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SCIENTIFIC REVIEW

Bioavailability File: Levofloxacin

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Bioavailability File: Levofloxacin

Summary

Levofloxacin (LVFX) is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative aerobic bacteria and atypical bacteria, and limited activity against most anaerobic bacteria. It exerts its antibacterial effects by inhibiting bacterial DNA gyrase and topoisomerase IV. LVFX is well absorbed with bioavailability of approximately 99%. Its volume of distribution is about 1.1 L/kg and protein binding 24-38%. It is excreted through the kidneys with 64-102% of the dose as unchanged drug. The half-life of LVFX is between 6-9 hours. According to Biopharmaceutics Classification System (BCS), LVFX is in Class 1 (high solubility/high permeability). The physicochemical properties, analytical methods, pharmacokinetics, bioavailability, and pharmacology of LVFX are discussed in this review.

Key Words: *Levofloxacin, pharmacokinetic, bioavailability, pharmacology, Biopharmaceutics Classification System (BCS).*

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Biyoyararlanım Dosyası: Levofloksasin

Özet

Levofloksasin (LVFX) Gram-pozitif ve Gram-negatif aerobik bakterilere, atipik bakterilere, geniş spektrumlu aktivite ve çoğu anerobik bakterilere karşı sınırlı aktivite gösteren bir florokinolon antibakteriyel ajandır. Antibakteriyel etkisini DNA giraz ve topoizomeraz IV'ü inhibe ederek gösterir. LVFX yaklaşık % 99 biyoyararlanım ile iyi emilir. Dağılım hacmi yaklaşık 1.1 L/kg ve proteinlere % 24-38'dir. Değişmemiş ilaç olarak dozunun % 64-102'si böbrekler yoluyla atılır. LVFX'in yarılanma ömrü 6-9 saat arasındadır. Biyofarmasötik Sınıflandırma Sistemi (BCS)'e göre Sınıf 1'de (yüksek çözünürlük/yüksek permeabilite) yer alır. Bu derlemede, LVFX'in fizikokimyasal özellikleri, analitik yöntemleri, farmakokinetiği, biyoyararlanımı ve farmakolojisi tartışılmıştır.

Anahtar kelimeler: *Levofloksasin, farmakokinetik, biyoyararlanım, farmakoloji, Biyofarmasötik Sınıflandırma Sistemi (BCS)*

INTRODUCTION

The fluoroquinolones are widely used synthetic antibacterial agents to rival the beta-lactam and the macrolide antibacterials for impact in clinical usage in the antibacterial therapeutic field. They have a broad antibacterial spectrum of activity against Gram-positive, Gram-negative and mycobacterial pathogens as well as against anaerobes. Furthermore, they show good-to-moderate oral absorption and tissue penetration with favorable pharmacokinetics in humans, resulting in high clinical efficacy in the treatment of many kinds of infections. They also exhibit excellent safety profiles comparable to those of oral beta-lactam antibiotics (1).

Levofloxacin (LVFX) inhibits bacterial DNA gyrase and topoisomerase IV; the primary enzymatic target varies for different species of bacteria (2,3). It has a broad spectrum of activity against Gram-positive and Gram-negative aerobic bacteria and atypical bacteria, but limited activity against most anaerobic bacteria (4-6).

PHYSICOCHEMICAL PROPERTIES

Levofloxacin (LVFX) (CAS100986-85-4) is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens. It is active against both penicillin-susceptible and penicillin-resistant Streptococcus pneumoniae (4,7). Chemically, LVFX, a

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chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate (8).

The chemical structure is shown in Figure 1. The molecule exists as a zwitterion at the pH conditions in the small intestine (8).

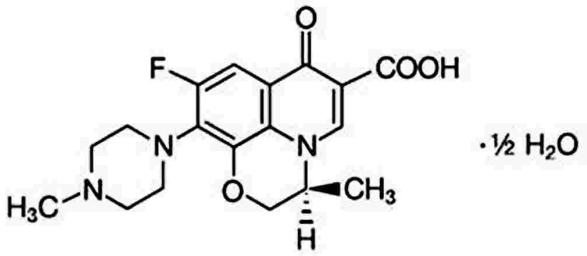

Figure 1 : The chemical structure of levoflox acin (7).

In solid form, LVFX is an odorless, white to yellow, crystallized powder with a melting point of 228.6°C. Its molecular weight is 361. LVFX is practically insoluble in water, but is soluble in ethanol and chloroform, and also in ethanol–water mixture, with an octanol:water partition coefficient (log P) of 0.6. LVFX possesses two ionizable functional groups: a carboxylic group (pKa_1=6.05 and 5.70) and a basic piperanyzyl group (pKa_2=8.22 and 7.90) (9). LVFX has pH-dependent solubility in a range of about 30–300 mg/mL within the range of pH 1–pH 8(8).

ANALYTICAL METHODS

In biological fluids, LVFX can be determined by high-performance liquid chromatography (HPLC) (10), chemiluminescence (11), and spectrofluorometric and micelle- enhanced spectrofluorometric (9) methods.

Santoro et al. (12) developed and validated an HPLC method for quantitative determination of LVFX in tablets and injection formulations. The wavelength (λ_{max}) was 295 nm for detection. The limit of detection (LOD) was 0.15 µg/mL.

Wong et al.(13) reported a simple reversed phase HPLC method for rapid stereospecific determination of LVFX in both human plasma and urine. µmax was 330 nm for detection. The method was linear from 0.08 to 5.18 µg/mL in plasma and from 23 to 1464 µg/mL in urine. This HPLC method was used by Chien et al. (10) for quantitative determination of LVFX in human plasma and urine. The limit of quantification (LOQ) for the assay was determined to be 82 ng/mL.

The chemiluminescence method shows the advantages of simplicity, rapidity and high sensitivity, and has been studied extensively for the analysis of pharmaceutical compounds. LOD was 0.007 mg/mL (11).

Gonzales et al. (9) used a spectrofluorometric method to determine LVFX in tablets and spiked human urine and serum. Two methods have been applied for LVFX determination: aqueous solution fluorescence and micelle-enhanced fluorescence. The fluorimetric method allows the determination of 20–3000 ng/mL of LVFX in aqueous solution for λ_{exc} = 292 and λ_{em} = 494 nm, respectively. Micelle-enhanced fluorescence improves the sensibility and allows LVFX direct measurement in spiked human serum (5 mg/mL) and urine (420 mg/mL) in 8 mM sodium dodecyl sulphate solutions at pH 5. Aqueous solution fluorescence method is recommended for LVFX determination in urine. Micelle-enhanced fluorescence method is recommended for determination in serum. Both methods were applied successfully for the determination of the active constituent in a commercial pharmaceutical (9).

Table 1. Minimal inhibitory concentrations (MIC) of LVFX for related microorganisms (5)

Microorganism	MIC (mg/L)
Streptococcus pneumoniae	1.0–2.0
Staphylococcus aureus	0.25–0.5
Haemophilus influenzae	0.008–0.12
Moraxella catarrhalis	≤0.03–0.06
Enterobacteriaceae	≤2.0
Chlamydia pneumoniae	≤0.5
Mycoplasma pneumoniae	≤1.0
Legionella spp.	≤0.03

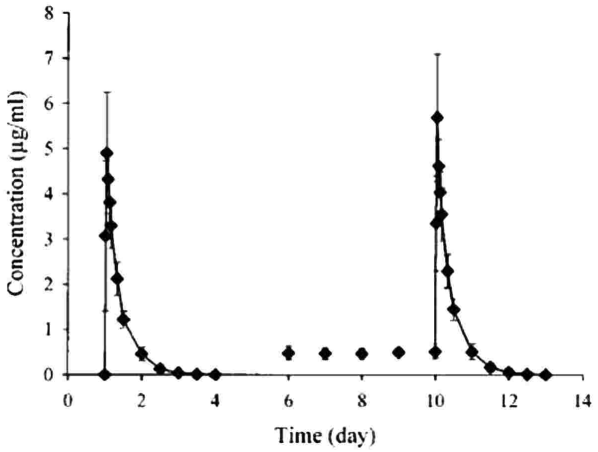

Figure 2 : Mean ± SD plasma LVFX concentration - time a profiles following the administration of LVFX hemihydrate (study A) as a single 500 mg oral dose on day 1 and 500 mg oral doses once daily on days 4 to 10 (22).

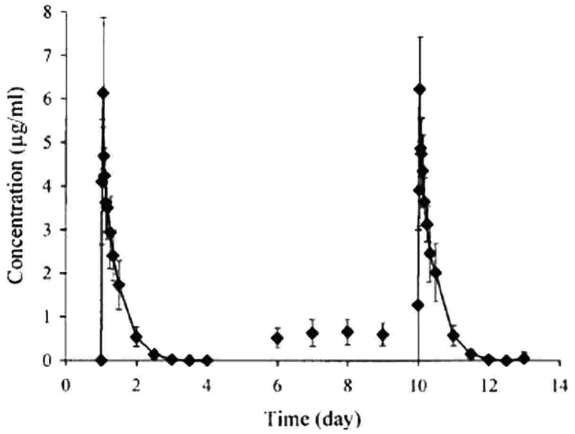

Figure 3 : Mean ± SD plasma LVFX concentration - time a profiles following the administration of single (day 1) and multiple once daily (days 4 to 10) 500 mg intracenous doses given as 1 h infusions (study B) (22)

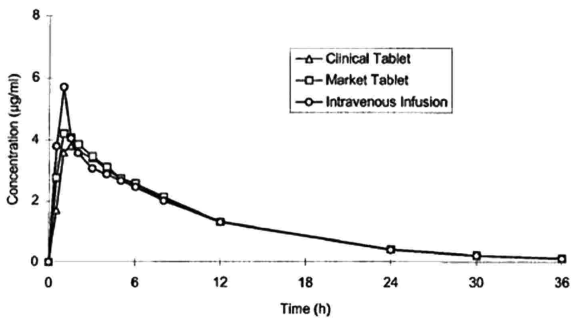

Figure 4 : Mean plasma LVFX concentration - time profiles for 23 healthy male subjects following the administration of single 500 mg doses of the clinical tablet and the intravenous infusion (study C) (22).

PHARMACOLOGICAL PROPERTIES

Levofloxacin is the L-isomer of the racemic drug ofloxacin. Like other fluoroquinolones, it inhibits both bacterial DNA gyrase and topoisomerase IV; the primary enzymatic target varies for different species of bacteria (2). LVFX has a broad spectrum activity against Gram-positive and Gram-negative aerobes and atypical bacteria. It has limited activity against anaerobes. LVFX appears to have improved activity against Streptococcus pneumoniae compared with ciprofloxacin or ofloxacin (4,8). LVFX activity against the microorganisms is given in Table 1.

Levofloxacin differs in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. It is widely used in the treatment of respiratory tract and urinary tract infections. LVFX penetrates well into polymorphonuclear leukocytes, which can act as vehicles for transport and delivery of the active drug to sites of infections (8).

DOSAGE AND ADMINISTRATION

The usual dosage of LVFX is 250, 500 or 750 mg once daily. It is available formulated for slow intravenous infusion over 60 minutes (min) for 250 or 500 mg dosages and over 90 min for 750 mg or as tablets. Sequential transfer from intravenous to oral therapy may take place without altering the dose.

Oral LVFX can be taken without regard to the timing of meals but should be administered at least 2 hours (h) before or after taking preparations such as antacids, metal cations (e.g. iron), multivitamins, and sucralfate (4).

ADVERSE EFFECTS

Levofloxacin is generally well tolerated in comparison with some other quinolones, with the most frequently reported adverse events being nausea and diarrhea. It has a low photosensitizing potential, and clinically significant cardiac and hepatic adverse events are rare (4,14-16). In dosage regimens ranging from 250 mg once daily 7 – 10 days to 500 mg once daily for 14 days, the drug was generally well tolerated and safe (17-20).

Table 2. Pharmacokinetic parameters of LVFX

	Regimen	C_{max} (µg/mL)	T_{max}(h)	AUC (mg.L/h)	CL/F (mL/min)	V_d/F (L)	$t_{1/2}$ (h)	CL_R
Single Dose	500 mg oral tablet(11)	5.08	1.7	48.0	-	-	6.9	-
	750 mg oral tablet(11)	7.13	1.7	82.0	-	-	6.9	-
	500 mg oral tablet(13) (Study A)	5.19 ± 1.21	1.3 ± 0.5	47.7 ± 7.6	175 ± 29.2	96.7 ± 11.9	7.4 ± 0.9	126 ± 30.0
	500 mg IV (13) (Study B)	6.34 ± 1.42	-	55.3 ± 11.9	157 ± 32.2	88.8 ± 18.5	7.1 ± 1.0	95.5 ± 23.0
	500 mg oral tablet(13) (Study C)	4.51 ± 0.9	1.57 ± 0.8	43.2 ± 7.1	199 ± 37	-	6.8 ± 0.6	-
	500 mg oral tablet(13) (Study C)	4.80 ± 1.0	1.37 ± 0.8	44.7 ± 6.7	191 ± 28	-	6.9 ± 0.6	-
	500 mg IV infusion(13) (Study C)	5.70 ± 0.8	1.00 ± 0.0	44.0 ± 7.3	195 ± 35	105 ± 16	6.7 ± 0.7	-
	250 mg oral tablet(15)	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	-	7.3 ± 0.9	142 ± 21
	500 mg oral solution(15)	5.8 ± 1.8	0.8 ± 0.7	47.8 ± 10.8	183 ± 40	112 ± 37.2	7.0 ± 1.4	-
	500 mg IV(15)	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.1	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
	750 mg oral tablet(15)	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	129 ± 24	83 ± 17	7.5 ± 0.9	-
	750 mg IV(15)	11.5 ± 4.0	-	110 ± 40	126 ± 39	75 ± 13	7.5 ± 1.6	-
	500 mg oral tablet(26)	6.92 ± 2.30	1.75 ± 0.64	47.6 ± 11.46	181 ± 42.8	114 ± 37.7	8.1 ± 1.90	-
	200 mg IV infusion(27)	2.4 ± 0.4	-	16.1 ± 1.4	-	-	6.3 ± 0.3	-
	500 mg oral tablet(30)	8.69	-	63.5	-	-	-	-
	500 mg oral tablet(30)	8.45	-	60.7	-	-	-	-
	500 mg IV(37)	7.6 ± 2.7	-	-	-	-	6.4 ± 0.9	-
	750 mg IV(36)	11.3	-	90.9	-	-	7.5	-
	750 mg oral tablet(38)	7.13 ± 1.44	1.9 ± 0.7	82 ± 14	157 ± 28	90 ± 14	7.7 ± 1.3	118 ± 28
	1000 mg oral tablet(38)	8.85 ± 1.86	1.7 ± 0.4	111 ± 21	156 ± 34	96 ± 22	7.9 ± 1.5	113 ± 2.6
Multiple Dose	500 mg every 24 h oral tablet(13)	5.72 ± 1.40	1.1 ± 0.4	47.5 ± 6.7	175 ± 24.5	102 ± 21.8	7.6 ± 1.6	116.2 ± 30.8
	500 mg every 24 h IV(13)	6.40 ± 0.82	-	54.6 ± 11.1	158 ± 28.8	90.6 ± 11.9	7.0 ± 0.8	99.0 ± 27.7
	500 mg or 250 mg every 24 h IV(15)	8.7 ± 4.0	-	72.5 ± 51.2	154 ± 72	111 ± 58	-	-
	750 mg every 24 h oral tablet(15)	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
	750 mg every 24 h IV(15)	12.1 ± 4.1	-	108 ± 34	126 ± 37	80 ± 27	7.9 ± 1.9	-
	200 mg IV infusion every 12 h(27)	2.9 ± 0.4	-	23 ± 6	-	-	6.2 ± 0.8	-
	500 mg IV every 24 h(37)	8.2 ± 2.2	-	-	-	-	6.9 ± 1.2	-
	750 mg IV every 24 h(36)	12.4	-	103	-	-		-
	750 mg every 24 h oral tablet(38)	8.60 ± 1.86	1.4 ± 0.5	91 ± 18	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
	1000 mg every 24 h oral tablet(38)	11.8 ± 2.52	1.7 ± 0.6	118 ± 19	146 ± 29	105 ± 27	8.9 ± 2.5	106 ± 23

PHARMACOKINETICS AND BIOAVAILABILITY

Absorption

Levofloxacin is well absorbed following oral administration and the absolute bioavailability is approximately 99%. Following 500 and 750 mg oral LVFX dose, it is absorbed quickly, attaining maximum plasma concentration (C_{max}) within approximately 1-2 h of oral administration daily for multiple-dose administration (21). Table 2 summarizes the pharmacokinetic parameters of LVFX according to the available literature.

Chien et al. (22) evaluated the pharmacokinetics of oral and intravenous LVFX following the administration of single and multiple 500 mg doses once daily to healthy male volunteers. The pharmacokinetics of once-daily oral LVFX (study A) or intravenous LVFX (study B) in 40 healthy male volunteers were investigated in two separate randomized, double-blind, parallel-designed, placebo-controlled studies. LVFX at 500 mg or placebo was

administered orally or intravenously as a single dose on day 1; daily oral or intravenous dosing resumed on days 4 to 10. In a third study (study C), the bioavailabilities of two oral and one intravenous LVFX formulations were investigated and compared in a study with 24 healthy male subjects in an open-label, randomized, three-way crossover study. LVFX at 500 mg as a single tablet or an intravenous infusion was administered on day 1; following a 1-week washout period, subjects received the second regimen (i.e., the other oral formulation or the intravenous infusion); the third and final regimen was administered following a 1-week washout period. Pharmacokinetic parameters were estimated by noncompartmental methods. In both study A (oral) and study B (intravenous), steady state was attained within 48 h after the start of the multiple dosing on day 4. LVFX pharmacokinetics were linear and predictable for the single and multiple 500 mg, once-daily oral and intravenous dosing regimens, and the values of the pharmacokinetic parameters for the oral and intravenous administrations were similar. Study C indicated that LVFX was rapidly and completely absorbed from the oral tablets, with mean times to the maximum concentration of drug in serum of approximately 1.5 h and mean absolute bioavailability of >99%. These results support the interchangeability of the oral and intravenous routes of LVFX administration. The plasma concentration–time profiles(22) are given in Figures 2-4, and the related pharmacokinetic parameters are given in Table 2.

Different dose and administration routes were evaluated for LVFX pharmacokinetics. Trampuz et al.(23) determined the pharmacokinetics of 500 mg single dose of LVFX oral tablets in 20 volunteers. Obtained pharmacokinetic parameters are given in Table 2.

Amsden et al.(24) characterized the single dose (500 mg, IV) and steady state (500 mg once daily for 7 days, IV) plasma pharmacokinetics of LVFX in 12 healthy volunteers. The plasma concentrations of LVFX were less than 1 mg/L for at least 6 h when given both as a single dose or at steady state. The pharmacokinetic parameters are summarized in Table 2.

Table 3. Distribution of LVFX to respiratory fluids and tissues (Sampling was performed following administration of single oral doses of LVFX, except for alveolar macrophages and epithelial lining fluid, for which samples were obtained after administration of multiple doses of intravenous or oral LVFX [once daily for 5 days] (4)

Tissue / fluid	Dose (mg) (hours post-dose)	Plasma concentration (mg/L)	Tissue/fluid concentration (mg/L)	Tissue/fluid plasma concentration ratio
Alveolar macrophages (29-31)	500(4)	4.1-5.3	27.7-97.9	2.3-18.5
	500(12)	1.6-3.1	18.3-36.7	11.2-12.0
	500(24)	0.4-0.6	5.6-13.8	11.7-23.0
	750(4)	6.6-12.0	81.7-105.1	8.8-12.5
	750(12)	3.5-4.1	36.2-78.2	8.9-22.2
	750(24)	0.8-1.7	13.5-15.1	8.9-15.8
Bronchial lavage fluid (33)	200(1-3)	2.5	0.12	0.06
Bronchoalveolar lavage fluid (33)	200(1-3)	2.5	0.21	0.1
Epithelial lining fluid (29-31)	500(4)	4.1-5.3	9.9-11.0	1.9-3.0
	500(6-8)	4.0	10.1	2.7
	500(12)	1.6-3.1	2.5-6.5	1.5-2.1
	500(24)	0.4-0.6	0.7-1.7	1.2-2.6
	750(4)	6.6-12.0	12.9-22.1	1.9-2.0
	750(12)	3.5-4.1	6.0-9.2	1.7-2.3
	750(24)	0.8-1.7	1.5-1.7	0.9-2.1
Lung (27)	500(4-6)	2.9	11.3	5.0
	500(21-25)	0.7	2.4	4.1
Sputum (32)	100(4)	1.1	1.3	1.2

Chien et al. (25) evaluated 750 and 1000 mg oral doses of LVFX in healthy volunteers. The study was conducted both in single dose and steady state (once daily for 10 days). The pharmacokinetics of oral LVFX at both dose levels were found to be similar based on comparable values of apparent clearance and volume of distribution, estimates of elimination half-life. The mean plasma LVFX concentrations versus time profiles are given in Figure 5 and the pharmacokinetic parameters are shown in Table 2. The pharmacokinetics of LVFX following the 750 and 1000 mg doses were similar to those obtained in a previous study (22) with 500 mg LVFX doses, showing that LVFX exhibits linear pharmacokinetics over the dose range 500–1000 mg. This study also demonstrated that high doses of LVFX are safe.

Almeida et al. (26) compared the relative bioavailability of two different LVFX 500 mg tablets in 21 healthy subjects. Two drugs were considered bioequivalent with C_{max} values of 11293.37 ± 2604.5 ng/mL and 12183.48 ± 2871.17 ng/mL and AUC values of 120465.59 ± 23750.03 ng.h/mL and 122234.40 ± 21229.89 ng.h/mL for reference and test drugs, respectively (26).

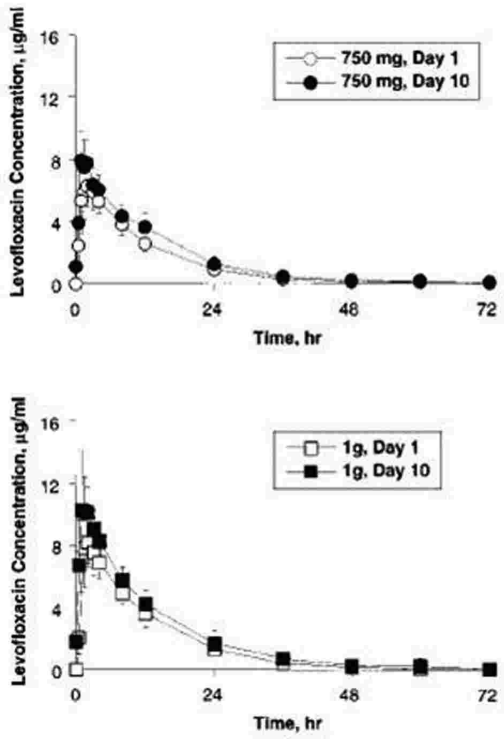

Figure 5 : Mean plasma concentration-time profiles following single and multiple once-daily 750 mg and 1000 mg oral doses of LVFX for 10 healthy volunteers (26).

Table 4. Summary of LVFX pharmacokinetic estimates in children (10)

	Age Group	N	C_{max} (µg/mL)	AUC (µg.h/mL)	$t_{1/2}$ (h)	T_{max} (h)	V_d/F (L/kg)	CL/F (L/h/kg)
Children; single 7 mg/kg oral dose (to max 500 mg)	**6 months to 2 years**							
	IV	6	5.19 ± 1.26	21.5 ± 6.1	4.1 ± 1.3	1	1.56 ± 0.30	0.35 ± 0.13
	Oral	8	4.21 ± 1.49	25.8 ± 9.2	5.0 ± 1.3	1.4 ± 0.4	2.32 ± 1.41	0.31 ± 0.13
	2 to 5 years							
	IV	7	6.02 ± 1.07	22.7 ± 4.7	4.0 ± 0.8	1	1.50 ± 0.21	0.32 ± 0.08
	Oral	8	4.56 ± 0.83	25.9 ± 4.8	4.6 ± 1.3	1.6 ± 0.5	1.81 ± 0.62	0.28 ± 0.05
	5 to 10 years							
	IV	10	7.30 ± 3.85	29.2 ± 6.4	4.8 ± 0.8	1	1.57 ± 0.44	0.25 ± 0.05
	Oral	8	4.64 ± 0.39	29.0 ± 10.0	5.3 ± 1.6	1.3 ± 0.4	1.88 ± 0.44	0.26 ± 0.06
	10 to 12 years							
	IV	7	6.12 ± 1.19	39.8 ± 11.3	5.4 ± 0.8	1	1.44 ± 0.35	0.19 ± 0.05
	Oral	8	3.99 ± 0.87	37.3 ± 9.8	5.5 ± 0.7	1.9 ± 0.9	1.57 ± 0.43	0.20 ± 0.06
	12 to 16 years							
	IV	10	6.34 ± 1.58	40.5 ± 7.6	6.0 ± 2.1	1	1.56 ± 0.53	0.18 ± 0.03
	Oral	8	4.76 ± 0.86	41.1 ± 6.8	5.8 ± 1.4	1.6 ± 1.0	1.40 ± 0.28	0.17 ± 0.04
Adults 500 mg	IV	23	6.18 ± 1.04	48.3 ± 5.40	6.0 ± 1.0	1	1.27 ± 0.12	0.15 ± 0.02
	Oral	36	5.41 ± 1.68	49.3 ± 12.5	6.9 ± 1.5	1.1 ± 0.9	1.44 ± 0.40	0.14 ± 0.03

Table 5. Summary of LVFX pharmacokinetic parameters in age and gender groups (38)

Parameter	Male (n=12)	Female (n=12)	Young (n=12)	Elderly (n=12)
C_{max} (µg/mL)	5.52 ± 1.07	6.96 ± 1.57	5.52 ± 1.02	6.96 ± 1.60
T_{max} (h)	1.2 ± 0.4	1.7 ± 0.5	1.5 ± 0.6	1.4 ± 0.5
V_d/F (L/kg)	1.11 ± 0.19	0.94 ± 0.14	1.13 ± 0.18	0.92 ± 0.12
AUC (µg.h/mL)	54.4 ± 18.9	67.7 ± 24.2	47.5 ± 9.8	74.7 ± 23.3
$T_{1/2}$ (h)	7.5 ± 2.1	6.1 ± 0.8	6.0 ± 0.9	7.6 ± 2.0
CL/F (mL/min)	166 ± 44	136 ± 44	182 ± 35	121 ± 33
CL_R (mL/min)	126 ± 38	106 ± 40	140 ± 33	91 ± 29

Table 6. Summary of drug interaction studies for LVFX

Interacted Drug	Interaction Type
Calcium, aluminium and magnesium containing antacids	Through the formation of non-absorbable chelates, absorption of LVFX can reduce (4,12,43)
Sucralfate, and metal cations containing nutritional supplements	Through the formation of non-absorbable chelates, absorption of LVFX can reduce (4,12,43)
Theophylline	No significant interaction (44,45)
Warfarin	No significant interaction (46)
Cyclosporine	No significant interaction (14)
Digoxin	No significant interaction (14)
Cimetidine, probenecid	Little or no changes in the rate of absorption; CL_R of LVFX can reduce (14,47)
Ranitidine	No significant interaction (43)
Zidovudine	No significant interaction (48)
Nelfinavir	No significant interaction (49)

The pharmacokinetics of LVFX are linear over the range of single doses of 500-1000 mg and multiple doses of 500-1000 mg once daily (22,25,27). Steady state plasma concentrations are reached within 48 h at commencing 500 and 750 mg once-daily dosing regimens (4).

Food Effect

Although administration of LVFX with food resulted in delayed absorption (60% increase in Tmax) and slight decrease in the Cmax (14%) and AUC (10%) (28), it does not cause clinically significant alterations in bioavailability of LVFX (12). Therefore, LVFX can be given orally without regard to food intake.

Distribution

Levofloxacin is 24-38% bound to plasma proteins (27), mainly albumin, and has a volume of distribution of 76-102 L following single and multiple 500 or 750 mg doses (20-22).

Levofloxacin displays good penetration into alveolar macrophages, bronchial mucosa, epithelial lining fluid, and saliva. Tissue and fluid concentrations often exceed serum concentrations (21). Tissue distribution is extensive with concentrations in most tissues (including the lung, prostate gland and skin) exceeding those in plasma. Their distribution into selected fluids and tissues (27,29-33) is summarized in Table 3.

Metabolism and Elimination

Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer,

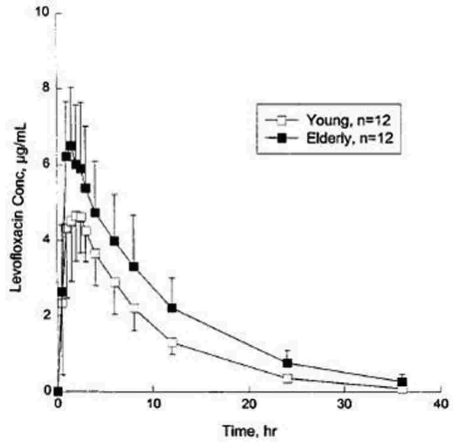

Figure 6 : Mean plasma concentration-time curves of LVFX in the age group after a single oral dose of LVFX (500 mg tablet) (38)

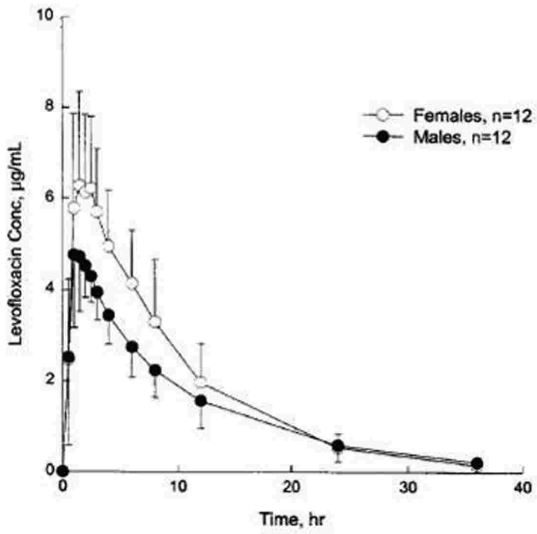

Figure 7 : Mean plasma concentration-time curves of LVFX in the gender group after a single oral dose of LVFX (500 mg tablet) (38)

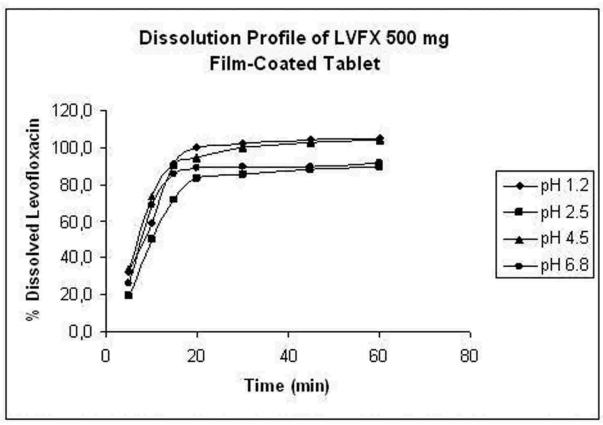

Figure 8 : Dissolution profile of LVFX 500 mg film-coated tablets at different pH values (10).

D-ofloxacin (34). LVFX is primarily excreted through the kidneys (35), with 64–102% of the dose being recovered as unchanged drug in the urine within the first 48 h following a single oral dose of 500 mg (22,36). Both glomerular filtration and tubular secretion of LVFX occur (4,27,37). The parent drug undergoes limited metabolism in the liver to demethyl-LVFX and LVFX-N-oxide, with less than 5% of an administered dose being excreted in the urine as these metabolites (4,27). These metabolites have little relevant pharmacological activity (34). In patients with renal impairment, dosage adjustment is required for LVFX21. The mean plasma elimination half-life is approximately 6-9 h (Table 2) after single and multiple doses of oral or intravenous LVFX 500 or 750 mg (22,27) . In healthy volunteers, mean total body clearance and renal clearance are approximately 8-12 and 6-8 L/h, respectively (22,27,36).

Pediatrics

To characterize the pharmacokinetics of LVFX in children, three single-dose, multicenter pharmacokinetic studies were conducted in 85 children in five age groups: 6 months-2 years, 2-5 years, 5-10 years, 10-12 years and 12-16 years. Each child received a single 7 mg/kg dose LVFX intravenously or orally. LVFX absorption (as indicated by C_{max} and t_{max}) and distribution in children are not age-dependent and are comparable to those in adults (10).

For comparison, pharmacokinetic data from adult male volunteers (aged 18-53 years) (22) were included that were derived from previously published methods (10) (Table 4). Pediatric patients cleared LVFX faster than adult patients, resulting in lower plasma exposures than in adults. LVFX elimination (reflected $t_{1/2}$ and clearance), however, is age-dependent (38).

Geriatrics and Gender

Chien et al. (38) evaluated the influence of age and gender on the pharmacokinetics of LVFX in healthy subjects. Twenty-four healthy male and female volunteer subjects participated in the study. Subjects were administered a single oral tablet consisting of 500 mg of anhydrous LVFX. Subjects were divided into four groups (6 young males, 6 young females, 6 elderly males, 6 elderly females). The mean plasma concentration-time curves of LVFX in the age group and in the gender group are shown in Figures 6 and 7, respectively. The mean pharmacokinetic parameters

determined from this study are summarized in Table 5. It was concluded that there were no clinically meaningful changes from baseline in any laboratory parameter, vital sign or physical examination. LVFX 500 mg tablet was found to be safe in geriatrics and both males and females (38).

Race

Flores-Murrietta (39) investigated the bioavailability of LVFX 500 mg tablets in 27 healthy Mexican male volunteers. There were no observed significant differences in pharmacokinetic parameters between Mexicans and other races.

Zhang et al. (40) evaluated the pharmacokinetics of infusion of multi-dose of LVFX instillation (200 mg) twice daily in healthy Chinese volunteers. IV infusion of LVFX instillation 200 mg within 60 min was given to 10 healthy male volunteers for 7 days (on day 1 and 7, once-daily; from days 2 – 6, twice-daily dosing). There was no observed accumulation of the drug after the repeated IV infusion with 200 mg LVFX instillation for 7 days. The pharmacokinetic parameters were not affected by the race of the subjects (34,39,40).

Renal Impairment

In patients with renal impairment (creatinine clearance (CL_R) <50 mL/min), clearance of LVFX is reduced and half-life prolonged, necessitating dosage adjustments to avoid accumulation (41,42). Neither hemodialysis nor continuous ambulatory peritoneal dialysis removes LVFX effectively (41,42); however, LVFX is removed by continuous venovenous hemofiltration in critically ill patients (43,44).

In one study, patients with reduced renal function (CL_R <80 mL/min) had higher C_{max}, AUC and t1/2 values than subjects with CL_R >80 mL/min. No increase in drug retention was observed and pharmacokinetics remained linear (20).

Hepatic Impairment

The effect of hepatic impairement on the pharmacokinetics of LVFX has not been established; however, it is not expected to be significant given the limited hepatic metabolism of the drug (4,8).

Drug Interactions

The absorption of LVFX is reduced by concurrent administration of some drugs (45-51). The drug interactions with LVFX are summarized in Table 6.

BIOPHARMACEUTICS CLASSIFICATION SYSTEM EVALUATION

The Biopharmaceutics Classification System (BCS) is a scientific outline for classifying drug substances based on their aqueous solubility and intestinal permeability(52). The Food and Drug Administration applied the principles of BCS to a regulatory bioavailability and bioequivalence guidance that recommends methods for classifying drug substances and products53. The Guidance explains that a waiver (biowaiver) for in vivo bioavailability and bioequivalence studies may be requested based on the approach of BCS.

In the current BCS Guidance, high solubility, high permeability, rapid and similar dissolution, wide therapeutic window, and previously used excipients are required for justifying a biowaiver request. The BCS Guidance provides methods and acceptance criteria for classifying a drug substance and product based on its solubility, permeability, and dissolution.

Amidon et al. (52) indicated that BCS Class 1 drugs have high solubility, high permeability and rapid dissolution characteristics. Evaluation of the BCS characterization (solubility, permeability and dissolution) for LVFX is as follows:

Solubility

Levofloxacin has a pH-dependent solubility (8). Solubility values of LVFX were between 32-91 mg/mL within the range of pH 1.2-6.8 at 37°C (54).

The parameter of dose number (D_0) is defined as the ratio of dose concentration to drug solubility (52). D_0 values were less than 1 for all pH values (54). Therefore, LVFX is a highly soluble drug.

Permeability

The permeability class boundary is based indirectly on the

extent of absorption of a drug substance in humans and directly on measurements of the rate of mass transfer across the human intestinal membrane. A drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be ≥90% of an administered dose based on a mass balance determination or in comparison with an intravenous reference dose (53). Acceptable methods for permeability classification are categorized as human (mass balance or absolute bioavailability studies), animal (in vivo or in situ intestinal perfusion), and in vitro (excised human or animal tissue, or epithelial cell monolayers).

LVFX is rapidly and essentially completely absorbed after oral administration, with an absolute bioavailability of ~99% at 500 and 750 mg. LVFX demonstrated concentration-dependent permeability (55).

Caco-2 cell monolayers are routinely used to evaluate the permeability properties of drugs for BCS classification (56-61). Volpe (62) used an in vitro cell culture model to categorize the permeability class of fluoroquinolones including LVFX with demonstrated method suitability according to the BCS Guidance. A drug substance (labetalol) was determined as a highly permeable internal standard (HP-IS) (P_{app} = 18.05 ± 1.90 x 106 cm/s) and a test drug classified as highly permeable when its permeability was equal to or greater than the HP-IS. Calculated P_{app} value of LVFX (P_{app} = 28.36 ± 1.93 x 106 cm/s) was greater than HP-IS. These results show that LVFX is classified as a highly permeable drug (62). Also, based on the human absolute bioavailability of LVFX determined in the study of Pickerill et al.(55), it was expected that LVFX would be classified as a highly permeable drug.

Dissolution

An immediate release (IR) drug product is considered rapidly dissolving when no less than 85% of the label amount of the drug substance dissolves within 30 min using the USP apparatus I at 100 rpm or USP apparatus II at 50 rpm in a volume of 900 mL or less in pH 1-7.5 (53).

Dissolution studies were conducted for LVFX 500 mg film-coated tablet formulation in four different buffer media (pH 1.2, pH 2.5, pH 4.5, and pH 6.8) using the USP apparatus II (54). The dissolution profiles are given in Figure 8. According to these dissolution results, more than 85% of LVFX was dissolved in 30 min, so LVFX is a rapidly dissolved drug.

In summary, it is concluded that LVFX is classified in BCS Class 1 because of its high solubility (54), high permeability (55,62) and rapid dissolution (54) characteristics.

Additionally, Wu et al. (63), designed a new system, Biopharmaceutics Drug Disposition Classification System (BDDCS) as an alternative to BCS. The BDDCS replaces the permeability criteria with the major route of elimination because of the belief that it is easier and less ambiguous to determine the assignment of BDDCS for marketed drugs based on the extent of metabolism rather than by using permeability. When initially proposed, "extensive metabolism" was defined as ≥50% metabolism of an oral dose in vivo in humans. LVFX is in Class 3 (high solubility/poor metabolism) according to BDDCS (63).

CONCLUSION

Levofloxacin is a broad-spectrum antibacterial agent with activity against a range of Gram-positive and Gram-negative bacteria and atypical organisms. It provides clinical and bacteriological efficacy in a range of infections, including those caused by both penicillin-susceptible and -resistant strains of S. pneumoniae. LVFX is a well-tolerated drug. It also has a pharmacokinetic profile that is compatible with once-daily administration and allows for sequential intravenous to oral therapy. The pharmacokinetics of LVFX are not significantly affected by age or sex in patients. It is rapidly and completely absorbed from the tablet formulations. LVFX shows high solubility, high permeability and rapid dissolution characteristics. Since absorption is almost complete and solubility is high, according to the BCS, LVFX is in Class 1. An IR solid oral dosage form, the active substance of which appears in BCS Class 1, is a potential biowaiver from in vivo bioequivalence studies. Consequently, in vivo bioequivalence studies are not required for IR oral dosage forms of LVFX.

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