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NOTES

Clinical Efficacy and Levels of Ciprofloxacin in Tissue in Patients with Soft Tissue Infection

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The clinical efficacy of ciprofloxacin was evaluated with 21 patients with soft tissue infection due mainly to gram-negative aerobic bacteria. Clinical cure was noted in 16 patients (76%), and clinical improvement was noted in the remaining 5 patients (24%). In addition, levels of ciprofloxacin were measured in the sera and tissues of 11 patients. Mean concentrations in tissue averaged 1.75 times the levels in serum. Ciprofloxacin should provide serum and soft tissue concentrations above the MICs for most gram-negative aerobic bacteria.

Ciprofloxacin (Bay 0 9867), a new quinolone carboxylic acid antibiotic, has been found to be active in vitro against many gram-negative aerobic bacteria including *Pseudomonas aeruginosa* (3). Studies of its clinical efficacy in urinary (1, 14), respiratory (13, 14), gastrointestinal (13, 14), and soft tissue (8, 13, 14) infections have been previously reported. Pharmacokinetic studies have shown good penetration of drug into tonsillar tissue (7), prostate (2), saliva (10), blister fluid (4), and muscle and bone (5, 8). The purposes of our study were to determine levels of ciprofloxacin in infected tissue and serum and to correlate these levels with clinical efficacy in patients with soft tissue infections due mainly to gram-negative aerobic bacteria.

Twenty-two patients with soft tissue infections were entered into the study between 1 July 1984 and 30 June 1986. Entry criteria were (i) presence of inflammatory changes at a discrete soft-tissue site (e.g., skin, subcutaneous tissue), (ii) isolation of a bacterial pathogen from the site of infection within 48 h of enrollment, (iii) susceptibility of the organism to ciprofloxacin by in vitro testing, and (iv) ability of the patient to take oral medications. Informed consent was obtained from all patients. Mean age of the patients was 58 (range, 26 to 81) years. Mean weight was 73.5 (range, 56 to 79) kg. Diseases concurrently present were diabetes in six patients, peripheral vascular disease in five patients, renal insufficiency in two patients, and carcinoma in one patient. One patient was removed from the study because of confusion after receiving one dose of the drug. Sites of soft tissue infection in the 21 patients were leg or foot in 14 patients, thigh or hip in 4 patients, sacrum in 2 patients, and external ear in 1 patient. Of the patients, 18 were infected with *P. aeruginosa*, 1 was infected with *Pseudomonas cepacia* and 1 each was infected with *Enterobacter aerogenes* and *Mycobacterium fortuitum*. In four cases, additional gram-negative bacteria were isolated, but in lower numbers. All organisms were susceptible to ciprofloxacin, as indicated by Kirby-Bauer disk testing. Therapy was given for a mean of 27 (range, 7 to 49) days. A concomitant antibiotic (clindamycin) was given to one patient. Laboratory tests (complete blood count, chemistry panel, and urinalysis) and microbiological cultures from the site of infection were performed when patients entered the study, once weekly while they were on therapy, and at the completion of the study. Only patients who completed at least 5 days of therapy were evaluated for clinical and microbiological efficacy. Clinical cure was defined as complete resolution of signs and symptoms of infection. Clinical improvement was defined as marked or moderate reduction in the severity of signs and symptoms. Failure was defined as lack of improvement or worsening of signs and symptoms of infection. Microbiological cure was defined as complete eradication of the suspected pathogen(s) from the site of infection.

Ciprofloxacin was given as a single oral dose of 750 mg every 12 h and was timed to be separated by at least 1 h from a meal. Levels were determined at 1 and 11 h after doses 1 and 4. Tissue specimens were collected with a scalpel by sharp dissection from the skin and subcutaneous tissue at the lateral margins of the site of infection. An attempt was made to select only tissue that showed signs of infection by visual inspection but that was not grossly necrotic or dead. After excess blood was blotted off, the samples were weighed and stored frozen at −70°C until assayed. Ciprofloxacin levels were determined as previously described (12). Briefly, ciprofloxacin levels were assayed by high-pressure liquid chromatography with an octadecylsilene column (Alltech Associates, Inc., Deerfield, Ill.) and an Integrator SP4270 (SpectraPhysics, Piscataway, N.J.) detector with column conditions similar to those described by Gau et al. (9). The serum samples and internal standards (isopropyl analog of ciprofloxacin) were prepared by dilution with 0.1 N phosphoric acid to a pH of 3. For determination of drug levels in tissues, the drug was extracted by alternating vortexing and ultrasonification until a homogeneous suspension was achieved. After filtration (0.45-μm pore size), the sample was adjusted to a pH of 3 with 0.1 N phosphoric acid and injected into the column. Concentrations of ciprofloxacin of 0.0125 to 3.0 mg/liter were used as standards. Calibration curves were linear at concentrations above 0.1 mg/liter. Recovery of ciprofloxacin and its metabolites was greater than or equal to 91%. Run-to-run variability was less than or

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TABLE 1. Concentrations of ciprofloxacin in serum and tissue in patients with soft tissue infection

Source and time of sample	No. of samples	Concn of drug (mean ± SD)
Serum		
Dose 1		
h 1[a]	11	2.30 ± 1.11 mg/liter
h 11	10	0.57 ± 0.42 mg/liter
Dose 4		
h 1	3	2.10 ± 0.23 mg/liter
h 11	3	1.30 ± 1.21 mg/liter
Tissue		
Dose 1		
h 1	11	4.03 ± 1.65 μg/g
h 11	10	1.26 ± 0.80 μg/g
Dose 4		
h 1	3	3.33 ± 2.21 μg/g
h 11	3	1.89 ± 1.08 μg/g

[a] Number of hours sample was obtained after dose of ciprofloxacin.

equal to 7%. The lower limit of sensitivity of the method was 0.01 mg/liter.

Clinical cure was achieved in 11 of 14 patients with leg or foot infection, 3 of 4 patients with thigh or hip infection, 1 of 2 patients with sacral decubiti, and 1 patient with an external ear infection (total cure rate, 76%). Clinical improvement was noted in the remaining 5 patients (24%). Microbiological cure was noted in 19 (95%) of the 21 patients. *P. aeruginosa* resistant to ciprofloxacin developed in two patients during therapy. These two isolates, found on cultures taken at completion of therapy, were felt to reflect colonization, since all clinical signs of infection had resolved, and neither patient required further antibiotic therapy. Overall, the drug was well tolerated. Gastric irritation occurred in two patients. Pseudomembranous colitis occurred in one patient who was also receiving clindamycin simultaneously.

Levels of ciprofloxacin in serum and tissue were determined for 11 patients by high-pressure liquid chromatography (Table 1). At 1 h after doses 1 and 4, mean levels in serum of 2.30 (range, 0.82 to 4.23) and 2.1 (range, 1.85 to 2.4) mg/liter, respectively, were noted. At 11 h after doses 1 and 4, mean levels in serum of 0.57 (range, 0.05 to 1.30) and 1.30 (range, 0.11 to 2.94) mg/liter, respectively, were noted. Penetration of drug into tissue at the site of infection was excellent, with mean levels in tissue of 4.03 (range, 1.47 to 5.9) and 3.33 (range, 1.38 to 6.42) μg/g occurring 1 h after doses 1 and 4, respectively. Mean levels in tissue at 11 h after oral administration of the drug were 1.26 (range, 0.10 to 2.18) and 1.89 (range, 0.96 to 3.41) μg/g for doses 1 and 4, respectively. The mean ratio of concentration of drug in tissue to concentration in serum was 1.75 with all four time points.

The complete-clinical-cure rate of 76% and partial-cure rate of 24% found in our study compare favorably with rates reported previously (6, 13, 14). This high rate of clinical response is particularly encouraging since 55% of our patients had chronic underlying diseases such as diabetes mellitus and peripheral vascular disease. Microbiological cure was found in all except two patients who developed resistant *P. aeruginosa* while on therapy. Side effects of the therapy were uncommon, and the drug was well tolerated even after prolonged courses of therapy.

Because little information is available on the penetration of ciprofloxacin into infected soft tissue (5, 8), we used high-pressure liquid chromatography to determine levels of ciprofloxacin in infected skin and subcutaneous tissue. We observed a mean level in serum of 2.3 mg/liter at 1 h after the first 750-mg dose. This level is similar to peak levels in serum (range, 2.12 to 4.5 mg/liter) reported by other investigators (10, 11). The mean concentration in serum of 0.57 mg/liter at 11 h after dose 1 measured in this study was higher than noted previously (11). Although mean levels in serum at 11 h postdose were noted to be higher after dose 4 than after dose 1, few samples were available to evaluate.

Penetration of ciprofloxacin into tissue obtained from the margins of infected areas was excellent and averaged 1.75 times the mean concentrations in serum found in this study. Similar studies of penetration into skin and subcutaneous tissue have not been previously reported. Reported levels of ciprofloxacin in muscle and bone, however, have averaged 0.7 to 2.0 times the concentration in serum (5, 8). Fong et al. (8) found levels which were 30 to 100% higher for infected bone than for bone in a control group. Mean levels of ciprofloxacin in muscle (2.4 μg/g) and bone (1.4 μg/g) after a 750-mg oral dose were lower than levels found in our study, but Fong et al. gave ciprofloxacin at 2 to 4 h before sample collection, whereas we gave the drug at 1 h before sample collection.

We found ciprofloxacin to be clinically useful in patients with skin and soft tissue infection due to susceptible gram-negative bacteria, particularly when parenteral therapy was not desired. Ciprofloxacin, 750 mg given orally every 12 h, should provide levels in serum and tissue above the MICs for most clinically encountered gram-negative bacteria. Because of the concern regarding the possibility of development of in vitro resistance while a patient is on therapy, careful clinical and microbiological follow-up is recommended.

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