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Evaluation of the Efficacy of Ciprofloxacin against *Streptococcus pneumoniae* by Using a Mouse Protection Model

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A mouse protection model was used to investigate the association of the pharmacokinetics and pharmacodynamics with the in vivo efficacy of ciprofloxacin compared with that of penicillin G in the treatment of mice infected with *Streptococcus pneumoniae* ATCC 6303. Mice were inoculated intraperitoneally with 10 times the minimum lethal dose of *S. pneumoniae*. For determination of the 50% protective dose, subcutaneous antibiotics were begun 1 h after infection and were continued for 24 h. The 50% protective doses of ciprofloxacin and penicillin G were 25.52 ± 1.95 and 0.307 ± 0.006 mg/kg of body weight, respectively, an 83-fold difference in efficacy. For 100% protection with penicillin G, the time that the drug concentration needed to remain above the MIC was 51 min, a value easily achieved in most clinical situations. For 100% protection with ciprofloxacin, the peak concentration/MIC ratio must reach a value of 10.6. This ratio is rarely achieved with this drug against *S. pneumoniae* in clinical practice. These pharmacodynamic differences probably contribute to the reported differences in clinical success between these agents.

Ciprofloxacin, a fluoroquinolone antibiotic, has excellent activity against most aerobic gram-negative bacteria, with achievable levels in serum (1.5 to 2.9 μg/ml following a 500-mg oral dose and 2.7 to 4.2 μg/ml following a 750-mg oral dose) greatly exceeding the MICs for most important pathogens such as members of the family *Enterobacteriaceae* (3, 17, 18, 26). Ciprofloxacin's activity against gram-positive bacteria, however, is somewhat weaker, especially against organisms such as *Streptococcus pneumoniae*, for which the MICs for 50% (0.5 to 2.0 μg/ml) and 90% (1.0 to 4.0 μg/ml) of strains tested are closer to achievable peak levels of the drug in serum (5, 25).

Clinical failures have occurred when ciprofloxacin has been used to treat pneumococcal infections in patients at our institution, and these have been described in several other published reports (7, 14).

The purpose of the present study was to evaluate the in vivo effectiveness and pharmacokinetics of ciprofloxacin in the protection of mice inoculated with a virulent strain of pneumococcus. Our aim was to determine the doses of ciprofloxacin and penicillin G required to protect 50% (PD_{50}) and 100% (PD_{100}) of mice after intraperitoneal injection of *S. pneumoniae*.

MATERIALS AND METHODS

Animals, bacteria, and antibiotics. Swiss albino mice weighing approximately 23 g were obtained from Taconic Laboratories, Germantown, N.Y. *S. pneumoniae* ATCC 6303 serotype 3 was used throughout the study. Bacteria were passaged periodically on blood agar plates to maintain viability. Ciprofloxacin powder for intravenous use and penicillin G sodium for intravenous use were obtained from Miles Laboratories, West Haven, Conn., and Squibb Laboratories, Princeton, N.J., respectively.

Bacterial and animal studies. MICs were determined in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.) by a microtiter dilution method (23). The minimum lethal dose, the lowest dilution of organisms at which 100% mortality occurred, was determined by intraperitoneal injection of groups of mice (eight mice per group) with 0.5 ml of bacteria in Mueller-Hinton broth at serial 10-fold dilutions (10^5, 10^4, 10^3, 10^2, and 10^1 CFU/ml). Animals were observed for 7 days, and the rate and number of deaths at each dilution were recorded.

The PD_{50} and PD_{100} were determined by intraperitoneal inoculation of groups of mice (15 to 30 mice per group) with 5×10^2 to 1.5×10^3 CFU/ml (approximately 10 times the minimum lethal dose) of an overnight culture of *S. pneumoniae* suspended in 0.5 ml of Mueller-Hinton broth. Inocula were confirmed by dilutional studies and direct plating. Antibiotics were administered by subcutaneous injection (rotating injection sites) to groups of animals beginning 1 h after inoculation. The following doses and dosing schedules were used: ciprofloxacin, 10, 15, 20, 25, 32.5, 35, 45, and 55 mg/kg of body weight every 3.0 h for a total of 8 doses; penicillin G, 0.2, 0.3, 0.35, 0.425, 0.5, and 1.0 mg/kg every 1.5 h for a total of 16 doses.

This dosing schedule was calculated from the following pharmacokinetic and clinical use data: (i) the half-life of ciprofloxacin is 55 min in mice (25% that observed in humans), and the half-life of penicillin G is 12 min in mice (40% that observed in humans), and (ii) ciprofloxacin and penicillin G are normally administered to humans every 12 and 4 h, respectively. Therefore, the following simple calculation was used to determine the dosing schedules in our mouse experiments: for ciprofloxacin, 25% of a 12-h dosing interval yielded a 3-h dosing interval, and for penicillin G,

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40% of 4-h dosing interval yielded a 1.6-h dosing interval (a 1.5-h interval was actually used).

Control mice for the ciprofloxacin and penicillin groups received saline injections every 3 or 1.5 h, respectively. Mice were observed for 7 days for survival. Blood samples were taken by cardiac puncture from some animals immediately following death, and the samples were inoculated onto agar plates to demonstrate the presence of pneumococcus.

A sigmoid E_{max} model (29) was fitted to the observed data to determine the PD_{50} (20). The PD_{100} was determined by observing the plateau of the sigmoidal dose-response curve.

Pharmacokinetic studies. Antibiotics were administered to noninfected groups of mice (five mice per time point for each drug) by subcutaneous injection. To determine the peak concentration and half-life of ciprofloxacin, mice were sacrificed by cardiac puncture at 5, 10, 15, 20, 40, 60, 120, and 180 min after administration of ciprofloxacin at its PD_{50}. To determine the peak concentration of penicillin G produced by its PD_{50}, mice were sacrificed at 5, 10, 15, and 20 min after dosing. To determine the half-life of penicillin G, we also injected groups of mice with penicillin G at 10 times the PD_{50}. These mice were sacrificed at 5, 10, 15, 20, 30, 45, 60, and 90 min following antibiotic administration. Penicillin pharmacokinetics have previously been shown to be linear (13).

Antibiotic concentrations produced by administration of ciprofloxacin and penicillin G were measured by large-plate microbiological assay. *Klebsiella pneumoniae* ATCC 31003 and antibiotic medium no. 11 (Difco) were used to assay ciprofloxacin. The relationship between zone diameter and concentration in serum was linear between the lowest standard (0.5 μg/ml) and the highest standard (6.0 μg/ml). The coefficients of variation for the ciprofloxacin assay were 4.35 and 4.45% for the highest and lowest control samples, respectively. All drug concentrations were above the assay's limit of sensitivity (0.5 μg/ml). All assays were done on the same day. *Bacillus subtilis* ATCC 6633 suspension and antibiotic medium no. 5 (Difco) were used to assay penicillin G. The relationship between zone diameter and concentration in serum was linear between the lowest standard (0.1 μg/ml) and the highest standard (5.0 μg/ml). The coefficients of variation for the penicillin G assay were 3.48 and 2.87% for the highest and lowest control samples, respectively. All drug concentrations were above the assay's limit of sensitivity (0.1 μg/ml). All assays were done on the same day.

The elimination half-life was obtained by a nonlinear least-squares regression program, PCNONLIN (20), using a weighting factor of 1.0, and the area under the serum concentration-versus-time curve from time zero to infinity ($AUC_{0-\infty}$) was calculated by the trapezoidal rule method.

TABLE 1. Antibiotic doses and corresponding survival data for mice in experiments for determination of PD_{50} and PD_{100}[a]

Expt no. and penicillin G dose (mg/kg)	% Survival	Ciprofloxacin dose (mg/kg)	% Survival
Expt 1			
0.5	100	10	0
1.0	100	15	0
1.5	100	20	33.3
2.0	100	25	33.3
2.5	100	32.5	46.7
Expt 2			
0.2	0	15	6.7
0.3	46.7	25	53.3
0.35	73.3	35	100
0.425	100	45	100
0.5	100	55	100
1.0	100		

[a] Fifteen mice were used for each drug dose in both experiments.

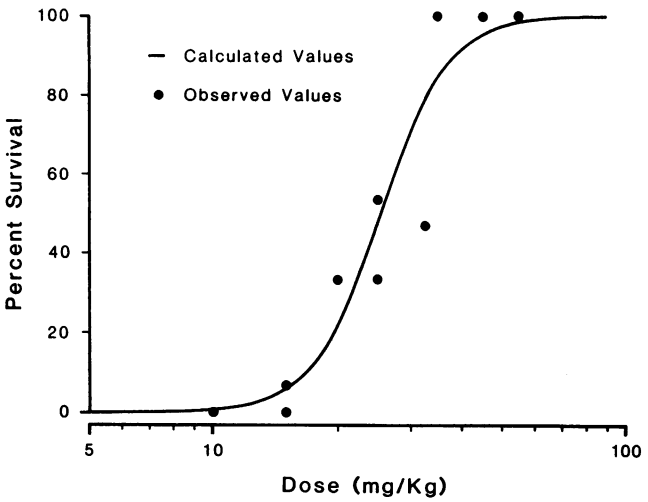

FIG. 1. Percent survival of mice treated with increasing doses of ciprofloxacin. The PD_{50} was 25.51 ± 1.95 mg/kg.

RESULTS

Bacterial studies. *S. pneumoniae* ATCC 6303 serotype 3 was used throughout the study and was selected because its susceptibility pattern was similar to the MICs for 90% of strains tested reported for both ciprofloxacin (2.0 μg/ml; range, 1.0 to 8.0 μg/ml) and penicillin G (approximately 0.01 μg/ml). The MICs of ciprofloxacin and penicillin G for this organism were determined to be 1.0 and 0.03 μg/ml, respectively.

The minimum lethal dose was $<2 \times 10^2$ CFU/ml. Therefore, an inoculum size of 10^3 (approximately 10 times the minimum lethal dose) was selected for subsequent PD_{50} studies.

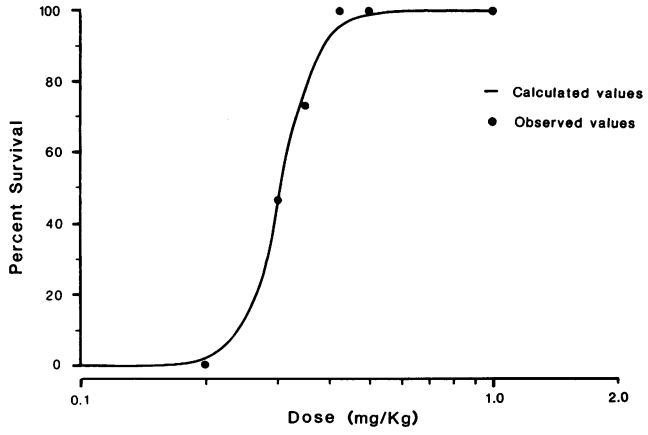

FIG. 2. Percent survival of mice treated with increasing doses of penicillin G. The PD_{50} was 0.307 ± 0.006 mg/kg.

TABLE 2. Pharmacokinetic parameters in mice after a single PD_{50} of ciprofloxacin or a single PD_{50} of penicillin G[a]

Agent, dose (mg/kg)	T_{max} (min)	C_{max}' (μg/ml)	C_{max}/MIC	$t_{1/2}$ (min)	Time above MIC (min)	% of dosing interval above MIC	AUC (μg · h/ml)
CIP, 25.51	20	4.5 ± 0.68	4.5	46.0 ± 3.5	130	72	6.7
PCN, 0.307	10	0.25 ± 0.04	8.3	11.6 ± 0.45[b]	41	45	0.0902

[a] T_{max}, time to maximum concentration in serum; C_{max}', maximum concentration in serum; $t_{1/2}$, half-life; AUC, area under the concentration-time curve; CIP, ciprofloxacin; PCN, penicillin G.
[b] The half-life for penicillin G was determined by administration of the drug at 10 times the PD_{50}.

PD_{50}s. The PD_{50}s of penicillin G and ciprofloxacin were determined with experiments performed on two separate occasions. On the basis of those data, dose-response curves were constructed (Table 1 and Fig. 1 and 2) by fitting an E_{max} model to the data with the aid of a linear least-squares regression analysis program (PCNONLIN) (20). The PD_{50} of ciprofloxacin was calculated from these curves to be 25.51 ± 1.95 mg/kg (95% confidence limits, 20.73 and 30.28 mg/kg), and the PD_{100} was observed to be 60 mg/kg. The PD_{50} of penicillin G was calculated to be 0.307 ± 0.006 mg/kg (95% confidence limits, 0.289 and 0.325 mg/kg), and the PD_{100} was observed to be 0.5 mg/kg.

In each experiment there was 100% mortality in the saline-treated control groups of mice. All saline-treated control mice died between 20 and 39 h after inoculation. Deaths in the penicillin G treatment groups occurred between 45 and 75 h after inoculation, while deaths in the ciprofloxacin treatment groups occurred between 36 and 70 h after inoculation.

Pharmacokinetic studies. Studies for the determination of pharmacokinetic parameters for penicillin G and ciprofloxacin in noninfected mice were performed simultaneously on the same day. Administration of the PD_{50} (25.51 mg/kg) of ciprofloxacin resulted in the following data, which are presented in Table 2 and Fig. 3: (i) the peak concentration was 4.5 ± 0.68 μg/ml; (ii) the half-life was 46.0 ± 3.5 min; (iii) the drug concentrations remained above the MIC for this organism for 130 min (72% of the dosing interval); and (iv) the AUC for the PD_{50} ($AUC_{PD_{50}}$) was 6.67 μg · h/ml.

The pharmacokinetic data resulting from the administration of penicillin G at the PD_{50} (0.307 mg/kg) are shown in Table 2 and Fig. 4 and are summarized as follows: (i) the peak concentration was 0.25 ± 0.04 μg/ml; (ii) drug concentrations remained above the MIC (0.03 μg/ml) for 41 min (45% of the dosing interval); and (iii) the $AUC_{PD_{50}}$ was 0.0902 μg · h/ml. Administration of penicillin G at 10 times the PD_{50} resulted in the following: (i) the peak concentration was 2.7 ± 0.08 μg/ml; (ii) the half-life was 11.6 ± 0.45 min; (iii) the concentration of penicillin G was 0.30 μg/ml at 42.5 min; therefore, drug concentrations divided by 10 remained greater than the MIC for 42.5 min (47% of the dosing interval); and (iv) the AUC was 0.895 μg · h/ml. Since pharmacokinetic data for penicillin G at the PD_{50} and 10 times the PD_{50} divided by 10 are nearly identical (maximum

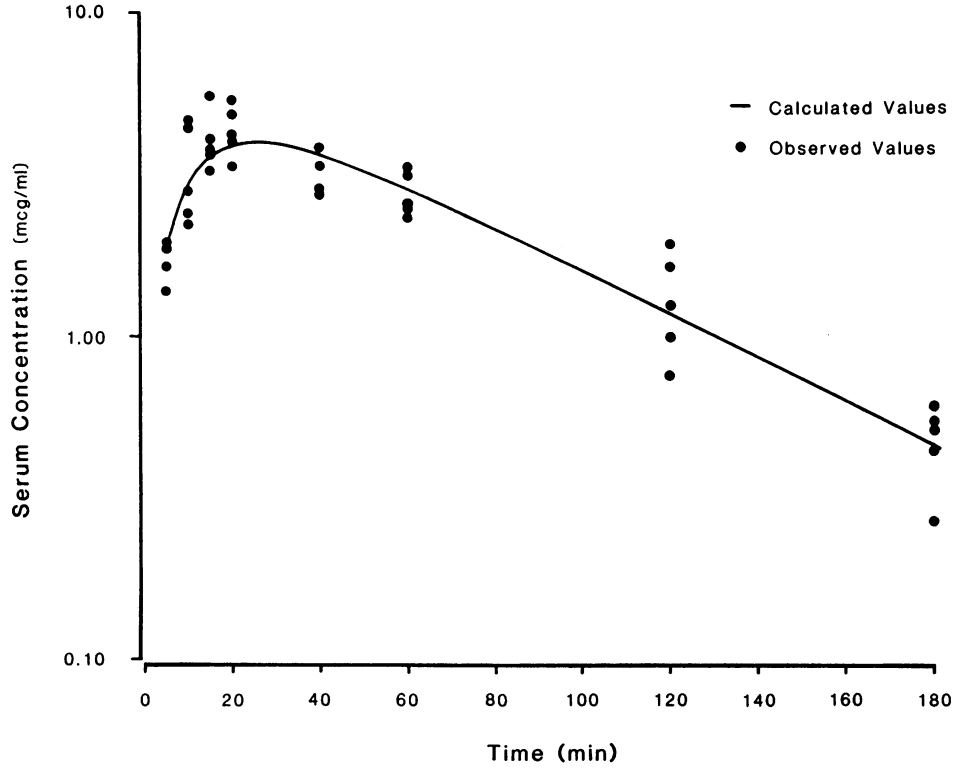

FIG. 3. Serum concentration-versus-time curve for ciprofloxacin administered at the PD_{50}.

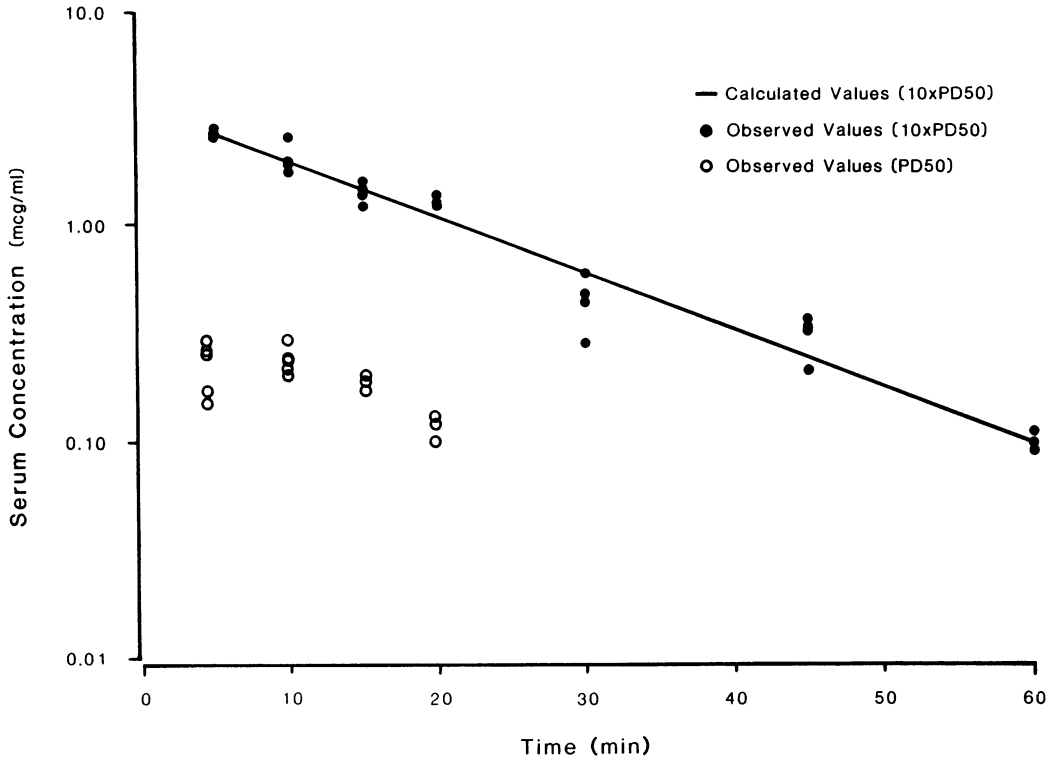

FIG. 4. Serum concentration-versus-time curve for penicillin G administered at the PD_{50} and at 10 times the PD_{50}.

concentrations in serum, 0.25 and 0.27 μg/ml; times above the MIC, 41 and 42.5 min; and AUCs, 0.0902 and 0.0895 μg h/ml, respectively), this demonstrates that penicillin's pharmacokinetics are linear over the dosing range and that the half-life of penicillin G at the PD_{50} should likewise be approximately 11.6 min.

DISCUSSION

The outstanding observation from the present study is the extremely low doses needed to reach the maximum effect for penicillin G (Fig. 2) compared with that for ciprofloxacin (Fig. 1). This is a reflection of the strong activity of penicillin against this typical strain of *S. pneumoniae* (MIC, 0.03 μg/ml). As a result, the PD_{50} and PD_{100} were 83 and 120 times, respectively, lower for penicillin G compared with those for ciprofloxacin (Fig. 1 and 2). Although it is difficult to extrapolate observations in an animal model to the clinical situation, the application of pharmacodynamic principles of antibiotics and microorganisms provides insight into understanding the importance of the findings of the present study to clinical situations.

Studies have shown that the duration of time that antibiotic concentrations remain above the MIC significantly correlates with efficacy for β-lactam antibiotics (22, 29). A single-dose study comparing 14 cephalosporins in a murine pneumococcal peritonitis model found that the only pharmacokinetic parameter which correlated with the 50% effective dose was the duration of time that the drug levels exceeded the MIC (15). In contrast, aminoglycosides and fluoroquinolones appear to have certain pharmacodynamic properties in common which differ from the pharmacodynamic properties of the β-lactams. It has been well established that aminoglycosides exhibit concentration-dependent bactericidal activity and that the maximum concentration of drug in serum and the AUC correlate with efficacy (2, 21, 29, 31, 32). More recently, the bactericidal capability of the fluoroquinolones has been shown to be concentration dependent (1, 9, 11, 12, 27, 28). Therefore, as with the aminoglycosides, optimal dosing of quinolones may involve the use of large single doses to attain the high levels in serum necessary to achieve a high ratio of maximum concentration in serum/MIC. In addition, aminoglycosides and fluoroquinolones exhibit postantibiotic effects (PAEs) against both gram-positive and gram-negative organisms (6, 24), while the penicillins and cephalosporins exhibit PAEs against gram-positive organisms only (4, 34). Against *S. pneumoniae*, penicillin G induces PAEs in vitro but not in vivo (30). Generally, with drugs that exhibit a prolonged PAE, there is no relationship between bacterial eradication and the duration of time above some critical concentration, e.g., MIC/MBC. This appears to be the case with aminoglycosides and quinolones. However, the ratio of the concentration in serum to the MIC does appear to correlate with the extent of the PAE. Maximal effects occur when organisms are exposed to drug levels of 5 to 10 times the MIC (8, 34).

On the basis of the data presented in Fig. 2, the PD_{100} is approximately 0.5 mg/kg. This dose results in penicillin concentrations that remain above the MIC for 51 min (56% of the dosing interval). This duration is easily achieved in clinical practice. Alternatively, the PD_{100} of ciprofloxacin is 60 mg/kg, resulting in a peak concentration/MIC ratio of 10.6, a value rarely achieved in clinical practice when this drug is used against *S. pneumoniae*. These differences in pharmacodynamic properties between penicillin G and cip-

rofloxacin are probably the basis for the differences seen with these agents in clinical practice.

The peak concentration/MIC ratio of 10.6 correlates well with the value of 8 described by Blaser and coworkers (1) in their in vitro pharmacokinetic capillary fiber model. In experiments with *Pseudomonas aeruginosa*, *K. pneumoniae*, *Escherichia coli*, and *Staphylococcus aureus*, regrowth occurred in all cultures during enoxacin treatment at peak concentration/MIC ratios of less than 8, despite the administration of subsequent doses. Bacterial regrowth resulted from the selection of resistant subpopulations, which was prevented when peak concentrations exceeded the MIC by a factor of 8 or more, demonstrating that the ratio of peak concentration to MIC may have been an important parameter in the clinical use of quinolones.

In addition to the serum-derived parameters described above, the dynamic interaction between the antimicrobial agent and the organism may also be important in interpreting the data. The pneumococcus may present a special penetration problem for ciprofloxacin, i.e., slow rate of antimicrobial uptake that allows effective concentrations to be attained only after several days of multiple dosing. Unfortunately, the organism is so virulent that the infected animals die before these levels are achieved unless extremely high doses are used, which would allow effective concentrations to be attained with the initial doses. For penicillin G, the same general situation may exist; however, the concentration to be exceeded in the organism is much lower.

The pneumococcus is a major cause of community-acquired respiratory tract infections. Published studies have indicated that ciprofloxacin performs well in the treatment of lower respiratory tract infections (10, 19, 33). Such studies, in general, have been poorly controlled or include few actual cases of pneumococcal pneumonia, and concern has been raised over the proper use of ciprofloxacin in this setting (14). Some 10 to 15% of pneumococcal isolates test susceptible to ciprofloxacin in vitro yet MICs are in the range of 0.5 to 2.0 μg/ml, which are close to the achievable levels of the drug in serum.

Our model suggests that peak levels of ciprofloxacin (approximately 10 μg/ml) which are approximately 10 times the MIC for *S. pneumoniae* ATCC 6303 are required to protect 100% of inoculated mice. Since a 750-mg oral dose of ciprofloxacin administered to humans produces levels in serum of approximately 3.0 to 4.0 μg/ml, achieving adequate protective levels of ciprofloxacin may be difficult against many, but not all, pneumococcal strains. Similar results have been obtained in other animal models (16).

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