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Quinolones in Everyday Clinical Practice: Respiratory Tract Infections and Nosocomial Pneumonia

Key Words
Fleroxacin
Ciprofloxacin
Pneumonia
Nosocomial
Community-acquired
Parenteral-oral sequential therapy

Abstract
Currently available fluoroquinolones have established their value in the treatment of lower respiratory tract infections due to gram-negative rods and *Staphylococcus aureus.* The fact that these drugs are absorbed (and well tolerated) when given orally is a major positive feature. The once daily dosage of fleroxacin [400 mg once daily intravenously (i.v.) for 2–4 days followed by oral doses of 400 mg for up to 10 days] was compared with twice daily ciprofloxacin (400 mg twice daily i.v. for 2–4 days followed by oral doses of 2 × 500 mg for up to 10 days) for treatment of inpatients with pneumonia confirmed by clinical signs and chest X ray. To date, 93 evaluable patients have been enrolled in this study. Clinical cure and improvement rates were 73.3% in the fleroxacin group and 79.2% in the ciprofloxacin group. The rate of adverse clinical or laboratory events was similar in both study groups.

Introduction and Overview

In general, therapeutic regimens for bacterial diseases of the lower respiratory tract must be selected empirically, on the basis of the spectrum of infectious agents expected in specific situations. Treatment is usually initiated before microbiological results are available and a causative diagnosis is often complicated by the fact that bacteriological cultures of respiratory tract specimens may yield an array of facultatively pathogenic microorganisms. On the other hand, acute bacterial exacerbations of chronic bronchitis (AECB) and pulmonary infections are major indications for the administration of antimicrobial agents providing high rates of benefit.

Leading pathogens of community-acquired and nosocomial pneumonia are compiled in table 1. While in community-ac-

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Table 1. Predominant etiological agents of community-acquired and nosocomial pneumonia

Community-acquired pneumonia	Nosocomial pneumonia
Streptococcus pneumoniae	*Staphylococcus aureus*
Haemophilus influenzae	*Klebsiella pneumoniae*
Mycoplasma pneumoniae	*Escherichia coli*
Chlamydia pneumoniae	Various Enterobacteriaceae
Legionella pneumophila	*Pseudomonas aeruginosa*
Moraxella catarrhalis	*Legionella pneumophila*

quired pneumonia leading pathogens are *Streptococcus pneumoniae, Haemophilus influenzae,* and *Mycoplasma pneumoniae,* nosocomial pneumonia is mainly caused by gram-negative bacteria in well over 50% of cases, Enterobacteriaceae, for example *Escherichia coli* or *Klebsiella pneumoniae* and *Pseudomonas aeruginosa,* being the main pathogens.

Because there is no reliable method to distinguish promptly between pneumonia caused by the agents of 'typical' acute bacterial disease and 'atypical' pneumonia, empiric antibiotic therapy of patients with pneumonia is difficult to establish.

In hospitalized patients with severe community-acquired pneumonia, antibacterial therapy before culture results often comprises a second-generation cephalosporin (e.g. cefuroxime or cefamandole) or a β-lactam/β-lactamase inhibitor combination (e.g. ampicillin/sulbactam or amoxicillin/clavulanic acid) with erythromycin added for *Legionella* coverage.

Elderly patients, especially those from nursing homes, or patients with significant underlying disease may have pneumonia caused by aerobic gram-negative rods. In such cases, reasonable regimens of antibiotic therapy would be combinations with third-generation cephalosporins (cefotaxime or ceftriaxone, or ceftazidime for infection with *P. aeruginosa*) or an extended-spectrum penicillin/β-lactamase inhibitor combination (piperacillin/tazobactam), all plus an aminoglycoside or a quinolone.

Before treatment regimens for nosocomial infections of the lower respiratory tract can be selected, several issues need to be considered: (1) the preceding antibiotic therapy that might have selected for more resistant organisms, (2) underlying chronic bronchitis that would increase the risk of *H. influenzae* infection, (3) the recent epidemiological experience in a given hospital or intensive care unit (e.g. a high incidence of multiresistant *Acinetobacter, Enterobacter,* or *Serratia* strains, and (4) potential pathogens with unusual antimicrobial resistance patterns known from prior surveillance cultures of the patient's bronchial secretions.

For the past few years, quinolones have been widely prescribed as therapy for AECB as well as for both community- and nosocomially acquired respiratory tract infections, not least as a consequence of the growing importance of β-lactam resistance due to β-lactamase-producing bacteria [1, 2].

The antibacterial spectrum of the quinolones as a group covers mainly gram-negative, aerobically growing bacteria at very low MICs of less than 0.1 mg/l for most of the important pathogens (table 2); gram-positive bacteria, with the exception of *Staphylococcus aureus,* are inhibited only by higher levels of most quinolones [3]. Sparfloxacin is effective

Table 2. Antibacterial activity of some fluoroquinolones against aetiological agents of respiratory tract infections (data from the literature)

Bacterial species	Fleroxacin	Ciprofloxacin	Ofloxacin	Sparfloxacin
Gram-negative organisms				
Haemophilus influenzae	0.06	≤0.06	≤0.06	≤0.06
Klebsiella spp.	0.5	0.125	0.5	0.25
Escherichia coli	0.125	≤0.06	0.125	0.06
Enterobacter spp.	0.125	0.125	0.5	0.25
Serratia spp.	1.0	0.25	1.0	1.0
Pseudomonas aeruginosa	4.0	0.50	4.0	2.0
Gram-positive and other organisms				
Streptococcus pneumoniae	8.0	2.0	2.0	0.25
Staphylococcus aureus	0.5	1.0	0.5	0.25
Streptococcus pyogenes	8.0	2.0	2.0	0.5
Mycoplasma pneumoniae	4.0	3.0	2.0	0.25
Legionella spp.	0.25	0.06	0.06	0.06
Chlamydia pneumoniae	0.5	0.25	1.0	1.0

Values are the MIC_{90} in mg/l.

against *S. pneumoniae* and the majority of other agents of community-acquired pneumonia (table 3).

The following overview will focus on the question: are there clinical data to support the efficacy of ciprofloxacin and fleroxacin in the treatment of lower respiratory tract infections and pneumonia?

In clinical trials involving patients with pneumonia and other lower respiratory tract infections, the clinical efficacy rates of ciprofloxacin compared favorably with those of amoxicillin [4] and imipenem [2] and were superior to that of pefloxacin [6].

In a prospective, randomized, double-blind multicenter trial by Fink et al. [7], intravenously administered ciprofloxacin (400 mg every 8 h) was compared with imipenem (1 g every 8 h) for the treatment of severe pneumonia. Among 405 patients, 79% required mechanical ventilation and 78% had nosocomial pneumonia. Ciprofloxacin-treated patients had a higher bacteriological eradication rate (69%) than imipenem-treated patients (59%). They also had a higher clinical response rate (69 vs. 56%). The greatest difference between the treatment groups was in eradication of members of the Enterobacteriaceae family (ciprofloxacin 93%, imipenem 65%). When *P. aeruginosa* was recovered from initial respiratory tract cultures, failure to achieve bacteriological eradication was common in both treatment groups (67% for ciprofloxacin and 59% for imipenem). Development of resistant *P. aeruginosa* during therapy occurred commonly in both groups (ciprofloxacin 33%, imipenem 53%). The authors concluded that monotherapy with ciprofloxacin or imipenem for severe pneumonia is a safe and effective initial strategy which needs to be modified if *P. aeruginosa* is suspected or recovered as a causative agent.

In two prospective, randomized clinical trials with fleroxacin, by Chodosh [4] and

Table 3. Fleroxacin clinical studies – published results with AECB and acute nonpneumococcal lower respiratory tract infection (ANPLRTI)

Indication	Design	Treatment	Duration days	Enrolled	Cure rates				Adverse events	
					clinical		bacteriological			
					cured/ evaluated	%	cured/ evaluated	%	patients/ evaluated	%
AECB [4, 5]	double-blind placebo group multicenter	fleroxacin 400 mg o.d.	7	417	131/144	91	114/146	97	103/145	25
		amoxicillin 500 mg t.i.d.	7	404	124/154	81	122/156	78	41/402	10
ANPLRTI [6]	open label placebo group multicenter	fleroxacin 400 mg i.v. o.d.	4–21	209	59/67	88	58/68	85	24/206	12
		ceftazidime 1–2 g b.i.d., 0.5–2 g t.i.d.	4–21	110	40/49	82	40/49	82	15/106	13

o.d. = Once daily; t.i.d. = three times a day; i.v. = intravenous; b.i.d. = twice daily.

Ulmer [5], conducted according to the same study protocol, more than 400 patients suffering from AECB were enrolled (table 3). The efficacy and safety of 400 mg fleroxacin once daily given orally for 7 days were compared to amoxicillin 500 mg three times daily. In the study published by Farkas [6], fleroxacin 400 mg given intravenously once daily was compared with ceftazidime plus erythromycin in patients with acute nonpneumococcal lower respiratory tract infection (table 3). The clinical cure rates of fleroxacin were 91 and 88% (table 3), in comparison to 81% for amoxicillin and 82% for ceftazidime. Bacteriological cure rates for fleroxacin were 97 and 85% (table 3). Compared to amoxicillin, the rate of adverse events was markedly higher in the fleroxacin group (25 vs. 10%), but in comparison to ceftazidime, the rate of adverse events was in the same range (12 vs. 13%; table 3).

Patients and Methods

The study to be described here was carried out as a prospective, randomized, double-blind multicenter trial. Adult patients of either sex were recruited from inpatient populations of twenty medical centers distributed through Germany.

Patients <18 years of age and pregnant or nursing women were excluded. Further exclusion criteria were hypersensitivity to quinolones and evidence of impaired hepatic and renal function. Patients who fulfilled the clinical inclusion criteria (table 4) were assigned, according to randomization lists, to fleroxacin or ciprofloxacin in a 1:1 ratio. The intravenous dosage was 400 mg fleroxacin once daily or 400 mg ciprofloxacin twice daily for up to 4 days, followed by oral administration of fleroxacin 400 mg once daily or ciprofloxacin 500 mg twice daily.

The total duration of treatment was up to 14 days and was based on the investigator's assessment of a patient's response to therapy according to the criteria listed in table 5.

After baseline examination, the clinical response was evaluated following a score of clinical signs and symptoms (fig. 1) and other laboratory and clinical findings. At the end of treatment, thorax control X ray was carried out.

'Clinical cure' was defined as the subsidence of all clinical signs and symptoms during treatment, 'improvement' as subsidence during treatment but incomplete resolution at the end of treatment, 'failure' as a lack of clinical response during the period of intravenous treatment.

For assessment of the bacterial etiology of disease, appropriate cultures from sputum, tracheal secretions or blood cultures had to be obtained prior to treatment.

Species identification and susceptibility testing of ciprofloxacin and fleroxacin by agar disc diffusion tests were carried out using standard laboratory methods.

MICs were determined by means of the epsilometer test [8] (AB Biodisk, Solna, Sweden) using Mueller-Hinton agar or, if necessary, Mueller-Hinton agar supplemented with 5% sheep blood and *Haemophilus* test medium (Becton Dickinson, Heidelberg, Germany).

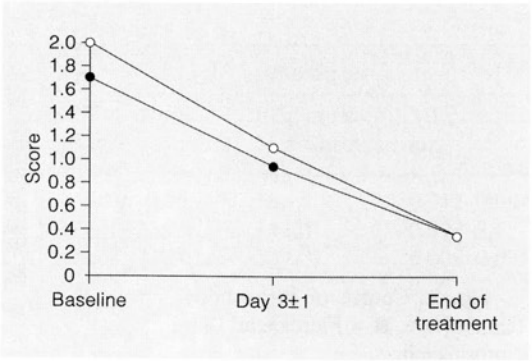

Fig. 1. Mean score of clinical symptoms (dyspnea, cough and rales). The scoring system was as follows: 0 = none; 1 = minor; 2 = moderate; 3 = severe. ● = Fleroxacin; ○ = ciprofloxacin.

Results

The aim of this paper is to present interim results of the ongoing study. To date, 49 patients have been enrolled in the fleroxacin and 53 patients in the ciprofloxacin group. Their demographic data are given in table 6. In both groups, male patients (about 70%) outnumber female patients; the mean age of patients in both groups (55 years) is relatively high. The rate of nosocomially acquired disease is slightly higher in the fleroxacin (61%) than in the ciprofloxacin (55%) group.

Among the bacterial strains isolated at baseline, members of the Enterobacteriaceae (e.g. *E. coli, Klebsiella* spp., *Enterobacter cloacae* and *Proteus mirabilis*) were the predominant infectious agents found in each study group. The MIC values were very low as were those for *H. influenzae* (table 7).

Among the Pseudomonadaceae (e.g. *P. aeruginosa,* and *Stenotrophomonas maltophilia*), two resistant strains were found in each study group. Among the isolates of *S. pneumoniae* which, in general, were only intermediately susceptible to fleroxacin, one resistant

Table 4. Inclusion criteria

Patients ≥ 18 years old (giving informed consent) with
nosocomial pneumonia or
community-acquired pneumonia due to gram-negative bacteria with new and persistent infiltration confirmed by X ray
At least two of the following criteria must be fulfilled:
(1) purulent tracheal secretion (>25 leukocytes/microscopic field, 100:1)
(2) >10,000 leukocytes/μl blood
(3) body temperature >38.5 °C
(4) typical auscultatory findings

Table 5. Primary efficacy parameters

Clinical signs and symptoms
Improvement of dyspnea, cough and rales
Improvement of X-ray findings
Body temperature ≤37.5 °C at the end of treatment
Improvement of secretion purulence
Lack of necessity to change the antibiotic treatment

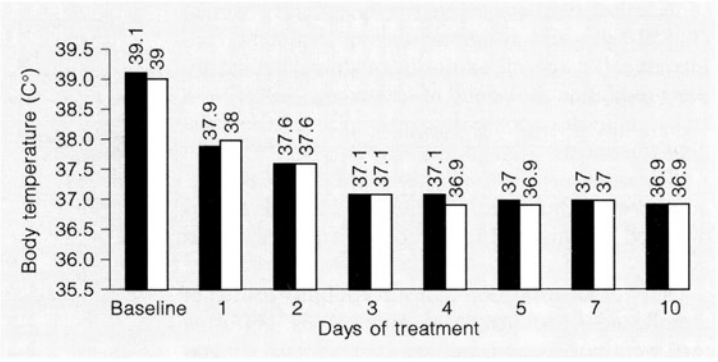

Fig. 2. Course of mean body temperature. ■ = Fleroxacin; □ = ciprofloxacin.

strain was found. All isolates of β-hemolytic streptococci and *S. aureus* were susceptible to both study drugs.

The improvement of clinical symptoms (dyspnea, cough, and rales), which was assessed by means of a scoring system, showed similar results in both treatment groups (fig. 1).

In both study groups, the rapid rate of defervescence was particularly impressive (fig. 2). In patients with a body temperature ≥ 38.5 °C at baseline, 3 days of quinolone treatment resulted in normalization of mean body temperature.

Among the evaluable patients (intent to treat), the following clinical outcome was documented (table 8): at the end of quinolone treatment, cure and improvement rates were 66.7 and 6.7% in the fleroxacin and 70.8 and 8.3% in the comparative group, respectively. The mean duration of quinolone therapy of about 10 days was similar in both groups.

The reasons why 4 patients in the fleroxacin and 5 in the ciprofloxacin group could not be evaluated are listed in table 8.

Twelve patients in the fleroxacin group and 10 in the ciprofloxacin group were recorded as treatment failures. The main reasons for this classification are given in table 9. In each group, lack of radiographic improvement of lung findings, as well as a change in the antimicrobial regimen in the fleroxacin and lack of defervescence in the ciprofloxacin treatment group were the main factors. In those cases where the results of baseline cultures were known, treatment failures were not primarily due to isolates resistant against fleroxacin or ciprofloxacin.

Table 6. Demographic data

	Fleroxacin (n = 49)	Ciprofloxacin (n = 53)
Gender (male/female)	36/13	36/17
Age[a], years	54.3 ± 15.8	54.8 ± 13.8
Height[a], cm	171.9 ± 8.2	171.6 ± 8.3
Weight[a], kg	72.7 ± 12.9	70.7 ± 14.6
Hospital/community acquired, %	61/39	55/45

[a] Mean ± SD.

The analysis of adverse events is compiled in table 10. In total, in the fleroxacin group, 17 adverse events were reported in 12 patients (25%), while in the ciprofloxacin group, 10 patients (19%) were affected by 16 adverse events. Among these, in the fleroxacin group, abnormal laboratory values were mainly recorded, while in the ciprofloxacin group, ad-

Table 7. Bacteriological results at baseline

Isolates	Fleroxacin		Ciprofloxacin	
	total number of isolates[a]	MIC range mg/l	total number of isolates[a]	MIC range mg/l
Enterobacteriaceae	11	0.016–0.25	18	0.012–0.064
Pseudomonadaceae	6 (2)	0.75–32.0	4 (2)	0.094–8.0
Haemophilus influenzae	6	0.03–0.094	10	0.008–0.023
Moraxella catarrhalis	0		1	0.25
Streptococcus pneumoniae	4 (1)	4.0–8.0	5	0.5–2.0
Streptococcus spp.	2	1.0–2.0	1	0.064
Staphylococcus aureus	9	0.125–1.0	5	0.25–1.0

[a] The values in parentheses are the number of resistant strains.

Table 8. Clinical outcome

	Fleroxacin (n = 45)		Ciprofloxacin (n = 48)	
	n	%	n	%
Evaluable patients (intent to treat)				
Cured	30	66.7	34	70.8
Improved	3	6.7	4	8.3
Failure	12	26.6	10	20.8
Days of quinolone therapy	10.0 ± 3.5		10.1 ± 3.6	
Unevaluable patients	4		5	
Pneumococci at baseline	0		1	
Refusal of X ray	1		0	
Dropout due to adverse events	2		2	
Death	1		1	
Missing data (visit 3)	0		1	

verse events related to the digestive (7.5%) and central nervous system (7.5%) were predominantly reported.

Overall, dropouts due to adverse events or concomitant illness were reported in 4 (fleroxacin) and 3 (ciprofloxacin) cases. Deaths (unrelated or remote) were due to cardiac failure (fleroxacin: 2, ciprofloxacin: 1) or to respiratory insufficiency (ciprofloxacin: 2) (table 10).

According to the study protocol, a comprehensive statistical analysis of the clinical and bacteriological response will not be provided before the end of the study, so these data are not yet available.

Table 9. Analysis of treatment failures

	Fleroxacin	Ciprofloxacin
Total failures (n)	12	10
Main reason for classification as failure		
No improvement in X-ray findings	4	4
No improvement in clinical signs	2	2
No defervescence	2	3
Change of antibiotic regimen	4	1
Microbiological results at baseline		
Staphylococci	1	1
Pneumococci	1	2
Gram-negative bacteria	1	2
Gram-positive + gram-negative bacteria	2	1
No positive culture	7	4

Table 10. Adverse events

	Fleroxacin (n = 49)		Ciprofloxacin (n = 53)	
	n	%	n	%
Adverse events				
Digestive system	2	4.1	4	7.5
Central nervous system	1	2.0	4	7.5
Skin and appendages	0		2	3.8
Respiratory system	3	6.1	1	1.9
Cardiovascular system	2	4.1	1	1.9
Other clinical adverse events	3	6.1	1	1.9
Abnormal laboratory values	6	12.2	3	5.7
Adverse events, total	17		16	
Number of patients with adverse events	12	24.5	10	18.9
Dropouts (regardless of causality, excluding deaths)	4		3	
Due to adverse events	2		3	
Due to concomitant illness	2		0	
Deaths (unrelated or remote)	2		3	
Due to cardiac failure	2		1	
Due to respiratory insufficiency	0		2	

Comment

Particularly in cases of nosocomial infection and when elderly patients with risk factors are affected [9], pneumonia is a condition associated with the highest mortality rates (20–50%) of all hospital infections [10].

Several quinolones have been studied for the treatment of nosocomial pneumonia. In general, cure rates with these agents have been comparable with those of more traditional regimens. In a double-blind randomized study, the efficacy of ciprofloxacin was compared to that of imipenem in the treatment of 205 patients with severe pneumonia, primarily associated with intensive care [11]. The clinical and bacteriological efficacy rates were significantly greater for patients treated with ciprofloxacin than for those treated with imipenem.

In a prospective multicenter study published by Lode et al. [2], the cure and improvement rates of ciprofloxacin in a treatment group of patients with lower respiratory tract infections were 39 and 50%, respectively. These data correspond well with the results of patients treated with β-lactams (37% cure and 48% improvement) [2]. In our study, in the ciprofloxacin group, cure or improvement was seen in 38 of a total of 48 patients after intravenous/oral switch and twice daily application of the drug. A similar clinical cure and improvement rate was reported with an intravenous/oral switch regimen of 400 mg fleroxacin once daily (33 of a total of 45 patients).

These interim results of our ongoing study support the conclusion that fleroxacin offers the possibility for once daily dosage and an early switch from parenteral to oral treatment.

Appendix: Participants of the Fleroxacin Study Group

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