverse effects or toxicity from antimicrobial therapy.

All but 1 of the 28 patients had a V greater than the 0.18 L/kg reported as the steady-state V for healthy volunteers ([Table 2](#)). [\[1\]](#) While the markedly elevated mean V seen in this group of patients would imply difficulty in achieving therapeutic drug levels with some antibiotics, 89% of the aztreonam concentrations were at or above the in vitro susceptibility breakpoint of 8 micro gram/mL, and 68% of the patients had aztreonam concentrations that were greater or equal to 8 micro gram/mL throughout the entire six-hour dosage interval. The 12 concentrations that were below 8 micro gram/mL were all troughs (before infusion or five hours after infusion) and occurred in nine patients, eight of whom had resolution of their infections. Four patients had a prolonged $t_{1/2}$ (7-26 hours), suggesting that steady state had not been reached at the time of blood sampling. These patients had concentrations well above 8 micro gram/mL, resolved their infections, and manifested no drug toxicity.

Variable	Value
Mean \pm S.D. V (L/kg)	0.38 \pm 0.11
No. patients with V of >0.28 L/kg	22/28
Mean \pm S.D. $t_{1/2}$ in hr (range)	4.4 \pm 5.5 (1.03-26.7)
No. (%) concentrations of ≥ 28 μ g/mL	99/111 (89)
No. (%) patients with concentrations of ≥ 28 μ g/mL throughout dosage interval	19/28 (68)
Mean \pm S.D. days in SICU before sampling (range)	7.5 \pm 6.6 (1-26)
Mean \pm S.D. serum aztreonam concentration in μ g/mL (median)	
Before infusion	39.5 \pm 52.4 (21.2)
After infusion:	
30 min	107.5 \pm 58.4 (86.9)
2.5 hr	63.5 \pm 57.4 (40.8)
5 hr	46.5 \pm 58.9 (22.2)

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Table 2. Pharmacokinetics of Aztreonam in Study Patients^a

Because of the wide variation in V and $t_{1/2}$, [Table 3](#) was constructed to stratify patients on the basis of V . There were only six patients whose V was less than 0.28 L/kg (heretofore the highest mean V reported in a group of patients with serious infections [\[7\]](#)). Although differences in mean APACHE II scores and time in the SICU before drug therapy seen with this small subset were not significant, this subset appears to have consisted of less critically ill patients whose infection occurred earlier in their SICU stay.

Variable	Value	
	$V < 0.28$ L/kg (n = 6)	$V \geq 0.28$ L/kg (n = 22)
Mean \pm S.D. age in yr	35.7 \pm 23.0	35.4 \pm 17.9
Mean \pm S.D. APACHE II score	12.5 \pm 4.8	21.1 \pm 6.5
Mean \pm S.D. days in SICU before sampling	3.8 \pm 1.5	6.6 \pm 7.3
No. (%) pts. with sepsis	3 (50)	19 (86)
Mean \pm S.D. V in L/kg (range)	0.22 \pm 0.04 (0.14-0.26)	0.39 \pm 0.98 (0.28-0.60)
No. (%) deaths	0	4 (18)

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Table 3. Characteristics of Patients with V Less than or Greater than 0.28 L/kg

Discussion [↑](#)

Aztreonam's pharmacokinetics have been studied in healthy volunteers, [\[1,6,15\]](#) older medical patients with intra-abdominal and pulmonary infections, [\[7,16\]](#) victims of penetrating trauma in the early postinjury period, [\[8\]](#) and noninfected pigs after resuscitation from hemorrhagic shock. [\[9\]](#) We studied the pharmacokinetics of aztreonam in a group of young, critically ill, largely trauma patients with intraperitoneal and pulmonary sepsis. While the mean V in this group was twice that previously reported for steady state, there was considerable variability among patients.

McKindley et al. [\[9\]](#) used noninfected pigs, which underwent resuscitation from experimental hemorrhagic shock, to study the pharmacokinetics of aztreonam. They identified a decreased steady-state aztreonam V but found the magnitude of the decrease to vary from day 1 to day 5 after resuscitation. In our study, patients who had a smaller V tended to have received their aztreonam infusion relatively early in their SICU course. Indeed, in this group of patients the mean V was only slightly greater than that seen in healthy volunteers ([Table 3](#)). The challenge of appropriately determining doses for patients in the early postinjury period has been well described. [\[17\]](#)

Our data suggest that the correlation between increasing V and increasing APACHE II score was poor ($r^2 = 0.046$). The study group was too small to provide sufficient statistical power to rule out a correlation

(power, 0.190), so a larger study will be necessary to confirm or deny a direct relationship between V and APACHE II score.

When dosage regimens are held constant, an inverse relationship is observed between a drug's V and its serum concentration. [14,18] The clinical significance of this is well described with antibiotics that exhibit dose-dependent killing when they are given to critically ill patients with sepsis and an expanded V. [5,6] Typically, these patients have subtherapeutic peak serum concentrations and difficulty clearing their infections if dosage adjustments are not made. [3,4]

Although aztreonam has an antibacterial spectrum very similar to that of the aminoglycosides, it has little postantibiotic effect, and its bactericidal activity is a function of the duration of therapeutic drug levels. [2] As a result, there is a need for the serum aztreonam concentration to be four times the minimum inhibitory concentration (MIC) for the organism in question throughout the dosage interval. [2,19] Fortunately, the drug has a wide therapeutic index, in that the MICs for most gram-negative bacteria are < 2 micro gram/mL. [2,19,20] Despite the widely variable V observed in this study, the standard aztreonam dosage of 2 g every six hours achieved targeted serum concentrations in most cases.

Of the 12 serum aztreonam concentrations below 8 micro gram/mL, 2 were nondetectable and 6 were > 4 micro gram/mL. Eight of the nine patients with an aztreonam concentration of < 8 micro gram/mL cleared their infection anyway, perhaps testifying to the drug's wide therapeutic index when used to treat gram-negative infections. This attribute is important when one considers the difficulty of interpreting pharmacokinetic data in a group of critically ill patients with fluid shifts and variable V and $t_{1/2}$. The absence of a steady-state value in patients with prolonged $t_{1/2}$ would cause difficulties in interpreting serum aztreonam concentrations early in the course of therapy. The availability of a single dosage regimen that does not require interpretation of serum drug levels is somewhat comforting for the clinician.

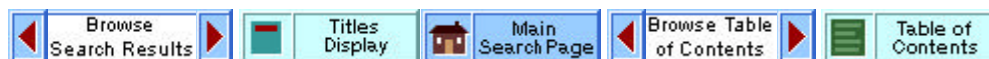
Conclusion

Despite observations of markedly increased and widely variable V in critically ill surgical patients, a standard dosage of aztreonam (2 g every six hours) was usually sufficient to maintain adequate serum drug levels.

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