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Pharmacokinetics of Sparfloxacin and Serum Bactericidal Activity against Pneumococci

M. TRAUTMANN,[1]* M. RUHNKE,[2] K. BORNER,[3] J. WAGNER,[4] AND P. KOEPPE[5]

Department of Medical Microbiology and Hygiene, University of Ulm, D-89075 Ulm[1]; Department of Internal Medicine, Klinikum Rudolf Virchow, Berlin[2]; and Institute of Clinical Chemistry and Clinical Biochemistry,[3] Institute of Medical Microbiology,[4] and Institute of Medical Physics and Laser Medicine,[5] Klinikum Benjamin Franklin, Berlin, Germany

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Sparfloxacin, a new fluorinated quinolone, exhibits higher in vitro activity against pneumococci than do ciprofloxacin and ofloxacin. Since up to 30% of cases of pneumococcal pneumonia are associated with bacteremia, and since an increasing percentage of pneumococci are resistant against penicillin, we studied the serum bactericidal activity of sparfloxacin against pneumococci in eight healthy, middle-aged volunteers. Pharmacokinetics in serum and urine after a 400-mg oral dose of sparfloxacin were comparable to those described by other authors. Inhibitory and bactericidal activities in serum were measured for four pneumococcal isolates representing penicillin-susceptible (one isolate), intermediately resistant (two isolates), and highly resistant (one isolate) strains. Geometric mean inhibitory titers ranged between 1:2.4 and 1:6.3 and bactericidal titers ranged between 1:1.3 and 1:3.6 during a time period of 1 to 6 h after drug intake. Although such titers were not sufficient to predict a clinical response based on previous pharmacodynamic studies using quinolone antibiotics, data obtained with volunteers may only partially reflect the clinical situation in which a rise of humoral antibodies directed against pneumococcal antigens may help to reinforce the bactericidal action of the antibiotic.

Sparfloxacin, a new fluorinated quinolone, is active against a broad range of gram-positive and gram-negative bacteria, including pathogens causing upper and lower respiratory tract infections. In particular, the spectrum of sparfloxacin includes pneumococci, *Haemophilus influenzae*, *Moraxella* (*Branhamella*) *catarrhalis*, *Staphylococcus aureus*, *Legionella* spp., *Mycoplasma* spp., and *Chlamydia* spp. (6–9, 16, 19). Compared to ciprofloxacin and ofloxacin, sparfloxacin is more active against pneumococci (MIC at which 90% of the isolates are inhibited [MIC_{90}], 0.25 to 1 versus 1 to 4 mg/liter) and *S. aureus* (MIC_{90}, 0.125 to 0.25 versus 0.5 to 1 mg/liter) (12, 24, 37). The favorable in vitro activity against pneumococci has become of major clinical interest since penicillin-resistant pneumococcal strains have been isolated with increasing frequency in various areas in the United States and Europe (2, 14, 23, 38). Since bacteremia occurs in up to 30% of cases of pneumococcal pneumonia (1, 2), we decided to study the bactericidal activity of sparfloxacin against penicillin-susceptible and penicillin-resistant pneumococcal isolates by means of the serum bactericidal test in volunteers. The pharmacokinetics of sparfloxacin and its glucuronide metabolite were also studied.

Eight healthy volunteers (five females, three males; age, 44.8 ± 9.9 years; weight, 68.1 ± 11.9 kg; height, 173 ± 7 cm; body surface, 1.81 ± 0.17 m^2; creatinine clearance, 126.7 ± 43.2 ml/min) were selected on the basis of physical and laboratory examinations performed 1 to 2 weeks prior to the start of the study. Inclusion criteria for the study were a normal creatinine clearance (> 90 ml/min) which was determined by sequential blood and urine creatinine determinations during a 3-day urine collection period, normal routine blood and urine laboratory tests, a normal electrocardiogram, and written informed consent. Exclusion criteria were pregnancy (as judged by a urine pregnancy test), concomitant medication, or any medication within 3 days before start of the study. The protocol of the study was approved by the Ethics Committee of the Free University of Berlin.

After zero time blood and urine samples were taken, volunteers received 400 mg (four tablets of 100 mg) of sparfloxacin orally with tap water under supervision by the investigator. Subjects remained fasting for 4 h after drug intake but were allowed to drink water during this time. They were allowed to have lunch after 4 h of fasting. Blood was taken from a peripheral vein at 1, 2, 4, 6, 8, 12, 24, 36, 48, 60, and 72 h after dosing. Blood samples were allowed to clot for 15 min at room temperature, after which each sample was centrifuged at 3,000 rpm in a refrigerated centrifuge and the serum was aspirated, divided in two aliquots, and stored frozen at −75°C. Urine was collected during the following time periods after drug intake: 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 h. The volume of each urine collection was recorded, and two 10-ml aliquots of each collection were frozen at −75°C.

Concentrations of sparfloxacin and its glucuronide metabolite in serum and urine were measured by high-performance liquid chromatography as described previously (5). The parameters C_{max}, t_{max}, and $t_{1/2\beta}$ were calculated by means of a two-compartment model for sparfloxacin and a one-compartment model for sparfloxacin-glucuronide and noncompartmentally for the others (32). The decision for a particular model was made according to the Schwarz criterion (34). The weighting scheme was based on the following sum of squares: $\Sigma (y_i - \hat{y}(x_i))^2 / \hat{y}(x_i)$. For the noncompartmental methods applied, we followed the example given by Gibaldi (13). The area under the data was estimated by the formula $AUD_{tot} = AUD_{t1 \rightarrow tn} + C_1 \cdot t_1/2 + C_n \cdot k_{el}$. The (by far) largest portion ($AUD_{t1 \rightarrow tn}$) was calculated by the (linear) trapezoidal rule. The coefficients

* Corresponding author. Mailing address: Department of Medical Microbiology and Hygiene, University of Ulm, Steinhövelstraße 9, D-89075 Ulm, Germany. Phone: 0049-731-5026951. Fax: 0049-731-5026949.

of variation for the mean AUD_{tot} and AUC_{tot} were 19 and 18%, respectively (all results for sparfloxacin, eight volunteers). The difference between AUD_{tot} and AUC_{tot} was less than 1%. The results for sparfloxacin-glucuronide were much less precise, with an AUD_{tot} range between 2 and 11.5 mg · h/liter. For nonlinear regression analysis, the calculations were done with our own programs (21); other calculations were performed by using an EXCEL worksheet. For simulation purposes, the estimated parameter values were imported into ORIGIN (Microcal Software, Inc.), a statistical and numerical analysis program, using the model chosen for data analysis. Because of the limited number of sparfloxacin glucuronide concentrations above the detection limit per subject, no individual model-dependent analysis could be done. If applicable, values were recalculated for dose per 70 kg of body weight.

Serum bactericidal activity against pneumococci was determined in serum samples obtained at 1, 2, 4, and 6 h after intake. Four pneumococcal strains exhibiting variable sensitivity to penicillin G were kindly supplied by B. Wiedemann, Institute of Medical Microbiology, Bonn, Germany. The origin of the strains was as follows: strain 1, Institut Pasteur, Paris, France, IP-no. 53146; strain 2, South African Institute for Medical Research, Johannesburg, South Africa, no. 01541; strain 3, Centre Hospitalier Intercommunal de Créteil, Paris, France, no. 6159-19; strain 4, Centre Hospitalier Intercommunal de Créteil, Paris, France, no. 6176-23F. MICs of penicillin G and sparfloxacin were determined by the broth microdilution method according to National Committee for Clinical Laboratory Standards guidelines (25) with the exception that Isosensitest broth (Unipath Ltd., Basingstoke, Hampshire, United Kingdom) was used as nutrient medium. Serum bactericidal activity was determined by the method of Reller and Stratton (31), with the following modifications. Twofold dilutions of the test sera were made in Isosensitest broth containing 50% heat-inactivated (56°C, 30 min) pooled normal serum. To prepare the pneumococcal inoculum, four to six colonies from an overnight agar culture were suspended in 20 ml of brain heart infusion broth (Unipath Ltd.) and incubated at 36°C for 1 h under constant shaking. Preliminary experiments showed that this suspension contained 4×10^7 to 6×10^7 organisms per ml. Using a multipoint inoculator (MIC-2000, Dynatech, Alexandria, Va.), 0.0015 ml of the suspension was transferred to each well (100 μl) of the microtiter plate, resulting in a final bacterial concentration of 6×10^5 to 9×10^5 organisms per ml which was confirmed in each experiment. Bacterial killing was determined by subculturing 5 μl from each well on blood agar plates which were incubated at 37°C for 18 to 24 h. The bactericidal endpoint was defined as the highest serum dilution producing a ≥99.9% reduction of the original inoculum (39).

The pharmacokinetics of sparfloxacin and its glucuronide metabolite are summarized in Table 1. Values for mean peak serum concentration and area under the concentration-time curve (AUC_{tot}) were in accordance with those described by other authors for a single oral dose of 400 mg (18, 36). However, the time to maximum concentration of drug in serum (t_{max}) was shorter than in previous studies (2.05 h compared to 4 to 5 h) while the half-life at ß phase ($t_{1/2ß}$) was longer (24.1 h compared to 16 to 20 h) (18, 36).

MICs of penicillin for the four pneumococcal strains were 0.015, 0.25, 0.25, and 2.0 mg/liter, and the corresponding values of sparfloxacin were 0.25, 1.0, 0.5, and 0.25 mg/liter. Thus, strain 1 was fully sensitive to penicillin, strains 2 and 3 exhibited reduced sensitivity, and strain 4 was categorized as resistant (25). Applying the breakpoints recommended for sparfloxacin by the European Study Group for Antibiotic Breakpoints (susceptible, MIC ≤ 1 mg/liter; resistant, MIC ≥ 4 mg/liter [9]), all four pneumococcal strains were categorized as susceptible.

TABLE 1. Pharmacokinetic parameters of sparfloxacin and its glucuronide metabolite after oral administration of 400 mg of sparfloxacin[a]

Parameter	Value (± 1 SD) for	
	SPA	SPA-glucuronide
C_{max} (mg/liter)	1.49 ± 0.42	0.21
t_{max} (h)	2.05 ± 1.01	1.2
$t_{1/2ß}$ (h)	24.1 ± 2.9	12.0
MRT (h)	17.0 ± 1.9	26.0 ± 8.0
AUC_{tot} (mg · h/liter)	32.3 ± 6.2	6.6 ± 3.3
Cl_{tot}/f (ml/min/1.73 m^2)	197.0 ± 39.0	NA
Cl_{ren} (ml/min/1.73 m^2)	25 ± 4.0	460.0 ± 380.0
Urinary recovery at 120 h (% of SPA dose)	10.9 ± 2.1	34.5 ± 7.2

[a] C_{max}, peak serum concentration; t_{max}, time of serum peak; $t_{1/2ß}$, elimination half-life; AUC_{tot}, area under the concentration-time curve; MRT, mean residence time; Cl_{tot}/f, total clearance; Cl_{ren}, renal clearance; f, bioavailability; SPA, sparfloxacin; SD, standard deviation; NA, not applicable. C_{max} and AUC_{tot} were recalculated for dose per 70 kg of body weight. C_{max}, t_{max}, and $t_{1/2ß}$ for SPA-glucuronide were estimated by using pooled serum concentration values instead of individual data. Therefore, no SD can be given for these values.

Serum inhibitory and bactericidal titers measured in the sera of the test persons are summarized in Table 2. In the samples taken before administration of sparfloxacin, no "intrinsic" inhibitory or bactericidal activity against pneumococci could be measured in volunteers 1 to 7. By contrast, relatively high inhibitory and bactericidal titers were found in volunteer 8, indicating a recent pneumococcal infection with a serotype related to that of strain 1. In fact, upon specific request, this volunteer reported having suffered from an upper respiratory tract infection approximately 3 months prior to the study. Therefore, we excluded the serum specimens from this volunteer from further analysis. In the remaining volunteers, bactericidal titers of the samples taken at 2 and 4 h after intake of sparfloxacin ranged between those measured at 1 and 6 h after drug administration (data not shown). Geometric mean inhibitory titers were between 1:2.4 to 1:6.3, while bactericidal titers ranged between 1:1.3 and 1:3.6.

Pneumococci continue to be an important cause of community-acquired respiratory tract infections (2, 3). Penicillin-resistant strains were first described in the 1960s but have become of major importance during the last decade (11, 14). Strains for which MICs are 0.1 to 1 mg/liter are categorized as intermediately resistant to penicillin, while strains for which MICs are higher (≥2 mg/liter) are termed highly resistant (25). In the United States, the overall incidence of penicillin resistance (intermediate and high) in different medical centers varies between 0 and 28%, with a mean of 7% (11). In Europe, resistance rates are highest in Spain (up to 44%) (23), Hungary, and Romania (11), while figures in Germany range between 2 and 7% (26). Although it has been shown that respiratory infections caused by intermediately resistant strains may respond to ß-lactam antibiotics (11, 27), this may hold true only for intravenous application of high doses (33). In a recent French study of otitis media in children (with pneumococcal etiology proven by paracentesis), response rates to a variety of oral ß-lactams including new oral cephalosporins and amoxicillin were significantly lower for intermediately penicillin-resistant compared to -susceptible isolates (3). Also, it has been shown that penicillin-resistant pneumococci are often also resistant against various other antimicrobial agents such as ma-

TABLE 2. Serum inhibitory and bactericidal titers after oral administration of sparfloxacin

Volunteer no. and time (h) after intake	Serum level (mg/liter)	Reciprocal inhibitory/bactericidal titer for strain:[a]			
		1	2	3	4
1					
0	0.00	—	—	—	—
1	1.27	4/2	4/2	4/2	8/4
6	1.25	4/2	4/2	4/2	8/4
2					
0	0.00	—	—	—	—
1	2.34	ND	4/4	ND	ND
6	1.78	2/2	2/2	4/4	4/4
3					
0	0.00	—	—	—	—
1	2.06	2/1	1/1	4/4	8/4
6	1.62	2/1	2/2	4/2	4/2
4					
0	0.00	—	—	—	—
1	1.08	2/1	4/4	4/2	8/4
6	1.00	2/1	4/4	2/2	4/4
5					
0	0.00	—	—	—	—
1	0.29	1/1	1/1	1/0	2/1
6	0.86	2/1	4/2	2/1	4/2
6					
0	0.00	—	—	—	—
1	1.90	4/2	8/4	4/2	8/4
6	1.13	4/2	4/2	4/2	8/4
7					
0	0.00	—	—	—	—
1	1.60	4/2	4/4	4/2	8/8
6	1.70	2/2	4/8	4/4	8/4
Mean for 1–7[b]					
1	1.51	2.5/1.3	3.0/2.4	3.2/2.3	6.3/3.6
6	1.33	2.4/1.5	3.3/2.7	3.3/2.2	5.4/3.3
8					
0	0.00	64/64	8/8	16/8	1/1
1	1.00	64/64	8/8	16/16	8/8
6	1.04	64/64	8/8	8/8	8/8

[a] —, no inhibition or killing; ND, not done.
[b] Arithmetic mean for serum concentrations and geometric mean for titer values.

crolides, tetracyclines, and co-trimoxazole (14, 23, 27). Thus, there is a need for alternative agents that can be administered orally in cases of upper respiratory infections and in slight to moderately severe pneumococcal pneumonia.

Among the quinolones, ciprofloxacin has been used in pneumococcal pneumonia, but therapeutic failures have been demonstrated in several instances (22, 28). On one hand, this may be explained by relatively high MICs of ciprofloxacin and ofloxacin for pneumococci which may not be reached in infected lung tissue. The ratio of tissue level to MIC may in fact be better for sparfloxacin. Honeybourne et al. found levels of 1.9 to 12.3 mg/g of bronchial mucosa after repeated oral administration of sparfloxacin in patients undergoing bronchoscopy with biopsy for medical reasons (17). This compares favorably with usual MICs of sparfloxacin for pneumococci (MIC_{90}, 0.25 to 1 mg/liter) (12, 24, 26).

On the other hand, bactericidal activity in the bloodstream may also play a role since up to 30% of the cases of pneumococcal pneumonia are associated with bacteremia (1, 2). Serum bactericidal tests performed with ciprofloxacin and ofloxacin after both oral (500 and 400 mg, respectively) and intravenous (500 mg) administration have shown that these drugs do not produce serum bactericidal activity against pneumococci (8). In the present study, we showed that a 400-mg oral dose of sparfloxacin, although producing lower peak serum concentrations than ciprofloxacin (1.49 mg/liter compared to 2.45 mg/liter after a 500-mg oral dose of ciprofloxacin) (8) effected serum killing of both penicillin-sensitive and penicillin-resistant pneumococcal isolates, with mean bactericidal titers in the range of 1:1.3 to 1:3.6 over a time period of 1 to 6 h after intake.

Correlations between certain threshold serum bactericidal titers and clinical outcome have been established for treatment of systemic infections with β-lactam antibiotics with or without aminoglycosides. In nonneutropenic patients, Klastersky et al. (20) and Platt et al. (29) found that peak serum inhibitory and bactericidal titers of ≥1:8 were associated with a favorable clinical response in ≥80% of cases. In patients with granulocytopenia or hematogenous osteomyelitis, higher peak titers of ≥1:16 were reported to correlate with clinical cure (30, 35). The role of serum bactericidal activity in endocarditis has been a matter of controversy (15); however, Weinstein et al. found that titers of ≥1:64 were highly predictive of cure (40). Overall, it appears to be accepted that a clinical response to ß-lactam antibiotics in immunocompetent patients not suffering from endocarditis is strongly correlated with serum antibacterial activity at dilutions of 1:8 or higher.

In contrast, only few studies have addressed the question of optimal therapeutic serum bactericidal activity for the quinolone antibiotics. Using an in vitro pharmacokinetic model mimicking serum kinetics of oral enoxacin, Blaser et al. found that titers of ≥1:10 correlated with an eradication of test organisms over a 28-h period of exposure to the antibiotics (4). However, neither serum components nor phagocytic cells were present in this test system, which thus reflected the worst clinical situation of a complete lack of host defense. A detailed in vivo analysis relating pharmacokinetic parameters and MICs to clinical outcome of treatment with intravenous ciprofloxacin was performed by Forrest et al. (10). Studying 74 acutely ill patients suffering from various types of infection, these authors found that an AUC/MIC ratio of ≥125 was the most reliable marker of therapeutic success, indicating clinical and microbiological cure in 80 and 82% of patients, respectively (10). In order to compare our data with this study, we integrated the mean reciprocal serum inhibitory titers measured in our volunteers over time, assuming a 24-h inhibitory titer of 2. The mean value for 24-h inhibitory activity calculated by this method was 81.9 and thus did not reach the value of 125 proposed by Forrest et al. (10). On the basis of the titers alone, a favorable response of bacteremic pneumococcal pneumonia to oral sparfloxacin can thus not be predicted. However, early clinical studies have documented an overall therapeutic efficacy of oral sparfloxacin (400 mg initially, followed by 200 mg daily) of 88.8% in bacteriologically proven pneumococcal pneumonia ($n = 181$) and 78.6% in the subset of patients with positive blood culture (1). Although no data concerning the serum bactericidal activity in these patients are available, it may well be that the humoral immune response in patients actually infected with pneumococci may help to increase the "net" effect of the antibiotic which was the sole parameter measured in the present study. Additional studies monitoring serum bactericidal activity of sparfloxacin during clinical pneumococcal disease are clearly warranted.

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