ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1978, p. 405-411
0066-4804/78/0013-0405$02.00/0

Vol. 13, No. 3
Printed in U.S.A.

Treatment of Osteomyelitis and Septic Arthritis with Cefazolin

ROBERT J. FASS

Division of Infectious Diseases, Department of Medicine, The Ohio State University College of Medicine, Columbus, Ohio 43210

Received for publication 16 August 1977

Sixteen cases of severe osteomyelitis and septic arthritis caused by staphylococci, streptococci, gonococci, and a variety of gram-negative bacilli were treated with 4 to 8 g of parenteral cefazolin per day; nine received subsequent therapy with oral cephalexin or ampicillin. Of 16 infections, 15 were apparently cured. Cefazolin concentrations in those patients were: serum (peak), 25 to 216 μg/ml; synovial fluid, 24 to 46 μg/ml; and bone, 3.2 to 10.6 μg/g. Bacterial pathogens had minimal inhibitory concentrations of cefazolin of 2 μg or less per ml and seemed to be eradicated from foci of infection during therapy. One infection in a diabetic patient did not respond; despite high concentrations of cefazolin in serum, no detectable antibiotic was present in her infected metatarsal, and the infecting *Escherichia coli* (minimal inhibitory concentration, 16 μg/ml) was not eradicated during therapy. Concentrations of cefazolin in bone in 10 uninfected patients who received 1-g intramuscular doses prophylactically before surgery were also measured. Concentrations in bones from those who had normal renal function ranged from <0.6 to 2.8 μg/g.

The cephalosporins, like the penicillins, are desirable choices for the antimicrobial treatment of osteomyelitis and septic arthritis because they can be given in high doses for prolonged periods of time with relatively little toxicity. Cefazolin is potentially more useful than cephalothin, the prototype of the cephalosporin antibiotics, because it is more active against cephalosporin-susceptible gram-negative bacteria (14), yields drug concentrations in sera that are fourfold higher after comparable intramuscular and intravenous doses, and is not desacetylated to a relatively inactive metabolite (9, 11). Despite those favorable characteristics, there are few data to substantiate the efficacy of cefazolin in the treatment of bone and joint infections, and such efficacy cannot be accepted based only on inference because cefazolin is highly bound to plasma proteins, has a small apparent volume of distribution (9, 11), and might not be delivered to diseased bone and joint tissues in therapeutic concentrations.

The present report describes the results of treating 16 cases of osteomyelitis and septic arthritis with cefazolin. Therapeutic cure and failure were correlated with the in vitro susceptibilities of individual pathogens, the achieved cefazolin concentrations in sera, synovial fluids, and bones, and the effectiveness of those concentrations in eradicating etiological agents in vivo. Additional data on concentrations of cefazolin achievable in bone and cartilage were obtained by assaying surgical specimens from 10 uninfected patients who received the drug prophylactically.

MATERIALS AND METHODS

Clinical studies. Fifteen adult patients (ages 17 to 72 years) with 16 episodes of severe osteomyelitis or septic arthritis or both, three of which had concomitant bacteremia, were treated with cefazolin in University Hospital, Columbus, Ohio. Anatomic diagnoses were based on clinical and radiographic criteria. Bacteriological diagnoses of eight of the infections were based on positive cultures of bone biopsies or joint aspirates. For seven, diagnoses were based on cultures of drainage from fistulae. When potentially contaminated drainage was the only specimen available for culture, multiple specimens were obtained, and culture results were correlated with Gram stains before etiological significance was attributed to isolates. In a single patient with gonococcal arthritis, the diagnosis was based on isolation of *Neisseria gonorrhoeae* from the pharynx and the presence of a suppurative (71,000 neutrophils per mm^3) synovial fluid.

Cefazolin was administered intravenously or intramuscularly in doses of 4 to 8 g per day for 10 to 90 (mean, 34.6) days. Nine patients received subsequent oral therapy, eight with 1 to 4 g of cephalexin per day and one with 2 g of ampicillin per day.

Clinical recovery from infection, radiographic resolution or stabilization, and absence of relapse during

prolonged follow-up (mean, 11 months after cefazolin was discontinued) was considered to represent therapeutic cure. Bacteriological responses were determined by obtaining follow-up cultures when possible from bones or joints (five patients) and healing fistulae or wounds (six patients) during and after therapy.

Patients were monitored for adverse reactions clinically and with serial measurements of hemoglobin, hematocrit, leukocyte, and differential cell counts, creatinine, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, bilirubin, and by urinalysis.

In vitro studies. Minimal inhibitory concentrations (MICs) of cefazolin, cephalothin, and cephalexin were determined for most patient isolates by a microdilution method (3) using tripticase soy broth (BBL), an inoculum of 10^5 to 10^6 colony-forming units per ml, and serial twofold concentrations of antibiotics such that final concentrations ranged from 32 to 0.03 μg/ml. For some patient isolates, susceptibilities were determined by a standardized disc diffusion test (17).

"Peak" and "valley" concentrations of cefazolin in sera were determined by a modified filter-paper disc agar-diffusion assay (15) using *Staphylococcus aureus* B2786E and brain heart infusion (Difco) agar; minimal sensitivity of the assay was 0.6 μg/ml. Sera for determination of peak concentrations were obtained at 0 to 1 h postintravenous infusion and at 1 h postintramuscular injection. Sera for determination of valley concentrations were obtained just before a dose. Serum concentrations of cephalexin were determined on samples obtained at various intervals after an oral dose using subtilis spore suspension (Difco) and antibiotic medium 1 (Difco) agar; minimal sensitivity of the assay was 2 μg/ml.

Synovial fluid assays were performed identically to the serum assays.

Bone and cartilage specimens obtained for assay were mechanically cleaned and vigorously rinsed in phosphate buffer (pH 6) to remove visible marrow and blood. Although diligent effort to remove all blood was made, quantification of that remaining with the bone and cartilage fragments was not attempted. The specimens were then blotted dry, frozen in liquid nitrogen, and crushed with a hammer. The fragments were placed in vials, to which phosphate buffer was added such that there was 0.5 g of bone or cartilage per ml of buffer. Specimens were stored in the buffer at 4°C overnight to extract the antibiotic present. The buffer was assayed as above, using antibiotic diluted in buffer rather than serum for standard curves, and the cefazolin concentrations in bone were calculated. Parallel assays of bone fragments pulverized by ultrasound or cryoimpacting in liquid nitrogen did not increase recovery (R.B. Prior and R.J. Fass, unpublished data).

Prophylaxis studies. Ten uninfected adult patients who were undergoing various orthopedic surgical procedures each received 1 g of cefazolin intramuscularly 2 to 5 h prior to removal of specimens of bone or cartilage or both. The surgical specimens were assayed for cefazolin concentrations as described above.

RESULTS

Clinical studies. The data from six patients with acute bone and joint infections caused by staphylococci, streptococci, or gonococci are shown in Table 1. The three cases of osteomyelitis were caused by contiguous spread from surgical wound infections. Case 1 had the wound aspirated and cases 2 and 3 had debridements of infected bone in addition to antimicrobial therapy. The three cases of hematogenous septic arthritis all had diagnostic arthocenteses; case 5 had six additional daily aspirations.

The data from five patients with recurrent osteomyelitis are shown in Table 2. All had had previous surgery or antimicrobial therapy or both and presented with documented relapses. In addition to cefazolin therapy, case 8 had a contiguous soft-tissue abscess drained and cases 9 and 10 had debridements of infected bone and skin flap grafts.

The data from five diabetic patients with infected feet are shown in Table 3. All had peripheral neuropathy, vascular disease, and previous episodes of foot ulcerations and infections which had been treated surgically or medically or both. In addition to cefazolin, two (cases 7 and 10) had debridements of infected bone, and three (cases 8, 9, and 11) had amputations which included single digits and metatarsals. Resections were conservative to preserve maximum function; obviously devitalized bone was removed without attempting to necessarily resect all infected tissues.

All pathogens tested from the 15 patients who were cured were inhibited by 2 μg or less of cefazolin per ml. In the 10 from whom follow-up cultures of bone, joint fluid, or drainage could be obtained, pathogens were eradicated during therapy. Isolates from those who received cephalexin or ampicillin were susceptible to those agents as well as to cefazolin.

The single patient (case 14) who did not respond to cefazolin had a mixed infection with *S. aureus* and *Escherichia coli*. The staphylococcus, which was considered to be cefazolin susceptible (MIC, 0.12 μg/ml), was eradicated, but the *E. coli*, which was considered to be relatively cefazolin resistant (MIC, 16 μg/ml), persisted.

During therapy with cefazolin, healing wounds were often colonized with cephalosporin-resistant *Enterobacteriaceae, Pseudomonas aeruginosa,* enterococci, or *Candida* without adverse effects.

Antibiotic concentrations. The cefazolin concentrations in sera and bone which were observed in infected patients receiving continuous therapy are shown in Table 4. Mean peak and valley serum concentrations from patients receiving 1.5- or 2-g intravenous doses every 8 h were 96.9 and 13.6 μg/ml, respectively. Peak serum concentrations from the two patients treated intramuscularly were lower, but valley concentrations were similar. Bone concentra-

TABLE 1. *Acute osteomyelitis and septic arthritis treated with cefazolin*

Case	Diagnosis	Pathogen	MICs (μg/ml)[a]			Cefazolin			Cephalexin		Outcome	Followup (months)[c]
			Cefazolin	Cephalothin	Cephalexin	Dose (g/day)	Route[b]	Days	Dose (g/day)	Days		
1	Postsurgical wound infection with osteomyelitis of femur	*S. aureus*	1.0	0.25	4	4–6	i.v.	46	1–2	222	Cure	34
2	Postsurgical wound infection with osteomyelitis of skull	*S. aureus*	ND	S	ND	2–3	i.v.	18	4	6	Cure	7
3	Postsurgical wound infection with osteomyelitis of sternum	*S. aureus*[d]	0.25	0.12	4	4.5–6	i.v., i.m.	90	4	30	Cure	16
4	Hematogenous septic arthritis of sacroiliac joint	*S. aureus*[d]	0.5	0.5	2	6	i.v.	28	2	24	Cure	1
5	Hematogenous septic arthritis of knee	*Streptococcus pyogenes*[d]	0.12	≤0.03	0.25	6	i.v.	28			Cure	3
6	Hematogenous septic arthritis of knee	*Neisseria gonorrhoeae*	ND	ND	ND	6	i.v.	10			Cure	2

[a] ND, Not done. S, Susceptible by disc diffusion test, MIC not done.
[b] i.v., Intravenous; i.m., intramuscular.
[c] Calculated from when cefazolin therapy was completed.
[d] Cultures from blood and local focus of infection.

TABLE 2. *Recurrent osteomyelitis treated with cefazolin*

Case	Diagnosis	Pathogen	MICs (μg/ml)[a]			Cefazolin			Cephalexin		Outcome	Follow-up (months)[c]
			Cefazolin	Cephalothin	Cephalexin	Dose (g/day)	Route[b]	Days	Dose (g/day)	Days		
7	Posttraumatic osteomyelitis of humerus	*S. aureus*	0.5	0.25	4	3–6	i.v., i.m.	48			Cure	21
8	Hematogenous osteomyelitis of humerus and scapula	*S. aureus*	0.25	0.25	2	6	i.v.	36	2	90	Cure	19
9	Paraplegia, decubitus ulcers, osteomyelitis of ischium	*S. aureus*	1.0	0.5	4	6	i.v., i.m.	42			Cure	8
10	Quadraplegia, decubitus ulcers, osteomyelitis of sacrum	*Streptococcus pyogenes*	0.12	0.12	0.5	6	i.v.	30			Cure	2
11	Sickle cell disease, osteomyelitis of femur	*Salmonella enteritidis*	2.0	S	128	8	i.v.	14	None[d]		Cure	21

[a] S, Susceptible by disc diffusion test, MIC not done.
[b] i.v., Intravenous; i.m., intramuscular.
[c] Calculated from when cefazolin therapy was completed.
[d] Treated with 2 g of oral ampicillin per day indefinitely. MIC, 1 μg/ml.

TABLE 3. *Recurrent osteomyelitis and septic arthritis in the feet of diabetics treated with cefazolin*

Case	Diagnosis	Pathogens	MICs (μg/ml)[a]			Cefazolin			Cephalexin		Outcome	Follow-up (months)[c]
			Cefazolin	Cephalothin	Cephalexin	Dose (g/day)	Route[b]	Days	Dose (g/day)	Days		
12	Osteomyelitis 4th and 5th metatarsals and phalanges	*S. aureus*	2.0	0.5	4	6	i.v.	30	2	34	Cure	11
		Streptococcus agalactiae	0.12	0.12	2							
13[d]	Osteomyelitis 1st metatarsal and proximal phalynx	*S. aureus*	ND	S	ND	4	i.v.	40			Cure	3
		Streptococcus sp.	ND	S	ND							
14[d]	Osteomyelitis 1st metatarsal and proximal phalynx	*S. aureus*	0.12	0.12	2	4–6	i.v.	42			Failed	Retreated
		E. coli	16	32	8							
15	Osteomyelitis 1st metatarsal and proximal phalynx	*E. coli*	2	8	8	6	i.v.	28	4	50	Cure	9
		Proteus mirabilis[e]	ND	S	ND							
		Streptococcus pyogenes[e]	ND	ND	ND							
16	Osteomyelitis 1st and 2nd metatarsals and tarsals	*Klebsiella pneumoniae*	ND	S	ND	4	i.v.	23	2	120	Cure	13
		Peptococcus sp.	ND	ND	ND							
		Peptostreptococcus sp.	ND	ND	ND							

[a] ND, Not done. S, Susceptible by disc diffusion test, MIC not done.
[b] i.v., Intravenous.
[c] Calculated from when cefazolin therapy was completed.
[d] Cases 13 and 14 were the same patient but separate episodes of infection.
[e] Eradicated prior to cefazolin therapy by previous antimicrobial therapy.

tions were 5.8 to 10.6 (mean 8.2) μg/g except in the two samples from the feet of diabetics, which were lower.

Cefazolin concentrations in samples of synovial fluid from case 5, each obtained on a different day, were 23.9 μg/ml at 1 h, 45.7 μg/ml at 4 h, and 27.8 and 22.1 μg/ml at 8 h after 2-g intravenous doses.

Cephalexin serum concentrations were determined at random times on five occasions from three patients. Except for one valley sample, concentrations ranged from 8.3 to 17.8 μg/ml.

The bone concentrations of cefazolin observed in uninfected patients who received a single 1-g intramuscular prophylactic dose of cefazolin are shown in Table 5. Concentrations were 2.8 μg/g or less in the samples from patients with normal renal function and 6.4 and 8.2 μg/g in those from the two azotemic patients.

Adverse reactions. There was no local intolerance to parenteral cefazolin or gastrointestinal intolerance to oral cephalexin or ampicillin. Two patients had elevated liver enzymes, one had probable drug fever, and one developed eosinophilia (10%) on cefazolin. None of the associated adverse reactions was considered serious.

DISCUSSION

In the present study, 15 of 16 serious bone and joint infections were cured with cefazolin. The pathogens that were tested were all susceptible to 2 μg/ml or less. Concentrations of cefazolin that were achieved in sera and infected tissues consistently exceeded 2 μg/ml and eradicated the organisms from foci of infection during therapy. The single patient who failed to respond had an infection caused by a relatively resistant *E. coli* (MIC, 16 μg/ml). Although that concentration was easily surpassed by concentrations achieved in her serum, the apparent penetration of cefazolin into the diseased bone in her vascularly compromised diabetic foot was inadequate to eradicate the organism.

Although the experience is scattered, previous reports (1, 4–8, 12, 13) have also shown that cefazolin is effective in treating a variety of bone and joint infections, particularly those caused by *S. aureus* (1, 4, 12). Experiences with treating infections caused by streptococci other than enterococci (1, 4, 12, 13), gonococci (7, 13), and facultative gram-negative enteric bacilli (1, 4, 6, 8) were more limited.

The present study is unique in reporting the results of treating bone and joint infections in diabetic feet with cefazolin. Such infections are usually mixed with combinations of staphylococci, streptococci (including enterococci), facultative gram-negative enteric bacilli, and anaerobes playing significant etiological roles (10).

TABLE 5. *Cefazolin concentrations in bone from uninfected patients receiving a single intramuscular 1-g dose of cefazolin for prophylaxis*

Case	Creatinine (mg/dl)	Time after dose (h)	Concn (μg/g)
17	1.2	1.8	1.8 (tibia)
18	1.0	2.0	<0.6 (femur)
19	1.4	2.5	1.2 (knee)
20	1.1	3.0	2.0 (hip)
21	1.0	3.5	1.4 (knee)
			2.0 (knee[a])
22	0.9	4.0	1.8 (elbow)
23	1.0	4.5	<0.6 (hip)
24	0.8	4.8	2.8 (fibula)
25	2.4	3.8	6.4 (hip)
26	4.1	5.0	8.2 (knee)

[a] Cartilage.

TABLE 4. *Cefazolin concentrations in sera and bones from infected patients receiving continuous therapy*

Dose regimen[a]	Case	Creatinine (mg/dl)	Serum concn (μg/ml)		Bone concn (μg/g)
			Peak	Valley	
1.5 g i.v. q8h	3	0.8	156	11	5.8 (sternum)
					9.0
2 g i.v. q8h	4	0.7	38	8	
	5	0.8	107	16	
	7	1.1	69	18	
	8	0.8	78	9	
	10	0.9	82	6	10.6 (sacrum)
	12	0.9	75	16	
	14	1.1	107	16	<0.6 (metatarsal)
			216	27	
	15	1.0	41	9	3.2 (metatarsal)
1 g i.m. q6h	1	0.6	25	11	
2 g i.m. q8h	9	0.5	41	17	7.4 (ischium)

[a] i.v., Intravenous. q8h and q6h, Every 8 h and 6 h, respectively.
[b] i.m., Intramuscular.

The appropriateness of cefazolin as a chemotherapeutic agent in an individual case would depend on the particular bacteriology of that infection, since the susceptibilities of the facultative gram-negative bacilli and anaerobes to cefazolin are variable, and enterococci are consistently cefazolin resistant (2).

Although there are ample data to indicate that achievable serum concentrations of cefazolin easily surpass the MICs of cefazolin-susceptible bacteria, there is little information on concentrations achievable in bone and joint tissues. In the present study, concentrations of cefazolin in bones (other than from the feet of diabetics) were 4 to 18% of peak serum concentrations. Concentrations in synovial fluid from one patient were 22 to 43% of a peak serum concentration. In other studies (5, 13), cefazolin concentrations were similar and also exceeded the MICs of cefazolin-susceptible bacteria. In this and another study (16), however, concentrations of cefazolin in bone after 1-g intramuscular doses administered for prophylaxis to patients with normal renal function were lower than those observed in infected patients and did not consistently exceed the MICs of cefazolin-susceptible bacteria.

I thank Valerie L. Helsel for technical assistance.

This study was supported by a grant from Eli Lilly and Co., Indianapolis, Ind.

LITERATURE CITED

1. **Arango, J. L., H. Trujillo, D. Worren, A. Uribe, N. H. Agudelo, and E. L. de Vidal.** 1976. Effectiveness of two new cephalosporins, cefazolin and cephapirin, administered intermittently in acute and chronic osteomyelitis in children. J. Int. Med. Res. **4**:183–194.
2. **Ernst, E. C., S. Berger, M. Barza, N. V. Jacobus, and F. P. Tally.** 1976. Activity of cefamandole and other cephalosporins against aerobic and anaerobic bacteria. Antimicrob. Agents Chemother. **9**:852–855.
3. **Fass, R. J., C. A. Rotilie, and R. B. Prior.** 1974. Interaction of clindamycin and gentamicin in vitro. Antimicrob. Agents Chemother. **6**:582–587.
4. **Gold, J. A., J. J. McKee, and D. S. Ziv.** 1973. Experience with cefazolin: an overall summary of pharmacologic and clinical trials in man. J. Infect. Dis. (Suppl.) **128**:S415–S421.
5. **Gould, S., P. Actor, J. J. McKee, and D. S. Ziv.** 1975. Cefazolin sodium: developmental review and update. Clin. Med. **82**:23–28.
6. **Hammer, G. S., B. S. Ribner, B. R. Meyers, and S. Z. Hirschman.** 1975. Clinical studies with cefazolin: a new cephalosporin antibiotic. Mt. Sinai J. Med. **42**:142–149.
7. **Handsfield, H. H., P. J. Wiesner, and K. K. Holmes.** 1976. Treatment of the gonococcal arthritis-dermatitis syndrome. Ann. Intern. Med. **84**:661–667.
8. **Kaye, D., S. P. Levison, K. Ries, D. Tanphaichitra, and M. E. Levison.** 1974. In vitro, pharmacological and clinical evaluation of cefazolin, a new cephalosporin antibiotic. Infection (Suppl.) **2**:88–90.
9. **Kirby, W. M. M., and C. Regamey.** 1973. Pharmacokinetics of cefazolin compared with four other cephalosporins. J. Infect. Dis. (Suppl.) **128**:S341–S346.
10. **Louie, T. J., J. G. Bartlett, F. D. Tally, and S. L. Gorbach.** 1976. Aerobic and anaerobic bacteria in diabetic foot ulcers. Ann. Intern. Med. **85**:461–463.
11. **Nightingale, C. H., D. S. Greene, and R. Quintiliani.** 1975. Pharmacokinetics and clinical uses of cephalosporin antibiotics. J. Pharm. Sci. **64**:1899–1927.
12. **Pickering, L. K., D. M. O'Connor, D. Anderson, A. C. Bairan, R. D. Feigin, and J. D. Cherry.** 1974. Comparative evaluation of cefazolin and cephalothin in children. Ped. Pharmacol. Ther. **85**:842–847.
13. **Reller, L. B., W. W. Karney, H. N. Beaty, K. K. Holmes, and M. Turck.** 1973. Evaluation of cefazolin, a new cephalosporin antibiotic. Antimicrob. Agents Chemother. **3**:488–497.
14. **Sabath, L. D., C. Wilcox, C. Garner, and M. Finland.** 1973. In vitro activity of cefazolin against recent clinical bacterial isolates. J. Infect. Dis. (Suppl.) **128**: S320–S326.
15. **Simon, H. J., and E. J. Yin.** 1970. Microbioassay of antimicrobial agents. Appl. Microbiol. **19**:573–579.
16. **Smilack, J. D., W. H. Flittie, and T. W. Williams, Jr.** 1976. Bone concentrations of antimicrobial agents after parenteral administration. Antimicrob. Agents Chemother. **9**:169–171.
17. **Sub-Committee on Antimicrobial Susceptibility Tests.** 1975. Performance standards for antimicrobial disc susceptibility tests. National Committee for Clinical Laboratory Standards, Villanova, Pa.