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In Vitro Activity of Sparfloxacin (CI-978; AT-4140) for Clinical *Legionella* Isolates, Pharmacokinetics in Guinea Pigs, and Use To Treat Guinea Pigs with *L. pneumophila* Pneumonia

PAUL H. EDELSTEIN,[1,2]* MARTHA A. C. EDELSTEIN,[1] JOEL WEIDENFELD,[1] AND MARY BETH DORR[3]

Departments of Pathology and Laboratory Medicine[1] and Medicine,[2] University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104-4283, and Parke-Davis Pharmaceutical Research Division, Ann Arbor, Michigan 48105-2430[3]

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The activities of sparfloxacin, ciprofloxacin, and erythromycin for 21 clinical *Legionella* isolates were determined by agar and broth dilution susceptibility testing and by growth inhibition assays in guinea pig alveolar macrophages (sparfloxacin and ciprofloxacin). All three antimicrobial agents had roughly equivalent activities when buffered charcoal yeast extract agar medium supplemented with 0.1% α-ketoglutarate was used as the test medium; the MICs for 90% of strains were 1.0 μg/ml for erythromycin and sparfloxacin and 0.5 μg/ml for ciprofloxacin. Buffered charcoal yeast extract medium supplemented with 0.1% α-ketoglutarate inhibited the activities of all the antimicrobial agents tested, as judged by the susceptibility of a control *Staphylococcus aureus* strain. Broth macrodilution MICs for two *L. pneumophila* strains in buffered yeast extract supplemented with 0.1% α-ketoglutarate were ≤0.03 μg/ml for sparfloxacin, 0.06 μg/ml for ciprofloxacin, and 0.25 μg/ml for erythromycin; only erythromycin was inhibited by this medium. Ciprofloxacin and sparfloxacin (both 0.25 μg/ml) reduced bacterial counts of two *L. pneumophila* strains grown in guinea pig alveolar macrophages by 2 $\log_{10}$ CFU/ml, but regrowth occurred over a 3-day period. Sparfloxacin, but not ciprofloxacin (both 1 μg/ml), caused a 3- to 4-day postantibiotic effect. Pharmacokinetic and therapy studies of sparfloxacin were performed in guinea pigs with *L. pneumophila* pneumonia. For the pharmacokinetic study, sparfloxacin was given (10 mg/kg of body weight) to infected guinea pigs by the intraperitoneal route; peak levels in serum and lung were 2.6 μg/ml and 1.6 μg/g, respectively, at 1 h, with a terminal-phase half-life of elimination from serum of 5 h. All 15 infected guinea pigs treated with sparfloxacin (10 mg/kg/day) for 5 days survived for 11 days post-antimicrobial therapy, whereas 14 of 15 guinea pigs treated with erythromycin (60 mg/kg/day) survived for 11 days and 2 of 14 guinea pigs treated with saline survived for 11 days. Sparfloxacin was effective against *L. pneumophila* in vitro and in a guinea pig model of Legionnaires disease and may have been more effective than erythromycin. Sparfloxacin should be evaluated as a treatment of human Legionnaires disease.

There is a continuing search for new antimicrobial agents effective for the treatment of Legionnaires disease because of the drawbacks of erythromycin treatment, the current drug of choice (13). Erythromycin is only inhibitory for *Legionella pneumophila* grown in macrophages, which probably explains the need for the long duration of therapy for Legionnaires disease, without which there is a danger of relapse (8, 12, 13). In addition, administration of the drug is often unpleasant for patients because of gastrointestinal side effects with oral administration and severe pain or phlebitis with intravenous administration. Assessment of the in vitro activities of antimicrobial agents for *L. pneumophila* is complex because of the need to measure antimicrobial intracellular activity and the inactivation of many antimicrobial agents by media that are optimal for the growth of the organism. The quinolone group of antimicrobial agents has been remarkably active against *L. pneumophila* in vitro and in an animal model of Legionnaires disease (4, 8, 10, 11, 17–19). We determined the activity of sparfloxacin (AT-4140; CI-978), a new quinolone antimicrobial agent, for *Legionella* isolates using four different test methods: agar dilution susceptibility, broth dilution susceptibility, inhibition of bacterial growth within alveolar macrophages, and treatment of guinea pigs with *L. pneumophila* pneumonia (15). As a prelude to the animal treatment studies, we determined the pharmacokinetics of sparfloxacin in *L. pneumophila*-infected guinea pigs.

* Corresponding author.

MATERIALS AND METHODS

Bacterial strains and growth conditions. All legionellae studied were clinical isolates, the majority of which had been passaged fewer than three times previously. These strains were identical to those used in a prior study and were composed of 1 strain of *L. bozemanii*, 2 strains of *L. dumoffii*, 2 strains of *L. longbeachae*, 2 strains of *L. micdadei*, and 14 strains of *L. pneumophila* (8). *Staphylococcus aureus* ATCC 29213 was used as a control organism for susceptibility testing. To obtain inocula for susceptibility testing, legionellae were grown on locally made buffered charcoal yeast extract medium supplemented with 0.1% α-ketoglutarate (BCYEα), and nonlegionellae were grown on commercial tryptic soy agar containing 5% sheep blood (5). Incubation of all media was at 35°C in humidified air for 24 to 48 h, depending on the organism and the growth rate.

Antimicrobial agents. Standard powders of sparfloxacin, erythromycin, and ciprofloxacin were obtained from Parke-Davis Pharmaceutical Research Division, Ann Arbor, Mich.; Abbott Laboratories, North Chicago, Ill.; and Miles

Laboratories, Inc., West Haven, Conn., respectively. To prepare sparfloxacin for injection, the standard powder was dissolved in sterile 0.49 M lactic acid in 5% glucose for injection (pH 2.2). The pH was slowly adjusted to 3.35 with 1 N NaOH. The drug concentrations were 7.9 mg/ml for the pharmacokinetic study and 7.2 mg/ml for the treatment study. A sparfloxacin solution for injection was made fresh daily and was used within 1 h of preparation. Erythromycin lactobionate for intravenous injection (Elkins-Sinn, Inc., Cherry Hill, N.J.) was dissolved in sterile water for injection and was diluted to the concentration used for administration (10.8 mg/ml) with sterile lactated Ringer solution. The erythromycin dose solution was made fresh daily and was administered within 8 h of preparation.

Antimicrobial susceptibility testing. Agar dilution susceptibility testing was performed by using antimicrobial agent-containing BCYEα and Mueller-Hinton agars as described previously (8). Briefly, bacteria were inoculated to antimicrobial agent-containing BCYEα agar by using a Steers Folz Graves inoculator. The plates were incubated for 48 h, at which time MICs were determined. Plates containing the control *S. aureus* strain were incubated for 24 h. Broth macrodilution susceptibility testing was performed with *L. pneumophila* F889 and F2111 as described previously (6, 8) by using BYEα broth (*Legionella* isolates) or Mueller-Hinton broth (*S. aureus*). All testing was done in duplicate; in the case of disagreement, the geometric mean value was used as the MIC. Antimicrobial susceptibility testing with ciprofloxacin and erythromycin for the same bacteria used in this study has been reported previously (8); these drugs were included in this study as controls (8).

Growth inhibition in alveolar macrophages. Guinea pig pulmonary alveolar macrophages were harvested and purified as described previously (8). The final concentration of macrophages was approximately 10^5 cells per well. Incubation conditions for all studies were 5% CO_2 in air at 37°C.

L. pneumophila F889 and F2111 grown overnight on BCYEα agar were used to infect the macrophages. Approximately 10^4 bacteria were added to each well. Bacteria were incubated with macrophages for 1 h in a shaking incubator and then for 1 day in stationary culture, as described previously (8). One set of replicate wells was washed (500 μl) three times with tissue culture medium and was then sonicated at low energy to release intracellular bacteria, which were quantified by using BCYEα agar. Antimicrobial agents were then added to the washed, nonsonicated wells; no antimicrobial agents were added to several wells, which served as growth controls. The infected tissue cultures were then incubated for 2 days, after which supernatant samples were taken for quantitative culture. The antimicrobial agents were then removed by washing, and the experiment was continued for 5 more days, with daily quantification of *L. pneumophila* in well supernatants. All experiments were done in duplicate or triplicate, and quantitative plating was done in duplicate. All wells were observed microscopically daily to detect macrophage infection and to quantify roughly the numbers of macrophages in the wells. In this system there was no extracellular growth of *L. pneumophila*, so all increases in bacterial concentration in the supernatant were the result of intracellular growth.

Guinea pig pneumonia model. Male Hartley strain guinea pigs (weight, ≈350 g) were used for the pneumonia model, as described previously (7). Animals were observed for illness 1 week prior to infection; in the case of the animals used for the treatment study, temperatures and weights were obtained during the preinfection period. The guinea pigs were infected with *L. pneumophila* serogroup 1, strain F889, administered intratracheally. About 7×10^6 CFU were administered in the pharmacokinetic study, and $\approx 3 \times 10^6$ CFU were administered in the treatment study.

Pharmacokinetic study. Concentrations of sparfloxacin in serum and lung were measured in guinea pigs with *L. pneumophila* pneumonia. The drug was given in a single intraperitoneal dose (10 mg/kg of body weight in 0.5 ml) to guinea pigs 1 day after infection. At timed intervals after drug injection, anesthetized animals in groups of two to three were exsanguinated by removal of heart blood under direct vision. The lungs were then removed, rinsed in sterile saline to remove adherent blood, blotted dry on gauze, and weighed. Heart blood was allowed to clot at room temperature, after which serum was separated from the other components by centrifugation at $1,000 \times g$ at 5°C for 10 min. The lung was homogenized in a known volume of 0.49 M lactic acid in 5% glucose. Lung homogenates were then centrifuged at $5,000 \times g$ at 5°C for 30 min, and the supernatants were filtered through a 0.22-μm-pore-size nylon membrane filter (MSI, Westboro, Mass.) to remove the bacteria. The serum specimens were filtered identically. Pilot studies showed that the nylon filters retained no drug. The filtrates were stored at −20° until they were analyzed for sparfloxacin by high-pressure liquid chromatography. Negative controls included filtered serum and lung homogenate supernatants from an uninfected guinea pig given identical anesthesia, but no antimicrobial agent, and the lactic acid-glucose solution.

Drug assay. Sparfloxacin was quantified in serum and tissue by using reversed-phase high-pressure liquid chromatography. Acetonitrile-perchloric acid (1:1; vol/vol; 50 μl) was added to filtered and centrifuged serum and tissue specimens (100 μl) to precipitate protein. An internal standard, PD 115100, was added (50 μl) to the supernatant, which was then analyzed by high-pressure liquid chromatography by using a C-18 column (Partisil, 25 cm [length] by 4.6 mm [inner diameter]; particle size, 5 μm; ODS-3; Whatman, Clifton, N.J.). The solvent system was isocratic and was composed of 21% acetonitrile and 79% of an aqueous ion-pairing solution containing 0.05 M citric acid, 0.1% ammonium perchlorate, and 1.15 mM tetrabutylammonium hydroxide. The column flow rate was 1.2 ml/min at 2300 lb/in^2. Column effluent was monitored spectrophotometrically at 380 nm. The retention time of sparfloxacin was ≈8.5 min, and that of the internal standard was ≈11.9 min. A standardization curve for peak-height ratios was determined by using different concentrations of sparfloxacin contained in normal guinea pig plasma and was found to be linear over the concentration range of 0.1 to 20.0 μg/ml. No interference by guinea pig serum or filtered lung homogenate occurred.

Animal treatment study. Guinea pigs that survived surgery were randomized into three treatment groups 1 day after infection. Starting on that day, treatment was given for 5 days. One group of 15 animals received sparfloxacin (10 mg/kg in 0.5 ml) each morning, another 15 animals received erythromycin lactobionate (30 mg/kg in 1.0 ml) in the morning and afternoon, and the last group of 14 animals received 0.5 ml of normal saline each morning. All antimicrobial agents were administered by the intraperitoneal route. Animal weights were taken periodically during the 16-day postinfection observation period. Necropsies and quantitative lung cultures were performed on all animals that died. All animals that survived for 16 days postinfection were killed with pentobarbital, and then necropsies were performed. Quantitative cultures and histologic examinations were performed on the lungs of saline-treated survivors and on half of

the other survivors; the lowest-weight animals in each antimicrobial treatment group were selected for culture and histologic studies (7). Heart blood from all survivors was analyzed for antibodies to *L. pneumophila* serogroup 1, strain F889, by using an indirect immunofluorescence microscopy technique (6). Fluorescein-labeled goat anti-guinea pig immunoglobulin G (Cappel, Malvern, Pa.) was used as the secondary antibody in the indirect immunofluorescent antibody technique. Reading of the indirect immunofluorescent antibody and histologic slides was performed blinded with respect to the antimicrobial agent treatment group assignments.

Statistical analysis. Calculation of mean MICs was done by a geometric method. Comparison of nonparametric values was by the Fisher exact test, the chi-square test with correction for continuity, and the Mann-Whitney test (2). The Epistat computer program was used for calculation of the Fisher exact test value (T. Gustafson, Round Rock, Tex.). The nonpaired, two-tailed Student *t* test was used to compare parametric mean values (3). Type II errors were calculated by the method of Cohen (1). Calculation of drug pharmacokinetic parameters was performed by using the SIPHAR computer program (SIMED, Creteil-Cedex, France).

RESULTS

Agar and broth dilution susceptibility. All 21 *Legionella* strains tested by the agar dilution method were susceptible to concentrations of sparfloxacin, erythromycin, or ciprofloxacin that are readily achievable in serum. Control plates indicated no antimicrobial carry-over or contaminants. There was no more than a single-dilution discrepancy between duplicate plates. The average MIC, the MIC required to inhibit 50% of strains, the MIC required to inhibit 90% of strains, and the range of MICs for sparfloxacin were 0.34, 0.5, 1.0, and ≤0.125 to 2.0 μg/ml respectively. For erythromycin they were 0.66, 0.5, 1.0, and 0.25 to 2.0 μg/ml, respectively. The respective MICs for ciprofloxacin were 0.5, 0.5, 0.5, and ≤0.25 to 1.0 μg/ml. The sparfloxacin MICs for *L. pneumophila* F889 and F2111 were 0.5 and 0.25 μg/ml, respectively. The erythromycin and ciprofloxacin MICs for both strains were 0.5 μg/ml. All three antimicrobial agents were inhibited by BCYEα medium, with sparfloxacin being inhibited the most; the MIC for the *S. aureus* control strain was 16-fold lower on Mueller-Hinton agar than it was on BCYEα agar for sparfloxacin, 2-fold lower for erythromycin, and 4-fold lower for ciprofloxacin.

Both *L. pneumophila* strains tested (F889 and F2111) were more susceptible to all three antimicrobial agents when they were tested in BYEα broth than when they were tested on agar. For both strains, MICs were ≤0.03 μg/ml for sparfloxacin, 0.06 μg/ml for ciprofloxacin, and 0.25 μg/ml for erythromycin. In contrast to BCYEα agar inhibition of antimicrobial agents, there was no difference in the MICs for the control *S. aureus* strain between BYEα and Mueller-Hinton broths for the quinolone antimicrobial agents, but for erythromycin the MIC obtained by using Mueller-Hinton broth was fourfold lower than that obtained by using BYEα broth.

Antimicrobial inhibition of intracellular growth. Both *L. pneumophila* serogroup 1 strains grown in guinea pig alveolar macrophages were significantly inhibited by both sparfloxacin and ciprofloxacin (Fig. 1 and 2). However, only 1 μg of sparfloxacin per ml caused a postantibiotic effect that lasted 3 to 4 days, especially for strain F2111. In none of the macrophage experiments did macrophage monolayers become detached before the onset of grossly evident infection with *L. pneumophila*.

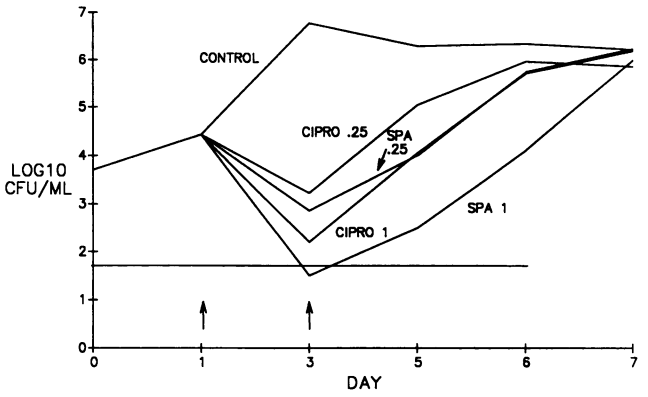

FIG. 1. Growth of *L. pneumophila* serogroup 1, strain F889 (log_{10} CFU per milliliter), in guinea pig alveolar macrophages versus day of incubation after initiation of infection. Antimicrobial agents were added to infected macrophages 1 day after infection and after wells were washed to remove extracellular bacteria. Two days later (day 3), after supernatant sampling, wells were washed to remove antimicrobial agents. The two vertical arrows designate the times of antimicrobial agent addition (day 1) and removal (day 3). Viable counts of *L. pneumophila* were determined from the culture supernatant on the specified days, except on day 1, when the absolute concentration of intracellular bacteria was determined by sonication and culture of replicate wells. All points represent the mean of triplicate wells counted in duplicate. Bacterial counts lower than 50 CFU/ml could not be detected, which is designated by a solid horizontal line. Control wells contained no antimicrobial agents, CIPRO .25 and CIPRO 1 contained 0.25 and 1.0 μg of ciprofloxacin per ml, respectively, and SPA .25 and SPA 1 contained 0.25 and 1.0 μg of sparfloxacin per ml, respectively.

Pharmacokinetic study. Pharmacokinetic data are given in Table 1. None of the negative control samples contained measurable drug. A biexponential decline in mean drug levels with time was noted, which was analyzed by using a two-compartment model. The terminal-phase half-life of elimination of sparfloxacin in serum was calculated to be ≈5 h, with the onset of the terminal phase being at ≈4 h postdose.

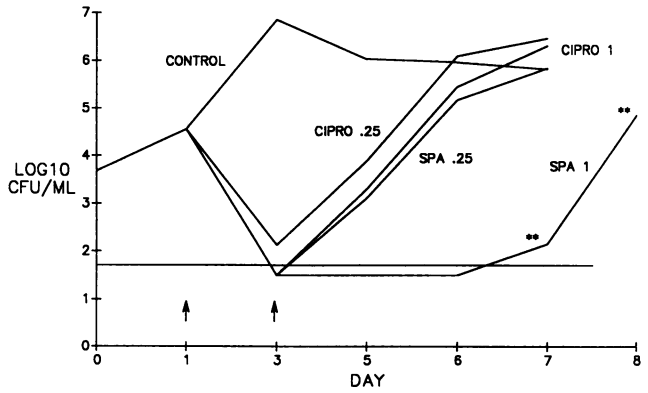

FIG. 2. Growth of *L. pneumophila* serogroup 1, strain F2111 (log_{10} CFU per milliliter), in guinea pig alveolar macrophages versus day of incubation after initiation of infection. Experimental conditions and abbreviations are the same as those described in the legend to Fig. 1. The two points marked by double asterisks represent results from a single well, as the other two wells contained no detectable *L. pneumophila*.

TABLE 1. Concentrations of sparfloxacin in sera and lungs of guinea pigs with *L. pneumophila* pneumonia after administration of 10 mg/kg by intraperitoneal injection

Time postdose (h)	No. of animals	Concn (μg/ml) in serum		Concn (μg/g) in lung	
		Mean	Range	Mean	Range
0.5	2	2.1	0.9–3.4	1.5	1.5[a]
1	2	2.6	2.5–2.7	1.6	1.5–1.6
2	2	1.8	1.7–1.9	0.8	0.7–0.8
4	3	0.4	0.1–0.7	0.2	0.2–0.3
8	3	0.3	0.2–0.4	0.1	0.1–0.2
12	3	0.1	0.1–0.2	0.1	0.1

[a] Only a single sample was tested.

Therapy in guinea pigs. Sparfloxacin was as effective as erythromycin in preventing deaths from *L. pneumophila* pneumonia in the guinea pigs ($P > 0.5$ by the chi-square test; $1 - \beta = 0.31$ for $\alpha_2 = 0.05$, where $1 - \beta$ is the power of the comparison and α_2 is the two-tailed significance level) (Fig. 3). Both antimicrobial agents were significantly more effective in preventing death than saline was ($P < 0.0001$ by chi-square). All lung cultures and necropsy results for animals that died before postinfection day 16 were diagnostic of *L. pneumophila* pneumonia. Several differences between erythromycin-treated and sparfloxacin-treated animals were noted. Animal weights were significantly lower during and after therapy in the group treated with erythromycin ($P = 0.05$ on day 6 postinfection, 0.01 on days 12 and 15 postinfection, and >0.1 on the day of infection and on day 4 postinfection; all by two-tailed nonpaired *t* test) (Fig. 4). Five of the seven lungs obtained for culture from erythromycin-treated survivors were positive for *L. pneumophila*, whereas none of the eight lungs from sparfloxacin-treated survivors gave such a result; this difference was significantly different ($P = 0.01$ by the Fisher exact test). The mean *L. pneumophila* concentration in the lungs from erythromycin-treated survivors was 4.4×10^3 CFU/g.

Erythromycin-treated survivors had significantly higher *L. pneumophila* antibody levels than did sparfloxacin-treated survivors ($P = 0.02$ by two-tailed Mann-Whitney test) (Fig. 5). No significant differences in lung histology were noted between survivors of either antimicrobial agent treatment group (Table 2).

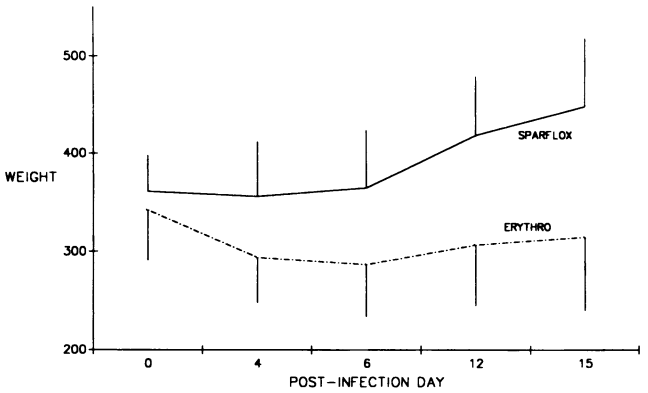

FIG. 4. Animal weight (in grams) versus postinfection day for animals treated either with sparfloxacin (SPARFLOX) or erythromycin (ERYTHRO). Vertical bars represent 95% confidence intervals.

DISCUSSION

Sparfloxacin, like other quinolone antimicrobial agents, is very active in vitro against *Legionella* species (4, 8, 10, 11, 17–19). The agar dilution MICs obtained with BCYEα medium were undoubtedly falsely high, as judged by the greater MICs for the control *S. aureus* strain when tested with BCYEα rather than Mueller-Hinton medium. The broth macrodilution MICs were probably much more accurate, especially for sparfloxacin, which was greatly inhibited by BCYEα agar. The results obtained with ciprofloxacin and erythromycin agreed within 1 twofold dilution with those obtained in a prior study of the same strains (8).

The lower agar and broth dilution MICs found for sparfloxacin were mirrored in the macrophage studies, which showed that sparfloxacin was more active than ciprofloxacin for the two strains studied. Prior studies have shown that erythromycin is purely inhibitory in the macrophage system, even at concentrations of 5 μg/ml, and is clearly less active than ciprofloxacin (8; unpublished data). The prolonged postantimicrobial effect noted with sparfloxacin was probably due to effective intracellular killing of *L. pneumophila*, but it could also have been due to the persistence of intracellular drug at concentrations near the extracellular MIC. Measurement of intracellular drug at such low concen-

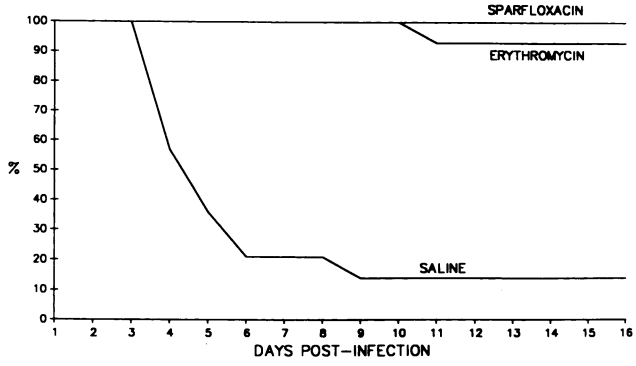

FIG. 3. Percent survival of guinea pigs with *L. pneumophila* pneumonia versus postinfection day. Animals were treated on postinfection days 1 to 5 with sparfloxacin ($n = 15$), erythromycin ($n = 15$), or saline ($n = 14$).

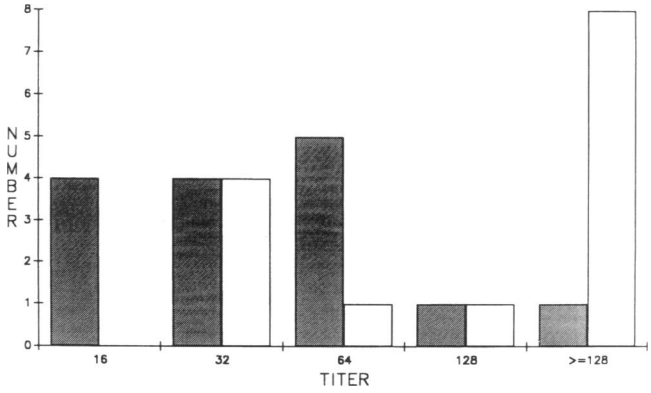

FIG. 5. Antibody levels to *L. pneumophila* serogroup 1, strain F889, in serum of guinea pigs that survived 16 days postinfection and that were treated with either sparfloxacin (shaded columns; $n = 15$) or erythromycin (open columns; $n = 14$).

TABLE 2. Lung histology results for survivors[a]

% Consolidated lung	No. of survivors treated with:	
	Sparfloxacin	Erythromycin
0	3	2
≤10	5	2
11–25	0	1
26–50	0	1

[a] Half of the survivors in each group were examined. $P > 0.40$ by the chi-square test; $1 - \beta < 0.3$, with $\alpha_1 = 0.05$, where $1 - \beta$ is the power of the comparison and α_1 is the one-tailed significance level.

trations is very difficult and has not been done for sparfloxacin. It is unclear from results of this study whether the differences noted between the activities of ciprofloxacin and sparfloxacin are clinically relevant. However, it is apparent that the in vitro differences noted between erythromycin and sparfloxacin activities had major correlates in the guinea pig model.

The pharmacokinetic profile of sparfloxacin in serum of guinea pigs is very similar to that measured in rodents (14). Our results differ from the rodent studies in that lung levels of sparfloxacin were consistently lower than concentrations in serum, in contrast to the 5:1 lung:serum concentrations found in rats and mice (14). Some of this discrepancy may be due to our use of infected rather than normal guinea pigs, the possibility that we lost drug while processing the lung tissue, and species differences. Regardless, a single dose of sparfloxacin provided lung concentrations above the extracellular broth MIC for strains F889 and F2111 for at least 12 h and probably 18 h.

Sparfloxacin was also very effective for the treatment of experimental Legionnaires disease, as are other quinolone antimicrobial agents (4, 10, 17, 18). The treatment study was designed to determine whether sparfloxacin treatment is more effective than saline treatment, and not to determine whether the drug is more effective than erythromycin therapy. Despite this, there were several indications that sparfloxacin is the superior therapy. The most convincing data supporting sparfloxacin superiority was the failure of erythromycin therapy to produce a bacteriologic cure compared with the lung sterilization observed in the sparfloxacin-treated survivors. Weight gain for the sparfloxacin-treated group, as opposed to weight loss in the erythromycin-treated group, also argues for the superiority of sparfloxacin. However, since erythromycin is toxic for uninfected guinea pigs, it is possible, in the absence of an adequate control group, that the weight loss was due solely to erythromycin therapy and not to infection (7). The discrepant *L. pneumophila* antibody levels between the sparfloxacin and erythromycin treatment groups was consistent with early lung sterilization by sparfloxacin and the lack of persistent antigen needed for antibody production. This appears to be the first study showing that effective antimicrobial therapy for Legionnaires disease can reduce antibody levels and can limit the utility of diagnostic antibody testing. There is no evidence that antibody production is required for recovery from infection, a point demonstrated in this study (9, 16). Although we did not measure erythromycin concentrations in sera and lungs in this study, low erythromycin levels are very unlikely explanations for the different efficacies of erythromycin and sparfloxacin. One of us has previously demonstrated good erythromycin levels in sera and lungs after identical dosing in this experimental model (7). Rather, the differences are most likely due to the bactericidal nature of sparfloxacin for *L. pneumophila*. One prior study demonstrated the superiority of pefloxacin over erythromycin, most certainly for identical reasons (4).

Contrary to a prior study (7), we were unable to demonstrate histologic correlates of bacteriologic cure, when rifampin therapy of *L. pneumophila*-infected guinea pigs was shown to result in significantly less pulmonary consolidation than did erythromycin therapy (7). This may be the result of the low numbers of animals used in the current study, as emphasized by the low power (high type II error) of the comparison.

Erythromycin is thought to be an effective drug for the treatment of Legionnaires disease on the basis of retrospective studies (13). Whether sparfloxacin would be more effective than erythromycin for the treatment of Legionnaires disease is unknown, but the macrophage model results suggest that sparfloxacin treatment would be a superior therapy. The animal model bacteriological and serological results, but not the treatment survival results, strongly support the superiority of sparfloxacin treatment over erythromycin therapy; these results do not help to determine which of the two quinolones would be superior in the absence of a ciprofloxacin treatment group. It is possible that short-course therapy with sparfloxacin or other selected quinolone antimicrobial agents may be just as effective or more effective than longer courses of erythromycin therapy, without the danger of relapse. These hypotheses need to be addressed by comparative clinical trials.

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