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Evaluation of Aztreonam in the Treatment of Spontaneous Bacterial Peritonitis in Patients with Cirrhosis

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To determine the efficacy of aztreonam in the treatment of spontaneous bacterial peritonitis in patients with hepatic cirrhosis, 14 patients (7 males, 7 females) with 16 Gram-negative infective episodes (12 *Escherichia coli* and 4 *Klebsiella pneumoniae*) were treated with aztreonam infusions at doses of 1 gm per 8 hr for a planned 14-day period. Ages ranged from 40 to 75 years with a mean of 57 ± 10 years.

All organisms were highly susceptible to aztreonam (minimal inhibitory concentration ≤ 0.06 to 0.12 μg per ml). Serum antibiotic levels were 61.9 ± 25.5 μg per ml (peak) and 27 ± 18.5 μg per ml (trough). Ascitic fluid antibiotic levels were 33.6 ± 22.5 μg per ml (peak) and 32.7 ± 16.8 μg per ml (trough).

Although the symptoms of infection were controlled within 3 days and ascitic fluid cultures became negative after 48 hr, 10 patients (62.5%) died, with hepatorenal syndrome and digestive tract hemorrhage as the principal causes of death. Three patients developed streptococcal superinfections during treatment; *Streptococcus faecalis* peritonitis in one case and spontaneous bacteremia due to *Streptococcus equinus* and *Streptococcus mutans* in the other two.

Aztreonam was well tolerated and clinically and bacteriologically efficacious in controlling the infection. Serum and ascitic fluid levels were considerably higher than the minimal inhibitory concentration for the causative organisms, suggesting that lower doses may achieve suitable therapeutic levels.

A negative aspect of the antibiotic therapy was the superinfections. The high mortality rate was attributable to the generally poor underlying condition of the patients.

Spontaneous bacterial peritonitis is one of the most frequent and severe infections in patients with cirrhosis (1, 2) with a mortality rate for culture-proven cases of approximately 60% (3–5). Because enterobacteriaceae are the causative organisms in 75% of cases (3, 5–10), aminoglycosides are widely used in spite of the fact that patients with cirrhosis are at high risk of developing aminoglycoside nephrotoxicity (11). Certain new β-lactam antibiotics with high activity against Gram-negative bacilli and absence of nephrotoxicity show therapeutic promise (1), even though their role is not yet clearly defined.

Aztreonam, the first member of a new class of monobactams, has a limited antibacterial spectrum against aerobic and facultative Gram-negative organisms similar to that of the aminoglycosides and excellent penetration into the tissues. It has proved efficacious in the treatment of Gram-negative infections (12–16) and may well be an alternative to aminoglycosides in the therapy of this type of infections.

However, no studies demonstrating the clinical efficacy of aztreonam in the therapy of spontaneous bacterial peritonitis in cirrhotic patients have been documented nor have antibiotic levels in the ascitic fluid of such patients been determined and correlated with the clinical course. This prompted us to undertake this study with aztreonam in the therapy of cirrhotic patients with spontaneous bacterial peritonitis.

MATERIALS AND METHODS

Between October, 1983 and December, 1984, all patients with cirrhosis and suspected or proven spontaneous bacterial peritonitis admitted to our hospital were included in our study and treated with aztreonam at doses of 1 gm per 8 hr, administered by intravenous infusion over 15 to 20 min. Concomitant therapy with other antibiotics—penicillin, cloxacillin, clindamycin or vancomycin—was permitted to insure full coverage against possible Gram-positive or anaerobic bacterial infection. Patients with negative cultures or Gram-positive infections or those who died during the first 48 hr of the study were excluded. The remaining patients, all with culture-proven, Gram-negative peritonitis, continued to receive aztreonam alone for a minimum of 14 days.

The diagnosis of cirrhosis was established using clinical and laboratory criteria not requiring histological confirmation. Peritonitis was considered spontaneous when it did not result from direct inoculation and an infectious intraabdominal focus could not be determined.

Routine paracentesis for cytological and bacteriological study was done before therapy, on Days 2 and 5 and at the end of therapy. Ascitic fluid was cultured at 37°C in blood agar plates, chocolate agar, MacConkey agar and thioglycolate broth. No specific media were used for anaerobes. Bacterial isolates were identified with routine laboratory methods (17). Antibiotic susceptibility was studied using standard agar dilution methods (18).

Blood and ascitic fluid samples (10 ml) for aztreonam assay were drawn before intravenous infusion of a new dose and at

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30 and 60 min after infusion (blood and ascitic fluid, respectively). The samples were frozen at −40°C and aztreonam assayed by microbiological agar diffusion with *Escherichia coli* SC 12155 (Squibb) as the indicator organism (19). Aztreonam was supplied by the Squibb Institute of Medical Research, Princeton, NJ. After being discharged from the hospital, patients were asked to return on an outpatient basis for clinical evaluation during the first 2 months after therapy.

The study was approved by the national health authorities and our local hospital committees. Informed consent was obtained from patients or relatives.

Statistical analysis was done using the Mann Whitney U test for comparison of the means.

RESULTS

Patients. Fourteen patients with 16 infection episodes were included. Six received concomitant therapy with penicillin, one with clindamycin and one with vancomycin; the other patients were given aztreonam only. The characteristics and clinical data of the patients are expressed in Tables 1 and 2. All had advanced cirrhosis and had been hospitalized on previous occasions with clinical signs of progressive liver dysfunction.

Microbiological Data. Ascitic fluid cultures were positive for *E. coli* in 12 cases and for *Klebsiella pneumoniae* in four. Blood cultures were positive for *E. coli* in 4 and for *K. pneumoniae* in 2 of the 13 patients (46%) in whom they were done. Three patients had associated *E. coli* urinary tract infection.

All organisms showed high "*in vitro*" susceptibility to aztreonam (minimal inhibitory concentration ≤ 0.06 to 0.12 μg per ml).

All control cultures were negative by the second treatment day.

Antibiotic Levels. Serum and ascitic fluid aztreonam levels were determined between treatment Days 2 and 7 (mean=3.6 ± 1.6 days) and are shown in Table 3.

TABLE 1. Patients' characteristics

No. of patients	14
No. of infective episodes	16
Sex (male/female)	7/7
Mean age in years (range)	57 ± 10 (40–75)
Diagnostic criteria for cirrhosis	
Clinical and laboratory only	8
Histological confirmation[a]	5
Laparoscopy	1
Presumed etiology of cirrhosis	
Alcoholic	8
Posthepatitic	3
Cryptogenic	3
Associated illness and other factors	
Previous splenectomy	2
Le Veen shunt	3
Gastric cancer	1
Chronic lymphocytic leukemia	1
Liver "function" tests	
Mean prothrombin time (percentage) (range)	40 ± 11 (19–56)
Mean total bilirubin (μmoles/liter) (range)	95 ± 90 (8–329)
Mean serum albumin (gm/dl) (range)	23 ± 4 (19–30)

[a] Four micronodular, one macronodular.

TABLE 2. Clinical characteristics

Signs and symptoms	No. of patients
Fever	10
Low grade fever	2
Apyrexic	4
Ascites	16
Abdominal pain	12
Rebound tenderness	11
Diarrhea	3
Hepatic encephalopathy[a]	11
Gastrointestinal bleeding[a]	4
Hypotension	2

[a] On admission or during treatment.

Samples for peak and trough levels were available from 12 patients; in the other four, some samples were missing. Although the range was variable with serum troughs at 3.1 to 64 μg per ml and peaks at 32 to 102 μg per ml and ascitic fluid troughs at 2.9 to 64 μg per ml and peaks at 8.8 to 90 μg per ml, levels always were more than 30 times higher than the minimal inhibitory concentration for the causative organisms, and all serum peaks were higher than the troughs, with means of 61.9 ± 25.5 and 27 ± 18.5 μg per ml, respectively. Ascitic fluid levels remained stable, with a mean of 33.6 ± 22.5 μg per ml for the peaks and 32.7 ± 16.8 μg per ml for the troughs. Patients with normal or only slightly altered renal function (creatinine < 1.5 mg per dl) had lower serum and ascitic fluid antibiotic peaks and troughs than did those with creatinine ≥ 1.5 mg per dl, although only with peak serum levels was this statistically significant ($p < 0.05$) (Figure 1).

Cell Count. The results of cytological study of ascitic fluid are expressed in Table 4. It is noteworthy that on the fifth treatment day, the ascitic fluid from seven patients remained cloudy with more than 1,000 polymorphonuclear (PMN) cells per mm^3; all of these patients had had an initial cell count above 10,000 PMN cells per mm^3. One patient who developed a superinfection during therapy had an ascitic fluid culture positive for *Streptococcus faecalis*. By the end of treatment, the ascitic fluid was clear in all patients. The fluid always was a transudate with protein ranging from 3 to 22.6 gm per 100 (mean = 10.29 ± 5.8) on the first day and from 2.7 to 17.2 gm per 100 (mean = 9.28 ± 4.6) on the day when samples for determinations were collected.

Clinical Outcome. Aztreonam elicited a favorable response, and patients became afebrile within 1 to 7 days (mean = 3 days), and abdominal pain and rebound tenderness abated within 1 to 6 days (mean = 2.7 days). Nevertheless, 10 patients died (Table 5), of these, seven died during the treatment period: four because of progressive hepatorenal syndrome with massive ascites, oliguria; encephalopathy and renal failure, two because of variceal hemorrhage, and one because of peritoneal superinfection (see below). Three other patients died after the end of treatment of causes not related to the infection.

Of the six patients who survived the peritonitis, five died because of complications of the cirrhosis between 1 month and 1 year after being discharged from hospital.

TABLE 3. Antibiotic therapy, renal function, aztreonam levels, superinfections and clinical outcome of patients

Patient no.	Age	Sex	Aztreonam		Renal function [creatinine (mg/dl)]	Treatment day of sample extraction	Aztreonam levels (μg/ml)				Associated antibiotic[a]	Superinfection	Course
			Dose	Treatment days			Serum		Ascitic fluid				
							Trough	Peak	Trough	Peak			
1	60	M	3 gm/day	15	1.3	6th	32	36	52	42	Ampicillin, 4 gm/day (Days 9–15)	No	Cured
2	71	F	3 gm/day	21	1.4	4th	—	32	27	26	—	No	Cured
3A	49	M	3 gm/day	14	0.8	6th	6.8	50	22	15.2	—	No	Cured
3B	49	M	3 gm/day	13	1.1	2nd	12.8	76	16.4	14.4	—	No	Death, Day 13[b]
4	69	F	3 gm/day	12	1	3rd	52	80	48	44	—	No	Death, Day 12[b]
5	40	M	3 gm/day	16	0.7	4th	3.9	32	—	8.8	—	Bacteremia *S. equinus*, Day 12[b]	Death, Day 25[c]
6	52	M	3 gm/day	14	1.2	2nd	3.1	32	2.9	13.2	Clindamycin, 1,800 mg/day (Days 6–14)	No	Death, Day 1[c]
7	53	M	3 gm/day	6	1.4	3rd	8	33	11.5	12	—	No	Death, Day 6[b]
8	66	F	3 gm/day	21	1.2	3rd	23	46	33	33	Clindamycin, 1,800 mg/day (Days 10–21)	No	Cured
9A	50	F	3 gm/day	15	1.5	7th	34	68	28	32	—	No	Cured
9B	50	F	3 gm/day	14	1.6	3rd	46	90	33	16	—	Bacteremia *S. mutans*, Day 13[b]	Death, Day 20[c]
10	64	M	3 gm/day	14	1.6	2nd	12	—	23	26	—	No	Cured
11	50	F	3 gm/day	9	1.8	3rd	46	102	—	40	—	No	Death, Day 9[b]
12	46	M	3 gm/day	5	1.9	3rd	32	62	48	50	—	No	Death, Day 5[b]
13	75	F	3 gm/day	6	1.9	6th	30	90	50	76	—	Peritonitis *S. faecalis*, Day 5[b]	Death, Day 6[b]
14	54	F	3 gm/day 2 gm/day	4 4	2.1	2nd	64	100	64	90	—	No	Death, Day 8[b]

[a] Empirically given antibiotics before culture results were known are not listed; the additional antibiotic administered to three patients during treatment was because of intercurrent pneumonia.

[b] Treatment days.

[c] Days after treatment.

Renal Function. Seven patients maintained normal renal function during treatment; four with initially altered renal function (serum creatinine = 1.6 to 2 mg per dl) recovered normal function during therapy. In another four patients with creatinine levels between 1.8 and 2.1 mg per dl, renal function worsened during treatment, with serum creatinine levels between 2.1 and 5.4 mg per dl. The finding of urinary sodium below 15 mEq per liter in these patients suggested the diagnoses of hepatorenal syndrome.

Superinfection. During aztreonam treatment, three patients developed clinically significant superinfections (18.9%), one with *S. faecalis* peritonitis on the fifth treatment day followed by death 24 hr later and the other two with *Streptococcus mutans* and *Streptococcus equinus* bacteremia on Days 12 and 13, respectively; ampicillin elicited a good response. The data related to the superinfections, type and duration of antibiotic therapy and aztreonam levels are given in Table 3. Tolerance of aztreonam was good, and there were no major adverse effects.

DISCUSSION

The advanced stage of cirrhosis and the bacteriological data of our patients as well as the "*in vitro*" susceptibility of the organisms to aztreonam are in agreement with previous reports (2, 5–9, 15, 20). The pharmacokinetics of aztreonam have been described using an open, two-compartmental model in healthy subjects (12, 21–23). A prolonged half-life (mean = 3.2 hr) and higher trough serum levels after 8 hr (mean = 7.6 μg per ml) associated with a decreased nonrenal clearance (mean = 0.2 ml per min per kg) have been reported after administration of a single dose of aztreonam in cirrhotic patients (24). While in our patients the trough serum levels were also very high (mean = 27 μg per ml), the peak serum levels (mean = 61.9 μg per ml) were similar to those reported in healthy subjects, probably because of the large distribution volume related to ascites.

It has been demonstrated that most antibiotics penetrate well into the ascitic fluid of cirrhotic patients after systemic administration (25–31). Our data showed that the peak fluid levels of aztreonam were 50 to 60% those of serum levels and remained stable during the interval between two doses, as has also been observed using other antibiotics (25–31). There was no relationship between the fluid levels and the cytological counts or ascitic fluid protein as noted elsewhere (27). It is not known if peritoneal inflammation alters antibiotic penetrance into the fluid, although the main factors determining these levels are the serum levels and the volume of the fluid itself (27, 32). The role of antibiotic protein binding in ascitic

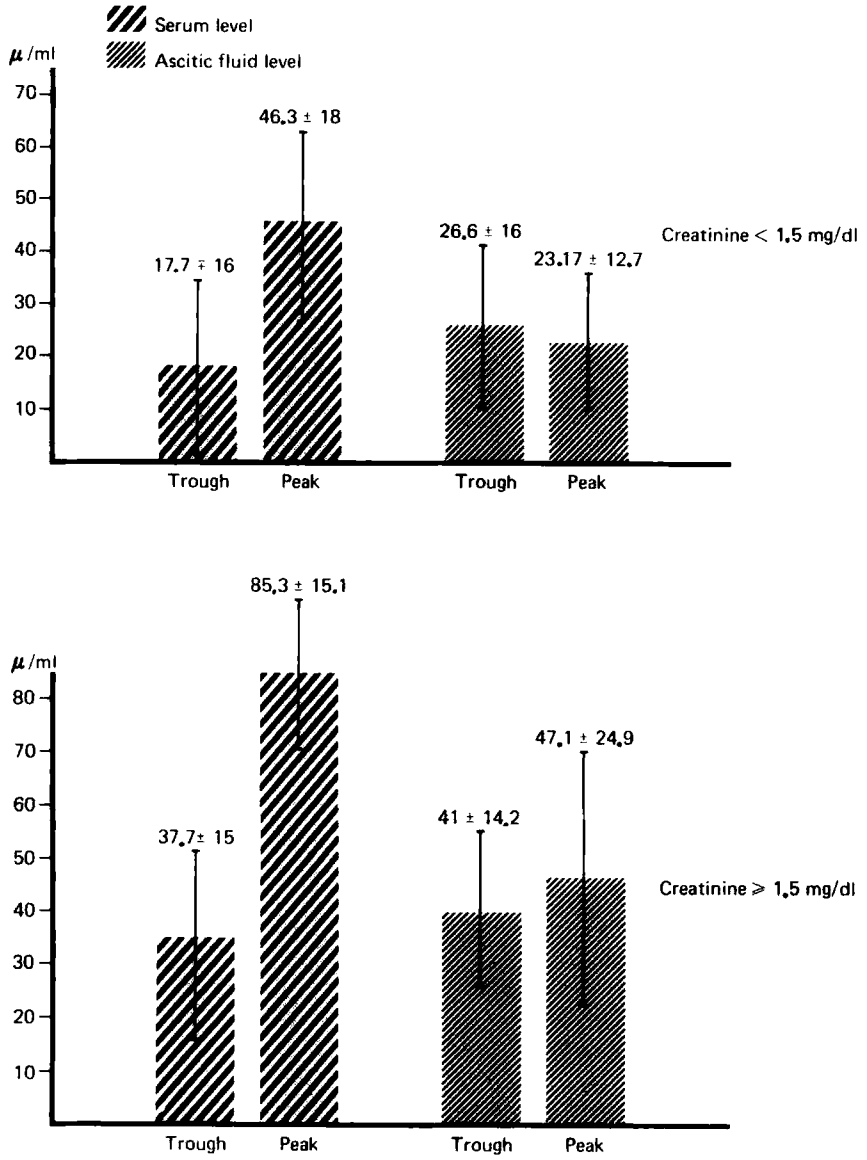

FIG. 1. Serum and ascitic fluid aztreonam levels in patients with creatinine < 1.5 mg per dl (*top*) and in patients with creatinine ≥ 1.5 mg per dl (*bottom*). Ascitic fluid levels of aztreonam (peak and trough) remained stable in both groups of patients, averaging about half of the corresponding peak serum levels.

TABLE 4. Ascitic fluid macroscopic aspect and PMN cell count of patients before, during and at the end of therapy

Ascitic fluid	Initial	On 2nd day	On 5th day	At the end of therapy
Macroscopic aspect				
Fluid cloudy	15	8	7	—
Fluid clear	1	4	7	9
Not performed	—	4	2	7
PMN cell count				
>5,000	8	6	4	—
1,000–5,000	2	2	3	—
250–1,000	1	2	1	—
<250	—	2	5	8
Not performed	5	4	3	8
Total	16	16	16	16

fluid penetrance is probably a minor one; protein binding is weak. The main antibiotic fraction which penetrates is the free fraction (33), and ascitic fluid protein in these patients is low in spite of infection (2, 3, 5).

There was a good correlation between the antibiotic efficacy and serum and ascitic fluid levels. The persistence of cloudy fluid and a count of >1,000 PMN cells per mm^3 on the fifth treatment day in half of our patients did not in itself indicate an unsatisfactory response to the therapy. The mortality rate of 62.5% was similar to that reported for previous studies with aminoglycosides (3–5). Although the infection probably exerted a strong influence, in particular on patients who died during treatment, in the majority the direct cause of death was hepatorenal syndrome or variceal hemorrhage.

The good tolerance and the absence of renal toxicity in our patients concurred with other authors' findings (13–15). Renal function worsened only in four of our patients, apparently due to hepatorenal syndrome; an effect of the antibiotic, however, cannot be entirely excluded. These findings suggest that aztreonam may offer an advantage over the aminoglycosides which, because of the risk of nephrotoxicity, pose difficulties in insuring adequate therapeutic levels. The high percentage of streptococcal superinfections in our patients corre-

TABLE 5. Cause of death for 10 patients

	No. of cases	Day of death
During treatment		
Hepatorenal syndrome	4	5, 8, 9, 12
Digestive tract hemorrhage	2[a]	6, 13
S. faecalis peritonitis	1	6
After treatment		
Aspiration pneumonia	1	1
Pneumonia, digestive tract hemorrhage	1[b]	25
E. coli sepsis	1	20
Total	10	

[a] One with accompanying pneumonia.
[b] Following esophageal transection 2 days earlier.

sponded to the asymptomatic colonization and superinfection with *S. faecalis* reported in 20 to 30% of aztreonam-treated patients (16, 34). In our patients, they were severe enough to be the cause of death in at least one case. A study in healthy volunteers investigating changes in intestinal flora following oral aztreonam administration showed a clear correlation between high intestinal antibiotic levels and increased stool enterococcal concentration (35). It is possible that the same may occur after systemic antibiotic administration because the high serum levels may result in high biliary excretion and thus high intestinal concentration of the antibiotic.

In conclusion, in our study, aztreonam was well tolerated and efficacious; ascitic fluid cultures became negative, symptoms of infection were controlled, and serum and ascitic fluid levels were very high. In a few cases, streptococcal superinfection was a negative aspect of the therapy. The high mortality rate was related to the poor underlying condition of the patients. The results of this study suggest that lower doses may be used to achieve therapeutic antibiotic levels. Further studies are needed to determine the position of aztreonam with respect to other β-lactams in the therapy of this type of infection.

REFERENCES

1. Felisart J, Rimola A, Arroyo V, et al. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. Hepatology 1985; 5:457–462.
2. Pinto Correia J, Conn HO. Spontaneous bacterial peritonitis in cirrhosis: endemic or epidemic? Med Clin North Am 1975; 59:963–981.
3. Ariza J, Fernández Viladrich P, Garau J, et al. Peritonitis espontanea del cirrótico. Consideraciones sobre su patogenia y factores pronósticos. A propósito de 59 casos. Med Clin 1982; 79:305–310.
4. Weinstein MP, Iannini PB, Stratton CHW, et al. Spontaneous bacterial peritonitis. A review of 28 cases with emphasis on improved survival and factors influencing prognosis. Am J Med 1978; 64:592–598.
5. Hoefs JC, Canawati HN, Sapiro FL, et al. Spontaneous bacterial peritonitis. Hepatology 1982; 2:399–407.
6. Conn HO. Spontaneous bacterial peritonitis. Multiple revisitations. Gastroenterology 1976; 70:455–457.
7. Sánchez Tapias JM, Terés J, Arroyo V, et al. Infección peritoneal en la cirrosis hepática con ascitis. Cinco años de experiencia. Gastroenterol Hepatol 1978; 1:15–21.
8. Pinzello G, Simonetti RG, Craxí A, et al. Spontaneous bacterial peritonitis. A prospective investigation in predominantly non alcoholic cirrhotic patients. Hepatology 1983; 3:545–549.
9. Javaloyas M, Ariza J, Gudiol F. La bacteriemia en el paciente con cirrosis hepática. Análisis etiopatogénico y pronóstico de 92 casos. Med Clin 1984; 82:612–616.
10. Crossley IR, Williams R. Spontaneous bacterial peritonitis. Gut 1985; 26:325–331.
11. Cabrera J, Arroyo V, Ballesta AM, et al. Aminoglycoside nephrotoxicity in cirrhosis. Value of urinary β_2-microglobulin to descriminate functional renal failure from acute tubular damage. Gastroenterology 1982; 82:97–105.
12. Wise R, Dyas A, Hegarty A, et al. Pharmacokinetics and tissue penetration of aztreonam. Antimicrob Agents Chemother 1982; 22:969–971.
13. Greenberg RN, Reilly PM, Luppen KL, et al. Treatment of serious gram-negative infections with aztreonam. J Infect Dis 1984; 150:623–630.
14. Henry SA, Bendush CB. Aztreonam: worldwide overview of the treatment of patients with gram-negative infections. Am J Med 1985; 78(Suppl 2A):57–64.
15. Scully BE, Neu HC. Use of aztreonam in the treatment of serious infections due to multiresistant gram-negative organisms, including *P. aeruginosa*. Am J Med 1985; 78:251–261.
16. Gudiol F, Pallarés R, Ariza J, et al. A comparison of aztreonam versus aminoglycoside in the treatment of gram-negative septicemia. J Antimicrob Chemother 1986; 17:661–671.
17. Martin WJ, Washington JA II. *Enterobacteriaceae*. In: Lennette EH, Ballows A, Hausler WJ, et al., eds. Manual of clinical microbiology, 3rd ed. Washington, D.C.: American Society for Microbiology, 1980: 195–219.
18. Washington JA II, Sutter VL. Dilution susceptibility test: agar and macrobroth dilution procedures. In: Lennette EH, Ballows A, Hausler WJ, et al., eds. Manual of clinical microbiology, 3rd ed. Washington, D.C.: American Society for Microbiology, 1980: 453–458.
19. Swabb EA, Leitz MA, Pilkiewicz FG, et al. Pharmacokinetics of the monobactam SQ 26776 after single intravenous doses in healthy subjects. J Antimicrob Chemother 1981; 8(Suppl E):131–140.
20. Sykes RB, Bonner DP, Aztreonam: the first monobactam. Am J Med 1985; 78(Suppl 2A):2–10.
21. Swabb EA, Sugerman AA, Platt TB, et al. Single dose pharmacokinetics of the monobactam aztreonam (SQ 26776) in healthy subjects. Antimicrob Agents Chemother 1982; 21:944–949.
22. Swabb EA, Sugerman AA, McKinstry DN. Multiple dose pharmacokinetics of the monobactam aztreonam (SQ 26776) in healthy subjects. Antimicrob Agents Chemother 1983; 23:125–132.
23. Scully BE, Swabb EA, Neu HC. Pharmacology of aztreonam after intravenous infusion. Antimicrob Agents Chemother 1983; 24:18–22.
24. McLeod CM, Bartley EA, Payne JA, et al. Effects of cirrhosis on kinetics of aztreonam. Antimicrob Agents Chemother 1984; 26:493–497.
25. Wilson DE, Chalner TC, Madaff MA. The passage of cefalothin into and out of ascitic fluid. Am J Med Sci 1967; 253:449–452.
26. Gerding DN, Hall WH. The penetration of antibiotics into peritoneal fluid. Bull NY Acad Med 1975; 51:1016–1019.
27. Gerding DN, Hall WH, Schierl EA. Antibiotic concentrations in ascitic fluid of patients with ascites and bacterial peritonitis. Ann Intern Med 1977; 86:708–713.
28. Moreau L, Durand H, Biclet P. Cefotaxim concentrations in ascites. J Antimicrob Chemother 1980; 6(Suppl A):121–122.
29. Garcia MJ, Dominguez-Gil A, Perez FD, et al. Disposition of cefoxitin in patients with ascites. Eur J Clin Pharmacol 1981; 20:371–374.
30. Benoni G, Arosio E, Raimondi MG, et al. Distribution of ceftazidime in ascitic fluid. Antimicrob Agents Chemother 1984; 25:760–763.
31. Richey GD, Schleupner CJ. Peritoneal fluid concentrations of gentamicin in patients with spontaneous bacterial peritonitis. Antimicrob Agents Chemother 1981; 19:312–315.
32. Gerding DN, Kromhout JP, Sullivan JJ, et al. Antibiotic penetrance of ascitic fluid in dogs. Antimicrob Agents Chemother 1976; 10:850–855.
33. Braude AI. Pharmacologic principles. In: Smith LH, ed. Antimicrobial drug therapy, Vol VIII. Major problems in internal medicine. Philadelphia, Pennsylvania: W. B. Saunders Company, 1976: 67–99.
34. Chandrasekar PH, Smith BR, LeFrock JL, et al. Enterococcal superinfection and colonization with aztreonam therapy. Antimicrobial Agents Chemother 1984; 26:280–282.
35. DeVries-Hospers HG, Welling GW, Swabb EA, et al. Selective decontamination of the digestive tract with aztreonam: a study of 10 healthy volunteers. J Infect Dis 1984; 150:636–642.