Penetration of sparfloxacin and ciprofloxacin into alveolar macrophages, epithelial lining fluid, and polymorphonuclear leucocytes

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Penetration of sparfloxacin and ciprofloxacin into alveolar macrophages, epithelial lining fluid, and polymorphonuclear leucocytes. P. Schüler, K. Zemper, K. Borner, P. Koeppe, T. Schaberg, H. Lode. ©ERS Journals Ltd 1997.

ABSTRACT: Sparfloxacin (SPX), a novel fluoroquinolone with a broad spectrum of antibacterial activity, has been shown, *in vitro*, to be more effective against common pulmonary pathogens, particularly *Streptococcus pneumoniae*, *Mycoplasma pneumoniae* and some intracellular organisms, than ciprofloxacin (CPX).

The objective of this open, comparative, randomized study in two parallel groups was to assess the serum concentrations and penetration of SPX and CPX into alveolar macrophages (AMs), epithelial lining fluid (ELF), and peripheral polymorphonuclear leucocytes (PMNs). Patients received either a single oral dose of SPX, 400 mg (16 patients), or CPX, 500 mg (15 patients), at various times before a routine diagnostic bronchoscopy was performed. Antibiotic concentrations were determined by using a microbiological assay.

The median serum elimination half-lives were 17.3 h for SPX and 5.3 h for CPX. Peak levels (median±68% confidence range) of CPX were attained in AMs (7.6±1.7 mg·L⁻¹) at 5 h after admission, and in both ELF (2.13±0.91 mg·L⁻¹) and PMNs (9.1±6.2 mg·L⁻¹) at 2.5 h after administration. SPX achieved comparable peak levels in PMNs (median±68% range, 9.4±1.1 mg·L⁻¹ at 5 h), but peak concentrations attained in AMs and ELF (35.1±15.4 and 32.2±28.2 mg·L⁻¹, respectively, at 24 h) were several times higher than those of CPX. SPX demonstrated substantially greater accumulation in all three sites than did CPX (peak site to serum ratios of 11.0±4.3, 65.5±28.4 and 63.0±66 versus 4.94±0.64, 10.6±3.7 and 10.6±3.7 for PMNs, AMs and ELF, respectively).

The results indicate, that sparfloxacin has a long elimination half-life and that it achieves higher concentrations in alveolar macrophages and epithelial lining fluid than ciprofloxacin. Site concentrations of sparfloxacin greatly exceeded the minimal inhibitory concentrations of common respiratory pathogens.

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Widely-used fluoroquinolones, such as ciprofloxacin and ofloxacin, exhibit a broad antimicrobial spectrum, with good *in vitro* activity against Gram-negative bacteria. However, they are less potent against some common respiratory pathogens, particularly *Streptococcus pneumoniae*, *Mycoplasma pneumoniae* and some intracellular organisms. Sparfloxacin is a novel quinolone derivative with comparable activity to ciprofloxacin and ofloxacin against gram-negative organisms, but it possesses greater activity than these quinolones against Gram-positive cocci (including *S. pneumoniae*), *Mycoplasma* spp., *Chlamydia* spp., *Mycobacteria* spp., and some anaerobes [1–10]. The pharmacokinetics of sparfloxacin are characterized by: good absorption after oral administration; good penetration into many tissues and body fluids; and a long plasma elimination half-life, ranging 16–24 h [11–14].

Epithelial lining fluid (ELF) has been considered to be an important site of infection in pneumonia, and both the alveolar macrophages (AMs) and the polymorphonuclear leucocytes (PMNs) represent important sites of intracellular infection [15]. The capability of intracel-

lular pathogens to penetrate and multiply in phagocytes plays an important role in the dissemination of the infectious process, since phagocytes can quickly pass vascular and nonvascular epithelial membranes. Hence, it follows that sufficient drug accumulation in phagocytes is needed to achieve activity against intracellular pathogens [16].

Fluoroquinolones, including sparfloxacin, have been shown to achieve high intracellular concentrations. The objective of this comparative study was to evaluate the penetration of sparfloxacin and ciprofloxacin into ELF, AMs, and PMN following administration of a single standard oral dose.

Materials and methods

Study design and subjects

This was an open, comparative, randomized clinical study in two parallel groups. A total of 31 patients (23

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males and 8 females; 26 smokers and 5 nonsmokers; age mean $\pm$ SD 60 $\pm$ 10 yrs; body weight 75 $\pm$ 16 kg; serum creatinine 79.4 $\pm$ 16.0 μ mol·L⁻¹) undergoing diagnostic fiberoptic bronchoscopy, in most cases for suspicion of lung cancer, were enrolled. All patients gave their written informed consent, and the protocol of the study was approved by the Ethics Committee of the Hospital Benjamin Franklin, Freie Universität, Berlin, Germany. Noninclusion criteria were: child-bearing potential; pregnancy; lactation; an existing lung infection; a severely immunocompromised status; a haemodynamically unstable condition; the use of any antibacterial agent before study entry; a concomitant disease that may interfere with the course of the study; human immunodeficiency virus (HIV) infection; renal insufficiency (creatinine >200 μ mol·L⁻¹), severe psychiatric disease; drug or alcohol abuse; significantly abnormal results on laboratory testing, allergy to quinolones; cardiac frequency <40 beats·min⁻¹; congenital prolonged QT syndrome; and concomitant therapy with either an antacid, iron salts, theophylline, anticoagulants, antipsychotics, anticonvulsants, antiarrhythmics or a medication known to cause QT prolongation. A complete physical examination and a common laboratory profile were performed before and at the end of the study.

All study subjects were divided into two groups: Group A (16 patients) were administered a single dose of 400 mg sparfloxacin; and Group B (15 patients) were administered a single dose of 500 mg ciprofloxacin.

Both groups were divided into three subgroups, which took the fluoroquinolones in accordance to a dose schedule: Subgroups A1 and B1 (5 patients per group) took their medication 2.5 h before bronchoscopy; Subgroups A2 and B2 (6 and 5 patients, respectively) 5 h before bronchoscopy; and Subgroups A3 and B3 (5 patients per group) took their dose 24 and 12 h before bronchoscopy, respectively. An interval of 12 h between Subgroups A3 (sparfloxacin) and B3 (ciprofloxacin) was set, because it had been decided to monitor the levels of each drug throughout their recommended dosing intervals, *i.e.* SPX for 24 h, and CPX for 12 h.

Bronchoalveolar lavage (BAL) and sample processing

Fiberoptic bronchoscopy (FBF 5; Olympus, Japan) was performed using a standard premedication consisting of 10–15 mg of nebulized 4% xylocaine, 0.5 mg atropine, 10–15 mg hydrocodone, and 1–1.5 mg midazolone, administered intramuscularly 20 min prior to bronchoscopy. The BAL was mainly performed in the lingula, or in the middle lobe if the lingula was suspect for malignancy. A conventional BAL using a volume of 160 mL of 0.9% saline (lavage divided into four aliquots) was performed. Gentle aspiration was performed following each of the four 40 mL aliquots. The aspirate of the first 40 mL was discarded to avoid any contamination of the sample with proximal airway cells and fluid [17]. The aspirates of the remaining three aliquots were pooled. The lavage fluid was filtered through a sterile gauze, and then centrifuged at 4°C and 500 $\times$ g for 10 min. Five to 10 millilitres of the supernatant were used to determine the antibiotic concentrations in a microbiological assay. The remaining volume of the

supernatant was used to determine the concentration of urea. All samples were stored frozen at -80°C, protected from light until assayed.

Preparation of AMs

The cell pellet remaining after centrifugation of the BAL fluid resuspended twice, washed and centrifuged in buffer (Hank's balanced salt solution (HBSS)), and counted with a haemocytometer. The viability of AMs was proved by 0.1% trypan blue (Sigma Chemicals, Dessenhofen, Germany) dye exclusion, and the macrophage population was visualized by nonspecific esterase (Sigma Chemicals) staining, to ensure that a uniform macrophage population was obtained [18]. The proportion of AMs was always greater than 90%. Cells were then resuspended in distilled water to obtain a concentration of 1×10^6 cells·200 μ L. The suspension of 1×10^6 macrophages was then ultrasonicated on ice for 1 min before measurement of antibiotic concentrations. All samples were stored at -30°C, protected from light.

Blood samples

Blood samples were taken prior to drug administration, 1 h before bronchoscopy, during bronchoscopy, and 1 h after bronchoscopy. Blood samples were allowed to clot at room temperature for 15 min, and then centrifuged at 3,000 rpm using a refrigerating centrifuge. Serum was then aspirated and divided into two aliquots to determine the concentrations of urea and antibiotic. All samples were stored frozen at -30°C, protected from light until assayed.

Preparation of PMN

Approximately 20 mL of venous blood obtained using a heparinized syringe (final concentration of heparin 500 IE) were placed in a 50 mL conical tube (Falcon; Becton Dickinson, NJ, USA) and then gently mixed with 10 mL of 1% dextran 40 (Onkovertin N; Braun, Melsungen, Germany). The tube was then incubated with 5% CO₂ at 37°C for 60 min. The supernatant containing the white blood cells was carefully transferred to a new conical tube and underlayered with Ficoll (Seromed Biochrome KG, Berlin, Germany), density 1,077. After centrifugation (45 min at 400 $\times$ g, 20°C), the supernatant containing lymphocytes and monocytes was discarded and the pellet consisting of the PMNs and residual red blood cells was saved. Erythrocytes were destroyed by hypotonic lysis with 0.2% saline. After centrifugation, the supernatant was discarded and the PMNs were resuspended in buffer (HBSS without Ca²⁺ and Mg²⁺) and again centrifuged. The viability of the PMNs was proved by dye exclusion, after staining the cells with 0.1% trypan blue (Sigma Chemicals, Poole, UK) [19]; and the cells were then counted using a haemocytometer. Thereafter, the cells were resuspended in distilled water and adjusted to a concentration of 2×10^7 cells·200 μ L⁻¹. The PMNs were then ultrasonicated on ice for 1 min and the antibiotic concentration was measured. All samples were stored frozen at -30°C, protected from light until assayed.

Buffers, media and antibiotic standards

Modified HBSS, final pH 7.3–7.4, containing: NaCl 8.0 g·L⁻¹, KCl 0.4 g·L⁻¹, NaHPO₄ 0.04788 g·L⁻¹, K₂HPO₄ 0.06 g·L⁻¹, and glucose 1.0 g·L⁻¹ (Sigma Chemicals, Poole, UK) was used as buffer for preparation of the AMs. The medium used for the microbiological assays was N-agar, containing: Na₂HPO₄ 2.0 g·L⁻¹, NaCl 3.0 g·L⁻¹, neutral-pepton 10.0 g·L⁻¹ (Oxoid, Wesel, Germany), labilemka 10.0 g·L⁻¹ (Oxoid), Bacto agar 15.0 g·L⁻¹ (Difco, Augsburg, Germany), and 1.0% dextrose, final pH 7.3–7.4. Sørensen buffer, consisting of a mixture of 400 mL of solution I (9.078 g KH₂PO₄ in 1.0 L H₂O) and 600 mL of solution II (11.876 g Na₂HPO₄ × 2H₂O in 1.0 L H₂O), final pH 7.0, was used for the antibiotic standards. The buffer was sterilized and then stored at 4°C. Pooled serum used for the antibiotic standards was provided by the blood donor service (DRK Blutspendedienst, Berlin) of the Hospital Benjamin Franklin, Freie Universität, Berlin.

Sparfloxacin and ciprofloxacin in powder form were provided by Rhône-Poulenc Rorer GmbH, Köln, Germany and Bayer AG, Wuppertal, Germany, respectively. Dilutions of the compounds were made on the day of use, according to the instructions of the manufacturers.

Microbiological assay

Concentrations of sparfloxacin and ciprofloxacin were determined microbiologically, using the agar diffusion method described by REEVES and BYWATER [20], with N-agar as growth medium. *Bacillus subtilis* American Type Culture Collection (ATCC) 6633 and *Klebsiella pneumoniae* ATCC 10031 were used as indicator organisms for sparfloxacin and ciprofloxacin, respectively. Prior to the assay, it was checked that the antibiotic-free samples had no inhibitory effect on the test organisms. After suitable dilution, the samples were incubated either at 30°C (*K. pneumoniae*) or 37°C (*B. subtilis*) for 18 h. The lower limits of sensitivity of the assays were 0.03 mg·L⁻¹ for sparfloxacin and 0.015 mg·mL⁻¹ for ciprofloxacin, respectively. The assay precision, as determined by the coefficient of variation (CV) for control samples with antibiotic concentrations ranging 0.5–2 mg·L⁻¹ were as follows: sparfloxacin-buffer 4.1–6.5%; sparfloxacin-serum 4.0–8.4%; ciprofloxacin-buffer 3.2–6.4%; and ciprofloxacin-serum 3.7–4.6%.

Calculation of the antibiotic concentration in the ELF

The concentration of urea in BAL was determined to quantify the volume of ELF [21]. After vacuum-concentration of BAL, the concentration of urea was determined using a modified Sigma Diagnostic Kit UV-66 (Sigma Chemicals, Poole, UK). The antibiotic concentrations in ELF were determined as follows [22]:

$$\text{ELF volume} = \frac{[\text{urea}] \text{ lavage} \times \text{volume lavage}}{[\text{urea}] \text{ serum}}$$

$$[\text{antibiotics}] \text{ ELF} = \frac{[\text{urea}] \text{ lavage} \times \text{volume lavage}}{\text{volume ELF}}$$

$$[\text{antibiotics}] \text{ ELF} = \frac{[\text{urea}] \text{ ELF} \times [\text{antibiotics}] \text{ lavage}}{[\text{urea}] \text{ lavage}}$$

Calculation of antibiotic concentrations in AMs and PMNs

Intracellular concentrations of antibiotics were determined according to the following formulae:

$$c(I) = f \times c(L) = 33.57 \times c(L)$$

mean cell volume: $V_{\text{cell}} = \dots \text{fL}$; total number of cells: $Z = 2 \times 10^7$ PMNs, $Z = 1 \times 10^6$ AMs; total cell volume: $V = Z \times V_{\text{cell}}$; suspension fluid (*aq dest*): $V(L) = 200 \mu\text{L}$; suspension volume: $V(L) + V$; factor of dilution: $f = [V(L) + V]/V$; measured concentration in suspension: $c(L)$; measured serum concentration: $c(E)$; accumulation factor: $A = c(I)/c(E)$, supposing that the mean cell volumes of PMNs and AMs are 307 fL [23] and 2,653 fL (data from our own experiments), respectively.

Pharmacokinetic and statistical analysis

The serum data were studied according to an open one compartment model (a) as well as noncompartmentally (b).

(a) The decision for this model was based on the criterion of SCHWARZ [24]. The results of the model approach are used to calculate the lag time (t_{lag}), the maximum concentration (C_{max}), the time to maximum concentration (t_{max}), the absorption rate constant (k_a) and the elimination rate constant (k_{el}).

(b) The serum area under the curve (AUC) was calculated as "area under the data" (AUD) by the linear trapezoidal rule, from time zero until time of the last measurement (t_{last}). The total area is approximated by: $\text{AUD}_{\text{tot}} = \text{AUD} + C(t_{\text{last}})/k_{\text{el}}$. The volume of distribution as well as the (total) clearance values were calculated from AUD_{tot} , i.e. noncompartmentally. The final values are expressed as median ± standard range (=68% confidence range) of the individual results.

The parameters directly depending on the dose were recalculated for dose per either 70 kg of body weight (C_{max} , AUD_{tot} , volume of distribution/unknown bioavailability (V_{ss}/F) or 1.73 m² of body surface (oral clearance/unknown bioavailability (CL/F)) [25, 26]. Due to lack of data during the absorption phase, it was not possible to determine the C_{max} and t_{max} of ciprofloxacin.

For analysis of multiple comparisons between the concentrations of the two quinolones, the test of WILCOXON and WILCOX [27] was used. A p-value equal to or less than 0.05 was considered significant, and a p-value equal to or less than was considered highly significant.

Results

Pharmacokinetic parameters

Serum concentration-time curves and pharmacokinetic parameters of sparfloxacin and ciprofloxacin are depicted in figure 1a and b.

Fig. 1. — Median ($\pm 68\%$ confidence range) concentrations of a single oral dose of a) ciprofloxacin, 500 mg ($n=15$) and b) sparfloxacin, 400 mg ($n=16$), in serum, peripheral granulocytes (PMNs), alveolar macrophages (AMs) and epithelial lining fluid (ELF). Concentrations were determined by bioassay. For ciprofloxacin (a), the concentrations of ELF were only detectable 2.5 h after dosage. —: serum regression function; ○: serum; ●: PMNs; ■: AMs; ▲: ELF.

Ciprofloxacin (median $\pm 68\%$ confidence range) serum concentrations determined at the time of the first blood sample (at 1.5 h) and at the end of the recommended dosing interval (at 12 h) were 2.68 ± 0.34 and 0.43 ± 0.23 mg·L⁻¹. The values obtained for the total area under the concentration-time curve (AUC_{tot}) and the elimination half-life were 17.7 mg·L⁻¹ × h and 5.3 h, respectively.

The highest serum concentrations of sparfloxacin were achieved at 6 h (1.10 ± 0.37 mg·L⁻¹) (fig. 1b). Concentrations at the end of recommended dosing interval (at 24 h) were 0.49 ± 0.22 mg·L⁻¹. The values obtained for the area under the concentration-time-curve (AUC_{tot}) and the elimination half-life at the β -phase were 35.5 mg·L⁻¹ × h and 17.3 h, respectively.

Intracellular concentrations

Values (median $\pm 68\%$ confidence range) of intracellular concentrations determined 2.5, 5 and 12 h after

Table 1. — Intracellular concentrations and factors of accumulation for sparfloxacin (SPX) at 2.5, 5 and 24 h and ciprofloxacin (CPX) 2.5, 5 and 12 h after dosage

Time h	n	Median 68% range	Serum concentrations		PMN intracellular concentrations		PMN factors of accumulation		AM intracellular concentrations		AM factors of accumulation		ELF intracellular concentrations		ELF factors of accumulation	
			SPX	CPX	SPX	CPX	SPX	CPX	SPX	CPX	SPX	CPX	SPX	CPX	SPX	CPX
2.5	5	0.90	2.33	5	5	5	7.3	4.7	5	5	40.0	5	5	5	5	4
		0.30	0.89				1.1	1.0			12.4				37.0	0.64
5	6	1.10	1.13	5	5	6	6	5	6	6	6	5	5	5	6.9	0.17
		0.40	0.16				8.0	4.9			41.9				BDL	BDL
12/24*	5	0.49	0.43	5	5	5	3.5	0.6	5	5	15.8	5	5	5	16.0	-
		0.22	0.23				11.0	3.6			65.5				9.2	-
							4.3	0.4			28.4				63.0	BDL
															66.2	-

All values for concentration are expressed in mg·L⁻¹. Two hours and 30 min after a single oral dose, ciprofloxacin reached the highest intracellular concentrations in granulocytes; whereas in alveolar macrophages and epithelial lining fluid, sparfloxacin had higher concentrations. Sparfloxacin reached higher factors of accumulation in granulocytes, alveolar macrophages and epithelial lining fluids. Five hours after a single oral dose, sparfloxacin reached higher intracellular concentrations and factors of accumulation in granulocytes, alveolar macrophages and epithelial lining fluid than ciprofloxacin. Twenty-four hours after a single dose of 400 mg, sparfloxacin reached the highest intracellular concentrations and factors of accumulation in granulocytes, alveolar macrophages and epithelial lining fluid of all groups. Pts: patients; PMN: polymorphonuclear leucocyte; AM: alveolar macrophage; ELF: epithelial lining fluid; BDL: below detection limits. *: at 12 h for CPX and 24 h for SPX.

ciprofloxacin and 2.5, 5 and 24 h after sparfloxacin administration are depicted in figure 1a and b and table 1.

The intracellular peak concentrations of ciprofloxacin and sparfloxacin in PMNs were 9.1 ± 6.2 and 9.4 ± 1.1 $\text{mg} \cdot \text{L}^{-1}$, respectively (difference not statistically significant). However, the maximum concentrations of sparfloxacin in AMs were five times higher than those of ciprofloxacin (35.1 ± 28.2 vs 7.6 ± 1.7 $\text{mg} \cdot \text{L}^{-1}$; $p \leq 0.01$). Sparfloxacin also displayed significantly greater penetration into ELF (32.2 ± 28.2 vs 2.13 ± 0.91 $\text{mg} \cdot \text{L}^{-1}$; $p \leq 0.01$).

Factor of accumulation

Values (median $\pm$ 68% confidence range) of the factors of accumulation determined at 2.5, 5 and 12 h after ciprofloxacin and 2.5, 5 and 24 h after sparfloxacin administration are depicted in table 1.

Sparfloxacin achieved significantly higher site to serum concentration ratios than ciprofloxacin for all three compartments (peak site to serum ratios of 11.0 ± 4.3 , 65.5 ± 28.4 and 63.0 ± 66 vs 4.94 ± 0.64 , 10.6 ± 3.7 and 10.6 ± 3.7 for PMNs, AMs and ELF, respectively) ($p \leq 0.01$).

Adverse events

No adverse event or significant change of laboratory values was observed during the study.

Discussion

This study demonstrated that sparfloxacin achieved higher concentrations in AMs and ELF than ciprofloxacin. This may be of particular relevance in the treatment of community-acquired pneumonia.

S. pneumoniae is still the predominant bacterial pathogen causing community-acquired pneumonia [28, 29]. Recently pneumococci with a decreased susceptibility to penicillin have been isolated with increasing frequency in many parts of the world, including Europe and the United States [30, 31]. Pneumococcal infections caused by penicillin intermediate and resistant strains have been shown to respond to high doses of intravenous penicillins and cephalosporins [32], but oral β -lactams are probably not sufficiently effective even for the treatment of penicillin intermediate isolates [33]. It has also been shown that penicillin-resistant pneumococci are often cross-resistant to many other antibiotics, such as macrolides, tetracyclines and co-trimoxazole [30, 34].

Therefore, fluoroquinolones have been considered as possible alternatives for the management of community-acquired pneumonia, because these agents possess a broad-spectrum *in vitro* activity, favourable pharmacokinetics, and exhibit high tissue distribution and effective penetration into extracellular fluids. Widely-used fluoroquinolones, such as ciprofloxacin and ofloxacin, have excellent activity against Gram-negative pulmonary pathogens, but they have only marginal activity against *S. pneumoniae* with the minimal concentration required to produce 90% inhibition (MIC₉₀s) ranging $1\text{--}4$ $\text{mg} \cdot \text{L}^{-1}$ compared to MIC₉₀s of <0.5 $\text{mg} \cdot \text{L}^{-1}$ for most of the Gram-negative pathogens [1, 2, 6]. Clinical studies have shown ciprofloxacin and ofloxacin to have

good clinical efficacy in the treatment of bronchopulmonary infections due to *S. pneumoniae* [35], but other investigators have reported low clinical success rates with a high rate of persistence of *S. pneumoniae* after therapy [36]. In addition, failures of pneumococcal pneumonia with breakthrough bacteraemia have been recorded [37].

The superior *in vivo* activity [38–40] of sparfloxacin is partly due to the higher intrinsic activity against these organisms *in vitro* [41] compared to that of other quinolones, but the pharmacokinetic properties seem to be of importance as well. We were able to demonstrate that after administration of a single oral dose, sparfloxacin 400 mg achieved considerably higher concentrations in the alveolar compartment of the lung compared to ciprofloxacin 500 mg. By using the BAL methodology it is possible to investigate the distribution of antimicrobial agents in two different potential sites of pulmonary infection, ELF and AMs. The present results indicate that concentrations of sparfloxacin in both compartments greatly exceeded those of ciprofloxacin. We must bear in mind that the factors of accumulation for sparfloxacin were artificially higher because of the low serum levels; however, the concentrations of sparfloxacin at tissue sites were also higher than the concentrations of ciprofloxacin in absolute terms.

ELF is considered to be an important site where pneumococcal pneumonia may develop. Sparfloxacin achieved concentrations in ELF that exceeded the minimum inhibitory concentrations (MICs) of *S. pneumoniae* (MIC₉₀ $0.25\text{--}0.5$ $\text{mg} \cdot \text{L}^{-1}$) during the whole recommended 24 h dosing interval by more than 40 times. In contrast, ciprofloxacin displayed relatively low penetration into the ELF.

AMs and PMNs both represent potential sites for intracellular infection. Compared to ciprofloxacin, sparfloxacin attained concentrations five times higher in AMs. The concentrations of sparfloxacin greatly exceeded the MICs of common intracellular pathogens, such as *Chlamydia pneumoniae* [8, 9]. Both quinolones achieved similar concentrations in PMNs, but ciprofloxacin was more rapidly released from the neutrophils than sparfloxacin.

The results of the serum concentration-time curves and the elimination half-lives of both quinolones are in accordance with data published previously [12–14, 42–44]. These investigators studied the penetration of several fluoroquinolones into AMs and ELF and bronchial mucosa, and found a better penetration by sparfloxacin compared to ciprofloxacin, lomefloxacin, temafloxacin and rifloxacin. *In vitro* studies demonstrated that the accumulation ratio of sparfloxacin in J774 macrophages and in infected and noninfected tissue culture cells was significantly higher than that obtained for other quinolones [45]. WISE and HONEYBOURNE [46] proposed that the better penetration of sparfloxacin into pulmonary tissues and fluids might be related to the physicochemical properties rather than the pharmacokinetic properties of this compound. Theoretically, the higher hydrophobicity of sparfloxacin facilitates the penetration through cell membranes, but the exact mechanisms involved have yet to be determined.

Excellent *in vitro* activity, improved pharmacokinetic properties, the possibility of single daily dosing and

the increased half-life of sparfloxacin as compared with the fluoroquinolones available at present makes it a suitable candidate for the treatment of lower respiratory tract infections [1, 47, 48]. However, the indication for treatment with sparfloxacin will have to be decided with care, because of some toxicological problems, such as photosensitivity and Qtc interval prolongation [49]. Our results confirm the approach of investigating the different pharmacokinetic characteristics of new antibiotics in the "lung compartment", before recommending rational dosages in lower respiratory tract infections.

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