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Review

Pharmacologic characteristics of prulifloxacin

Maria Gabriella Matera*

Unit of Pharmacology "Leonardo Donatelli", Department of Experimental Medicine, School of Medicine, Second University, Naples, Italy

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Abstract

Prulifloxacin, the prodrug of ulifloxacin, is a broad-spectrum oral fluoroquinolone antibacterial agent. After absorption, prulifloxacin is metabolized by esterases to ulifloxacin. The drug has a long elimination half-life, allowing once-daily administration. In vitro, ulifloxacin is generally more active than other fluoroquinolones against a variety of clinical isolates of Gram-negative bacteria, including community and nosocomial isolates of *Escherichia coli*, *Klebsiella* spp., *Proteus*, *Providencia* and *Morganella* spp., *Moraxella catarrhalis*, *Haemophilus* spp., and *Pseudomonas aeruginosa*. Gram-positive organisms, including methicillin- or oxacillin-susceptible *Staphylococcus aureus*, *Enterococcus* spp. and *Streptococcus pneumoniae*, are susceptible to ulifloxacin. In well-designed clinical trials, prulifloxacin showed good clinical and bacteriological efficacy (similar to that of ciprofloxacin) and was generally well tolerated, demonstrating a similar tolerability profile to that of ciprofloxacin.

In conclusion, the in vitro inhibitory and bactericidal activities exhibited by ulifloxacin and the favorable characteristics shown by its prodrug (prulifloxacin) in clinical trials, particularly indicate this drug for the treatment of lung and urinary infections.

Keywords: Prulifloxacin; Antimicrobial activity; Pharmacodynamics; Pharmacokinetics

Contents

*Corresponding author. Via del Parco Margherita 24, 80121 Napoli, Italy.
E-mail address: mariagabriella.matera@unina2.it.

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1. Introduction

The history of quinolones begins with nalidixic acid (NA), developed in 1962. Breakthroughs in the design of the drug scaffold and basic side chains allowed improvements in the first new quinolone, norfloxacin (NFLX), patented in 1978. The introduction of fluoroquinolones (i.e. molecules fluorinated in the C-6 position) marked a dramatic improvement. Although the compounds synthesized all over the world are over 10,000, only 2% of them have been developed and tested in clinical studies [1,2].

The earlier fluoroquinolones, developed in the late 1970s and 1980s, were suitable for a far wider clinical use by virtue of their broader spectrum, encompassing Gram-positive bacteria, and the good systemic distribution. Other fluoroquinolones, which had further-enhanced activity against Gram-positive bacteria and were also variably active against anaerobes, were developed in the 1990s [3]. These show good-to-moderate oral absorption and tissue penetration, along with favorable pharmacokinetics in humans, which results in a high clinical efficacy in the treatment of many kinds of infections. Among these fluoroquinolones, ofloxacin (OFLX) and ciprofloxacin (CPUFX) are acknowledged in several respects as superior to oral beta-lactam antibiotics as antibacterial agents. Focusing on OFLX and CPUFX, numerous research groups have entered the antibacterial therapeutic field, triggering intense competition in the search for newer, more effective quinolones. Since NFLX was put on the market, another 11 kinds of new quinolones have been launched in Japan. They are enoxacin (ENX), OFLX, CPUFX, lomefloxacin (LFLX), fleroxacin (FRLX), tosufloxacin (TFLX), levofloxacin (LVFX), sparfloxacin (SPUFX) and gatifloxacin (GFLX). The advantages of these compounds, e.g. LVFX, SPUFX and GFLX, rest on their spectrum, including Gram-positive as well as Gram-negative bacteria species and their improved bioavailability when administered in daily doses for systemic infections [1–3]. However, unexpected adverse reactions have been reported in the clinical evaluations or post-marketing surveillance of several new quinolones. In addition, multi-drug-resistant Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCNS), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin-resistant enterococci (VRE), have posed a serious problem in the medical community. While the new quinolones have proven a highly successful class of antibacterials in the therapeutic field, the increased isolation of quinolone-resistant bacteria has become a normal consequence. These problems of multi-drug resistance have been the driving force for the development of newer quinolones. The next generation of quinolone antibacterial agents should be potent against multi-drug-resistant bacteria, such as MRSA, and provide a lower rate of resistance emergences. Further, they should have favorable safety profiles so as to reduce adverse reactions. The future of quinolones as the ultimate in pharmaceuticals must be handled cautiously if they are to realize their potential in the medical community [1–3].

Prulifloxacin (PUFX) is a new thiazeto-quinolone antibacterial agent prodrug of the quinolone carboxylic acid ulifloxacin (Fig. 1), characterized by a potent and broad-spectrum antibacterial activity. Prulifloxacin structure contains the skeletal quinolone with a four-member ring in the 1,2-position including a sulfur atom to increase antibacterial activity and an oxodioxolenylmethyl group in the 7-piperazine ring to improve its oral absorption; it is immediately and quantitatively transformed into the active metabolite ulifloxacin. Therefore, the in vitro antimicrobial activity studies were performed using ulifloxacin (UFX) [4].

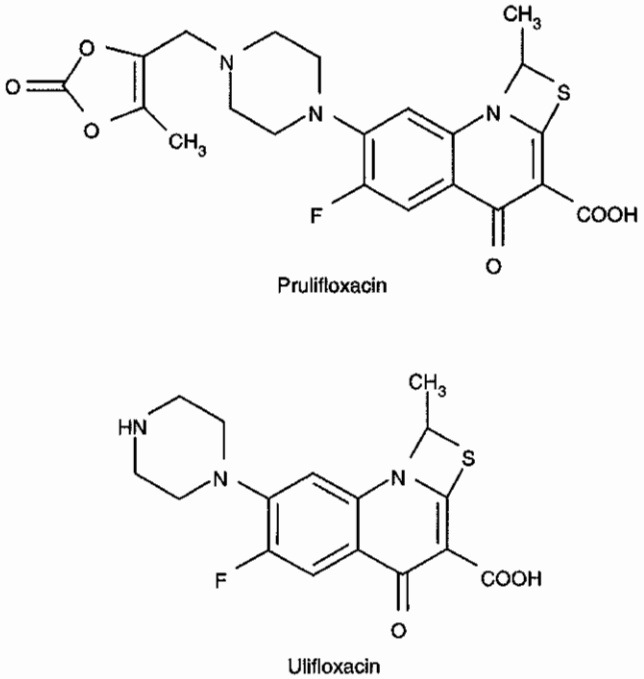

Fig. 1. Prulifloxacin and its active metabolite.

2. Pharmacodynamic profile

2.1. In vitro activity

Quinolones inhibit the bacterial DNA gyrase and topoisomerase IV functions. Like other quinolones, UFX showed a good inhibitory activity on the different bacteria. The inhibitory activity of UFX against *P. aeruginosa* type-II topoisomerase was compared with those of CPUFX, LVFX and GFLX. The 50% inhibitory concentrations (IC_{50}s) of prulifloxacin for the supercoiling activity of DNA gyrase and the decatenation activity of topoisomerase IV were 1.21 and 21.1 μg/ml, respectively. The IC_{50} of UFX was equal to that of CPUFX and lower than those of LVFX and GFLX. The inhibitory activity of the four drugs for DNA gyrase also corresponded to the antimicrobial activity of the drugs for *P. aeruginosa* PAO1. The IC_{50} values shown by the drugs tested for the decatenation activity of topoisomerase IV were 17.4 to 24.2 times higher than those for the DNA gyrase supercoiling activity. These results show that DNA gyrase is more sensitive to quinolones than topoisomerase IV and may be a primary target of quinolones in *P. aeruginosa*, and that PUFX exerts the potent antimicrobial activity through its strong inhibitory activity on DNA gyrase [5,6].

PUFX showed a broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, and several anaerobic and atypical bacteria associated to chronic bronchitis and urinary infections [6].

The minimal inhibitory concentrations (MICs) were determined by standard microdilution broth tests as recommended by the National Committee for Clinical Laboratory Standards. MIC_{50} and MIC_{90} refer to the minimal concentrations required to inhibit the growth of 50% and 90% of strains, respectively [7–10].

The minimal bactericidal concentrations (MBCs) were established by extending the MIC procedure to the evaluation of the bactericidal activity and were determined by a twofold broth dilution method. The MBC was read as the lowest antibiotic concentration which resulted in 0.1% survival in the subculture [7–10].

UFX showed potent and broad-spectrum antibacterial activity against Gram-negative and -positive recent clinical isolates. UFX was tested in different geographic areas for in vitro sensitivity against Gram-negative (*Escherichia coli*, *Klebsiella* spp., *Proteus*, *Providentia*, *Morganella* spp., *P. aeruginosa*, *Moraxella catarrhalis* and *Haemophilus* spp., etc.) and Gram-positive (*Streptococcus aureus*, *Enterococcus* spp., and coagulase-negative *staphylococci*, etc.) bacteria (Figs. 2, 3) [6,11–15].

As the reference drugs results were interpreted using NCCLS breakpoint, the European susceptibility breakpoints proposed for UFX are sensitive for pathogens with a MIC values $\leqslant 1$ mg/l, resistant for MIC $\geqslant 4$ and intermediate for MIC > 1 and < 4. In vivo, PUFX is expected to eradicate pathogens located in tissues or fluids where high drug levels have been detected (i.e. lung and kidney) [4].

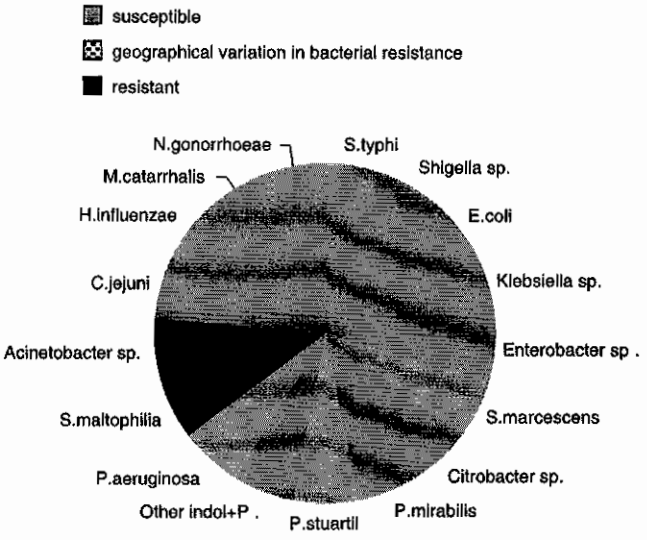

Fig. 2. In vitro activity of prulifloxacin against Gram-negative aerobic isolates [6,14,15].

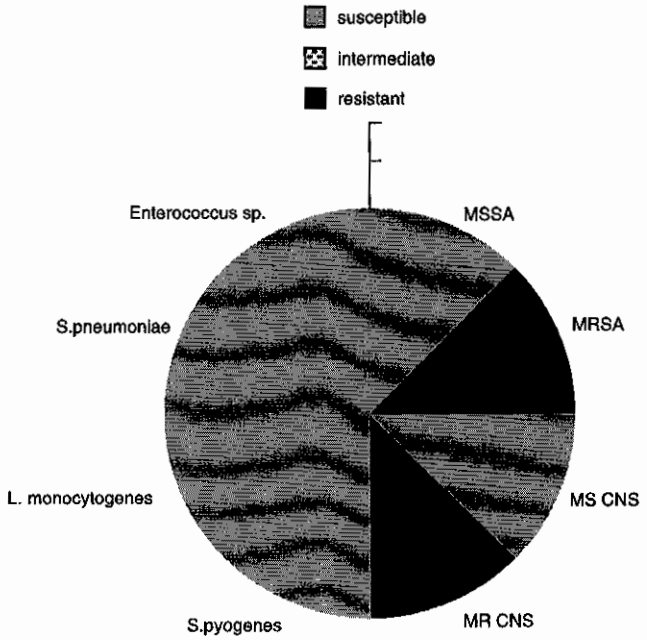

Fig. 3. In vitro activity of prulifloxacin against Gram-positive aerobic isolates [15].

The antibacterial activity and susceptibility rate at clinical breakpoint were compared with those of NFLX, OFLX, CPUFX, TFLX, FRLX, SPUFX, moxifloxacin (MXFX), and LVFX [11–15].

The MBCs of UFX for Gram-positive isolates were usually identical to or twofold the respective MICs; higher MBC/MIC ratios were observed less frequently [4,6]. The MBCs of UFX for Gram-negative isolates usually ranged from identical to fourfold the respective MICs. These MBC/MIC ratios were generally comparable to the other fluoroquinolones [4,6,15].

Table 1
In vitro antibacterial activity against Gram-negative bacteria [14,15]

Microorganisms (no. tested)	Antibacterial agent	Susceptibility	MIC (range mg/l)	MIC_{90} (mg/l)
Escherichia coli (37)	Ulifloxacin	S≤1R≥4	≤0.015–1	0.12
	Ciprofloxacin	S≤1R≥4	≤0.015–8	0.5
	Levofloxacin	S≤2R≥8	≤0.015–4	0.25
Klebsiella spp. (15)	Ulifloxacin	S≤1R≥4	≤0.015–0.25	0.12
	Ciprofloxacin	S≤1R≥4	≤0.015–0.5	0.25
	Levofloxacin	S≤2R≥8	0.03–0.5	0.25
Proteus, *Providencia*, and *Morganella* spp. (23)	Ulifloxacin	S≤1R≥4	≤0.015–2	0.5
	Ciprofloxacin	S≤1R≥4	≤0.015–2	1
	Levofloxacin	S≤2R≥8	≤0.015–2	0.5
Pseudomonas aeruginosa (75 Spanish isolates)	Ulifloxacin	S≤1R≥4	0.015–1	1
	Ciprofloxacin	S≤1R≥4	0.06–1	1
	Levofloxacin	S≤2R≥8	0.25–4	2
Pseudomonas aeruginosa (16 Italian isolates)	Ulifloxacin	S≤1R≥4	0.06–64	32
	Ciprofloxacin	S≤1R≥4	0.06–128	64
	Levofloxacin	S≤2R≥8	0.5–128	64
Haemophilus spp. (24)	Ulifloxacin	S≤1R≥4	≤0.015–0.03	≤0.015
	Ciprofloxacin	S≤1R≥4	≤0.015	≤0.015
	Levofloxacin	S≤2R≥8	≤0.015–0.06	0.03

On the whole, against Gram-negative bacteria, UFX was more active than CPUFX and generally more active than the reference drugs. The activity of UFX against Gram-positive bacteria was greater than that of OFX, similar to or greater than that of CPUFX, similar to or lower than those of LVFX and SPUFX, and at all times lower than those of trovafloxacin and MXFX [6,11–15].

2.2. Activity against Gram-negative bacteria

Representative studies were performed to establish the in vitro antibacterial activity of UFX against clinically isolated Gram-negative strains (Table 1).

The MIC values shown by UFX against Italian *P. aeruginosa* strains obtained between 1988 and 2000, were always lower than those observed with other fluoroquinolones [15]. UFX also showed a good activity against clinical isolates of ciprofloxacin-susceptible *P. aeruginosa* (MIC_{90} 1.0 μg/ml) and gentamicin-resistant *P. aeruginosa* (MIC_{90} 0.2 μg/ml) [4,14].

Against community isolates of *E.coli*, the MIC_{90} of UFX ranged between 0.015 and 0.12 μg/ml. Compared with UFX, the MIC_{90} values of CPUFX against *E.coli* isolates showed ranging from identical to four times higher [14,15].

All fluoroquinolones tested were highly active against *Moraxella catarrhalis* and *Haemophilus* isolates.

Based on the correlation analysis of MIC values, the antibacterial activity shown by UFX for *Citrobacter freundii*, *Serratia marcescens* and *P. aeruginosa* was two to four times higher than that of LVFX [14]. Among the quinolones tested, UFX was the most active against Gram-negative bacteria [6,11–15].

2.3. Activity against Gram-positive bacteria

Numerous studies in different countries investigated the in vitro antimicrobial activity of UFX against Gram-positive bacteria. The MIC_{50} and MIC_{90} values of UFX in nosocomial and community *S. aureus* strains were identical (0.25 μg/ml) for oxacillin-susceptible isolates and were 16 and 32 μg/ml, respectively, for oxacillin-resistant isolates [15]. Against methicillin-susceptible *S. aureus*, both MIC_{50} and MIC_{90} values were equal to 0.5 μg/ml [14].

The MIC_{50s} and MIC_{90s} against Italian community isolates of *Streptococcus pneumoniae* were 0.5 and 1 μg/ml, and ranged from 1 to 4 μg/ml against Spanish penicillin-susceptible -intermediate and -resistant isolates [14,15] Noteworthy, the activity of UFX against *Streptococcus pyogenes* [15] (Table 2).

Compared with the respective values of UFX against Gram-positive bacteria, the $M1C_{50}$ and MIC_{90} values ranged from equal to four times higher for CPUFX and OFX, from equal to four times lower (but to two times higher for *L. monocytogenes* strains) for LVFX and SPUFX, and from equal to eight times lower for trovafloxacin and MXFX [3,6,11–15].

2.4. Activity against Lactobacillus strains

Vaginal lactobacilli play an important role in protecting the host from urogenital infections. The microbial balance between lactobacilli, as the dominating flora and other, mainly Gram-positive anaerobes, can be upset and frequently result in the bacterial vaginosis syndrome [16].

Table 2
In vitro antibacterial activity against Gram-positive bacteria [15]

Microorganisms (no. tested)	Antibacterial agent	Susceptibility	MIC (range mg/l)	MIC_{90} (mg/l)
Staphylococcus aureus, oxacillin-susceptible (26)	Ulifloxacin	S≤1R≥4	0.12–05	0.25
	Ciprofloxacin	S≤1R≥4	0.12–0.5	0.5
	Levofloxacin	S≤2R≥8	0.06–0.25	0.25
Streptococcus pyogenes (21)	Ulifloxacin	S≤1R≥4	0.12–2	1
	Ciprofloxacin	S≤1R≥4	0.25–2	1
	Levofloxacin	S≤2R≥8	0.25–2	1
Streptococcus pneumoniae (36)	Ulifloxacin	S≤1R≥4	≤0.015–2	1
	Ciprofloxacin	S≤1R≥4	≤0.015–2	1
	Levofloxacin	S≤2R≥8	≤0.015–1	1
Enterococcus faecalis (26)	Ulifloxacin	S≤1R≥4	0.12–64	2
	Ciprofloxacin	S≤1R≥4	0.25–64	2
	Levofloxacin	S≤2R≥8	0.25–32	2
Enterococcus faecium (18)	Ulifloxacin	S≤1R≥4	0.03–>128	16
	Ciprofloxacin	S≤1R≥4	0.5–>128	16
	Levofloxacin	S≤2R≥8	0.12–>128	16

As reported in some studies showing a significant association between antibiotic therapy and development vulvovaginitis, many factors, such as sexual intercourse, oral contraceptives, pregnancy, presence of intra-uterine devices, and use of many pharmacological therapies including antibiotics, may alterate the vaginal microflora [16,17].

In vitro, UFX showed a very low activity against lactobacillus strains, lower than that observed with amoxicillin clavulanic acid (MIC_{90} 64 vs. 0.5 μg/ml) [18]. Therefore, UFX is capable of respecting the vaginal microflora.

2.5. Activity against resistant bacteria

The antibacterial activity of UFX was tested against methicillin-resistant *S. aureus*, Gram-negative ß-lactamase-producing bacteria (*H. influenzae* and *Moraxella*), gentamycin-resistant *P. aeruginosa*, imipenem-resistant *Bacteroides fragilis*, vancomycin-resistant enterococci, *S. pneumoniae* with different degrees of susceptibility to G penicillin, and against nalidixic acid-resistant Gram-negative and Gram-positive bacteria; UFX was more active than the other quinolones against quinolone-resistant Gram-negative bacteria, and comparable to CPUFX against quinolone-resistant Gram-positive bacteria [4,6].

2.6. Bacterial drug accumulation and time-kill curves

It has been reported that some antibiotics increase the bacterial membrane permeability [19]. Fluoroquinolones accumulate in pathogens such as *P. aeruginosa*, *K. pneumoniae* and *Legionella pneumophila* [20,21]. The in vitro short-term bactericidal activity and accumulation of UFX in isolates of *S. aureus*, *E. coli* and *P. aeruginosa*, were stronger and higher than those observed with CPUFX, LVFX and GFLX [22]. In this study, the accumulation of fluoroquinolones in bacterial cells correlated with their MICs for *E. coli* and *P. aeruginosa*, but not for the *S. aureus*. The potent short-time bactericidal activity of UFX against *S. aureus* and *P. aeruginosa* may be ascribed to its high accumulation in the bacterial cells [22].

Time-kill assays, using selected isolates of oxacillin-susceptible *S. aureus*, ciprofloxacin-susceptible and -resistant *E. coli* and *P. mirabilis*, proved that the bactericidal activity of UFX was at least similar to that of ciprofloxacin [15].

In addition, the post-antibiotic effect (PAE) (delay in regrowth of surviving organism following exposure to an antimicrobial agent) of UFX was longer than that of CPUFX, against Gram- and Gram-positive bacteria [23].

2.7. Uptake and activity in polymorphonuclear neutrophils and macrophages

The efficacy of an antibiotic in the treatment of bacterial infections is the result of bacteria, drug and phagocytes interaction. It has been previously demonstrated that some antimicrobial agents penetrate into the human polymorphonuclear neutrophils (PMNs) and macrophages, with intracellular concentrations resulting several times higher than the extracellular concentrations, and exert in this way their activity against phagocytosed bacteria. Some quinolones, including NFLX, CPUFX, OFX, LVX and trovafloxacin, are effective against facultative intracellular pathogens, such as mycobacteria and *Legionella* spp., and against *S. aureus*, which in certain circumstances can survive within phagocytic cells [24–27].

Although different mechanisms may be involved [28], both UFX and pefloxacin (PFX) strengthened the phagocytic and microbicidal activities of the peritoneal macrophages against *K. pneumoniae* [29]. When intracellularly concentrated, either quinolone can kill the bacteria directly or make them more susceptible to the phagocyte bactericidal effect.

UFX penetrates into PMNs similarly to CPUFX, showing intracellular activity against phagocytosed bacteria (*P. aeruginosa*, *K. pneumoniae* and *S. aureus*) [22,30].

In addition, some quinolones enhance PMN activities. The effect of co-amoxiclav, sanfetrinem, clarithromycin, UFX and tobramycin on the release of cytokines from PMNs was assessed in an inflammatory context. All the drugs tested were capable of modulating the PMN in vitro synthesis of pro-inflammatory cytokines, such as IL-8, IL-1 beta, TNF-alpha and IL-6, but not that of the anti-inflammatory cytokine IL-10. The degree of their stimulatory or inhibitory potency varied with the cytokine examined [31].

2.8. Induction of resistance

Since many antibacterial drugs may induce bacterial resistance with augmented use [32], several studies were performed to evaluate the degree of resistance induced by UFX. Following bacteria exposure to UFX, the rate of appearance of resistant mutants was similar to or less than with the other quinolones [6,12].

2.9. In vivo activity

2.9.1. Systemic infection

In mice and dogs, PUFX showed a potent in vivo antibacterial activity against systemic infections induced by both Gram- and Gram-negative bacteria. The comparative activity of UFX was evaluated in systemic infections induced by *S. aureus*, *S. pyogenes*, *S. pneumoniae*, *P. mirabilis*, *K. pneumoniae*, *E.coli* and *P. aeruginosa* [33–35]. The results demonstrated that the efficacy of PUFX against Gram-positive clinical isolates was lower than that of LVFX and TFLX, and equal to that of OFX and CPUFX, whereas against Gram-negative clinical isolates, PUFX showed the highest activity in comparison with the reference drugs [32–34].

The therapeutic effect of PUFX was assessed in experimental urinary tract infections induced in mice by *E. coli*, *P. aeruginosa* and *E. cloacae*. Against *E. coli*, its activity was equal to that of TFLX and CPFX and superior to that of OFX and LVFX. The therapeutic effect of PUFX in infections due to *P. aeruginosa* was equal to that of TFLX and CPUFX, and higher than that of OFX. Of all the drugs tested against urinary tract infection with ofloxacin-resistant *Enterobacter cloacae*, PUFX was the most effective [6,35].

In experimental respiratory tract infections induced in mice by *K. pneumoniae* and *S. penumoniae*, PUFX interestingly showed a better efficacy than that of OFX and CPUFX (ED_{50} 0.98, 2.24 and 1.18 mg/kg, respectively) [6,33,34].

3. Pharmacokinetic profile

Several pharmacokinetic studies have been carried out in rats, dogs, monkeys and humans [4].

PUFX, the prodrug of UFX, offers a clear advantage over the active metabolite with regard to absorption after oral administration. PUFX is absorbed in the upper small intestine and then metabolized to UFX by esterases, mainly paraoxonase, partly in the intestinal membrane and mostly in the portal blood and the liver (first pass or presystemic metabolism) [4,36]. Thus, PUFX is not detectable in the systemic circulation.

In a concentration range of 0.1–10 μg/ml, the proportion of UFX that binds to serum proteins is 41–59% [37]. Following oral administration of PFUX, the maximum concentration of UFX in rat tissues was reached within 1 h, and thereafter decreased along with the plasma concentration. At 0.5 h, the concentrations were the highest in the liver and kidney, moderately high in the spleen, pancreas, lung and mandibular gland, and extremely low in the cerebrum and cerebellum [37]. In human lung tissues, the concentrations of UFX were up to 5 times higher than in plasma, but extremely low in the cerebrospinal fluid [4]. In humans, the salivary concentrations of UFX were approximately 20% of the plasma concentrations, while in the bile UFX reached concentrations of approximately 42 mg/l, definitely higher than the MIC values of the most common pathogens [38,39]. After oral administration of PFUX 200 mg, the concentration of UFX in gynaecological tissues ranged from 1.20 to 2.16 mg/kg, at 1.4–3.5 h postdose [40].

The metabolism of the PUFX, investigated after oral administration, showed a similar pattern in rats, dogs, monkeys and humans [38,41]. UFX, UFX acyl glucuronide, the ethylenediamino form, the diol form and the amino form were found in the urine of all species, while the oxo form was detected in the urine of humans and monkeys only. UFX was the main metabolite in the urine of rats, dogs and monkeys and in plasma and feces of rats. PUFX was transformed into a variety of minor metabolites, but most of the drug administered was metabolized to UFX by hydrolytic cleavage of the dioxolene ring [36].

Following oral administration of ^{14}C-prulifloxacin, the concentrations of radioactivity in the excreta collected in rats, dogs and monkeys over a 96-h period were 96–98% of the oral dose (urine, 22–32%; feces, 64–75%), 35% of the radioactivity was excreted in the bile of rats during a 48-h period, and only a small portion of the biliary radioactivity was reabsorbed [37]. In humans, UFX is excreted unchanged in urine (17–46%) by glomerular filtration and active tubular secretion [4,38,42].

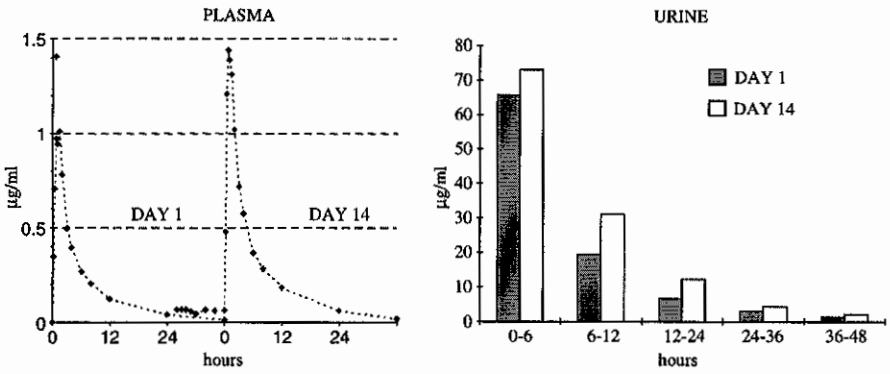

Fig. 4. Plasma and urine concentrations of ulifloxacin after single and repeated administrations of prulifloxacin 600 mg once daily.

3.1. Pharmacokinetic parameters after single dose administration

The pharmacokinetics of labeled PUFX was investigated after i.v. (^{14}C-UFX) or oral (^{14}C-PFUX) administration in rats, dogs and monkeys [37]. After i.v. administration of ^{14}C-UFX (5 mg/kg), the plasma concentration of radioactivity decreased biexponentially with an elimination half-life equal to 4.2, 5.8 and 7.0 h, respectively. After oral administration of ^{14}C-PUFX (20 mg/kg), the maximum plasma concentration of radioactivity reached at 0.7–3.3 h.

The pharmacokinetic properties of prulifloxacin have been investigated in a randomized, cross-over study performed in 12 Caucasian young male subjects [42]. PUFX was administered as a single oral dose at the dosages of 300, 450 and 600 mg, and the concentrations of UFX were determined in urine and blood samples collected before (pre-dose) and at different times after dosing. PUFX was rapidly absorbed (t_{max} of 0.75–1.0 h), and UFX reached mean maximum plasma concentrations (C_{max}) included between 1 and 1.6 μg/ml. The half-life ranged between 10.6 and 12.1 h, whatever the dose. The urinary excretion was significantly correlated with the AUC and the renal clearance was invariably equal to approx. 170 ml/min, indicating that the renal elimination is not dose-related. The urinary concentrations of UFX were very high up to 48 h after dosing, often exceeding more than 10 times the MIC values of the most frequent uropathogens. The very high urinary concentrations and the relatively long terminal half-life (Fig. 4), suggested the once-daily administration as adequate to achieve clinical efficacy.

3.2. Pharmacokinetic parameters after repeated oral administration

Following repeated oral administration of ^{14}C-PUFX (20 mg/kg) in rats, the plasma concentrations of radioactivity were almost constant [43]. The average cumulative urinary and fecal excretion of radioactivity did not differ from the corresponding values after single administration. After the last dose, the radioactivity concentration decreased in most tissues along with that in plasma, whereas a slower elimination was observed in skin and bone.

Repeated oral administration of 20 or 200 mg/kg of PUFX in male rats did not affect the activity of the drug-metabolizing hepatic enzymes [43]. In pregnant rats, following single oral administration of ^{14}C-PUFX (20 mg/kg), the maximum concentration of radioactivity in the fetus was lower than that detected in the maternal plasma. Furthermore, the total amount of radioactivity in the fetus was only 0.01% of the dose at 0.5 h. In lactating rats, the concentration of radioactivity in milk was substantially higher than in plasma [43].

After repeated PUFX 600 mg once daily dosing for 12 days in healthy volunteers (Fig. 4), the C_{max} of UFX was 2 μg/ml at 0.75 h. At the steady state, the $t_{1/2}$ and renal clearance values of UFX were 7.6 h and 193 ml/min, respectively. Approximately 18% of the PUFX dose administered, was excreted as UFX in the urine [4].

3.3. Pharmacokinetic parameters in the elderly

After oral administration, the pharmacokinetic parameters of PUFX in Caucasian elderly subjects were similar to those observed in young healthy volunteers: C_{max} and renal clearance were not modified, whereas T_{max}, AUC and $t_{1/2}$ were slightly increased in the elderly [4].

3.4. Pharmacokinetic parameters in renal failure

After a 600 mg single administration of PUFX in patients with renal failure, the pharmacokinetic parameters of UFX were modified. T_{max}, AUC and $t_{1/2}$ were increased, while CL_R was reduced compared to values observed in healthy subjects. These changes were probably related to the degree of renal failure. In nephropathic patients, the PUFX dose should be reduced according to the degree of renal failure [4].

3.5. Interaction

3.5.1. Food interaction

The C_{max}, AUC, and urinary excretion rates of UFX were not altered by food intake, whereas the T_{max} was slightly prolonged [38].

3.5.2. Drug interaction

Some antibiotics, including quinolones, may affect the pharmacokinetic parameters of theophylline [44]. The effect of PUFX single doses (600 mg) for 8 days on the pharmacokinetics of theophylline (6 mg/kg) was studied in healthy Caucasian volunteers [45]. Co-treatment with PUFX did not modify C_{max} and T_{max} of theophylline, but it induced a small increase in the AUC (about 15%). This increase was similar to that observed with other antibacterial drugs routinely used for the treatment of exacerbation of chronic bronchitis, but definitely lower than that reported with ciprofloxacin (up to 308%) [46]. PUFX can be included in the group of drugs which only cause a weak alteration in theophylline disposition.

Various drugs, such as antiacids, cimetidine, and iron-containing supplements, can reduce the absorption of PUFX in humans [4].

Probenecid reduced the renal excretion of UFX, by inhibiting the active tubular secretion ([4]).

4. Safety and tolerability

Chondrotoxicity, CNS effects, drug–drug interaction, hepatotoxicity, cardiotoxicity (e.g. QTc interval prolongation of ECG) and phototoxicity are adverse reactions that, in some cases, led to withdrawal of several quinolones from the market, and focused the attention on their safety profiles.

The acute, subacute, and chronic toxicity studies, including teratology, fertility and mutagenic studies, carried out in animals confirmed that PUFX shows the same tolerability profile as the other currently marketed quinolones [47–49].

PUFX is devoid of remarkable effects on the peripheral and autonomic nervous system, and on the gastrointestinal and renal systems [50,51]. No alteration of QT and QTc intervals were observed in dogs after oral administration of PUFX up to the highest dose tested (150 mg/kg p.o.), and UFX did not show significantly inhibitory effect on the HERG ion channel [52]. In addition, recent evidence in a rabbit proarrhythmia model demonstrated that the infusion of UFX (4 mg/kg/min) did not cause a prolonged QT interval, whereas, sparfloxacin and gatifloxacin did [53].

PUFX did not induce convulsions when administered alone. Oral co-administration of PUFX and fenbufen or theophylline-induced convulsions and death in mice [54]. Nevertheless, the degree of this convulsant activity was moderate when compared with the other fluoroquinolones. The convulsant activity of prulifloxacin, as well as the other fluoroquinolones in presence of fenbufen, is thought to be partly mediated by inhibition of the GABA$_A$ receptor binding, while the effects observed in combinations with theophylline were probably due to the increased blood concentration and prolonged half-life of theophylline [45].

The safety of PFUX was also evaluated in healthy male volunteers given the drug in single and multiple oral doses of 600 mg for 12 days. No clinically significant abnormalities were observed in symptoms and signs, laboratory tests, and electrocardiograms [4,42].

5. Therapeutic indications

In vitro and in vivo preclinical studies suggested that PUFX is a broad spectrum (vs. Gram- and Gram-positive bacteria) quinolone.

The clinical efficacy and safety of PFUX has been evaluated in randomized, controlled and multicenter studies performed in patients with acute exacerbation of chronic bronchitis (AECB), or acute uncomplicated and complicated lower urinary tract infections (UTIs). In a statistical viewpoint, PUFX was considered not inferior to the reference drugs (CPUFX, amoxicillin/clavulanate, PFX) [4].

These studies suggested that PFUX at the dosage of 600 mg once daily can be efficiently used in the treatment of lower uncomplicated UTI in single administration, and in AECB and lower complicated UTI with a treatment period up to 10 day.

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