Clin. Pharmacokinet. 1997 Feb; 32 (2): 101-119
0312-5963/97/0002-0101/$09.50/0

The Clinical Pharmacokinetics of Levofloxacin

Douglas N. Fish[1] and *Andrew T. Chow*[2]

1 Department of Pharmacy Practice, University of Colorado Health Sciences Center, Denver, Colorado, USA
2 Drug Metabolism Department, R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, USA

Contents

Summary

Levofloxacin is a fluoroquinolone antibiotic and is the optical *S*-(−) isomer of the racemic drug substance ofloxacin. It has a broad spectrum of *in vitro* activity against Gram-positive and Gram-negative bacteria, as well as certain other pathogens such as *Mycoplasma, Chlamydia, Legionella* and *Mycobacteria* spp. Levofloxacin is significantly more active against bacterial pathogens than *R*-(+)-ofloxacin. Levofloxacin hemihydrate, the commercially formulated product, is 97.6% levofloxacin by weight.

Levofloxacin pharmacokinetics are described by a linear 2-compartment open model with first-order elimination. Plasma concentrations in healthy volunteers reach a mean peak drug plasma concentration (C_{max}) of approximately 2.8 and 5.2 mg/L within 1 to 2 hours after oral administration of levofloxacin 250 and 500mg tablets, respectively. The bioavailability of oral levofloxacin approaches 100% and is little affected by the administration with food. Oral absorption is very rapid and complete, with little difference in the serum concentration-time profiles following 500mg oral or intravenous (infused over 60 minutes) doses.

Single oral doses of levofloxacin 50 to 1000mg produce a mean C_{max} and area under the concentration-time curve (AUC) ranging from approximately 0.6 to 9.4 mg/L and 4.7 to 108 mg • h/L, respectively, both increasing linearly in a dose-proportional fashion. The pharmacokinetics of levofloxacin are similar during multiple-dose regimens to those following single doses. Levofloxacin is widely distributed throughout the body, with a mean volume of distribution of 1.1 L/kg, and penetrates well into most body tissues and fluids. Drug concentrations in tissues and fluids are generally greater than those observed in plasma, but penetration into the cerebrospinal fluid is relatively poor (concentrations approximately 16% of simultaneous plasma values). Levofloxacin is approximately 24 to 38% bound to serum plasma proteins (primarily albumin); serum protein binding is independent of serum drug concentrations.

The plasma elimination half-life ($t_{1/2\beta}$) ranges from 6 to 8 hours in individuals with normal renal function. Approximately 80% of levofloxacin is eliminated as unchanged drug in the urine through glomerular filtration and tubular secretion; minimal metabolism occurs with the formation of no metabolites possessing relevant pharmacological activity. Renal clearance and total body clearance are highly correlated with creatinine clearance (CL_{CR}), and dosage adjustments are required in patients with significant renal dysfunction. Levofloxacin pharmacokinetics are not appreciably affected by age, gender or race when differences in renal function, and body mass and composition are taken into account.

Important drug interactions exist with aluminium- and magnesium-containing antacids and ferrous sulfate, as with other fluoroquinolones, resulting in significantly decreased levofloxacin absorption when administered concurrently. These agents should be administered at least 2 hours before or after levofloxacin administration. Cimetidine and probenecid decrease levofloxacin renal clearance and increase $t_{1/2\beta}$; the magnitudes of these interactions are not clinically significant. Levofloxacin appears to have only minor potential for significantly altering the pharmacokinetics of theophylline, warfarin, zidovudine, ranitidine, digoxin or cyclosporin; however, patients receiving these drugs concurrently should be monitored closely for signs of enhanced pharmacological effect or toxicity. Levofloxacin pharmacokinetics are not significantly altered by sucralfate when administration of these drugs is separated by at least 2 hours.

Levofloxacin (DR-3355, RWJ-25213, *l*-ofloxacin) is a fluoroquinolone antibacterial agent. It is the optical *S*-(−) isomer of ofloxacin. Levofloxacin possesses a wide spectrum of bactericidal activity *in vitro* against both Gram-positive and Gram-negative pathogens, as well as *Mycoplasma, Legionella, Chlamydia* and *Mycobacteria* spp. and mycobacteral species.[1] It is currently licensed for clinical use in Japan. Levofloxacin was approved by the US Food and Drug Administration for market-

ing in December 1996, and was submitted to the regulatory agencies of Canada and several South American countries in mid 1996.

Additional phase III clinical studies were also being conducted in the US and Europe at the time this article was prepared. Most of the available published data concerning levofloxacin were obtained during preclinical and clinical studies conducted in Japan and the US. Other data were obtained from a number of studies which are not yet published. This review focuses on the pharmacokinetic profile of levofloxacin.

1. Chemistry and Pharmacology

Levofloxacin is a pyridone carboxylic acid derivative structurally related to nalidixic acid and newer fluorinated quinolone antibacterial agents (fig. 1). Ofloxacin, the parent compound, is a racemic mixture of *S*-(−) and *R*-(+) isomers resulting from the presence of a methyl group at the 3-carbon position of the oxazine ring. Levofloxacin is distinguished from ofloxacin in that it is the pure *S*-(−) isomer of ofloxacin. The molecular weight of levofloxacin hemihydrate, the commercially formulated product, is 370.38D.

Levofloxacin is freely soluble in glacial acetic acid and chloroform, and sparingly soluble in water. It has been investigated as both an oral tablet and an intravenous preparation; pharmacokinetic studies have been conducted on both formulations.[2]

S-(−)-Ofloxacin is reportedly 8 to 128 times more active against Gram-positive and Gram-negative bacteria than *R*-(+)-ofloxacin.[2,3] Therefore it is responsible for the majority of the antibacterial activity of ofloxacin. Due to its wide distribution throughout the body and extensive intracellular penetration, levofloxacin is active against both intracellular and extracellular pathogens. *In vitro* activity is based on determinations of the mean minimum inhibitory concentration (MIC) necessary to inhibit growth in 90% of tested strains (MIC_{90}). Representative *in vitro* activities of levofloxacin against various organisms are illustrated in table I. Compared with other fluoroquinolones, levofloxacin is similar or slightly more potent *in vitro* against Gram-positive organisms than either ofloxacin or ciprofloxacin, with 2- to 4-fold lower MIC_{90} values.[1,2,5] Although comparative Gram-negative activity is variable, levofloxacin generally exhibits MIC_{90} values which are 50% lower than those of ofloxacin and 50% higher than those of ciprofloxacin against Enterobacteriaceae and other Gram-negative pathogens. Against *Pseudomonas aeruginosa*, ciprofloxacin generally exhibits MIC_{90} values which are approximately 50% lower those that of either levofloxacin or ofloxacin.[1,2]

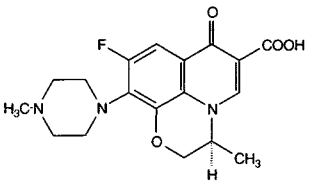

Fig. 1. Structural formula of levofloxacin.

From the *in vitro* activity of levofloxacin against various organisms, the following MIC break-points have been approved and established by the US National Committee on Clinical Laboratory Standards (NCCLS): susceptible = 2 mg/L (zone of inhibition 17mm); intermediate = 4 mg/L (zone of inhibition 14 to 16mm); and resistant = 8 mg/L (zone of inhibition 13mm).[2]

Levofloxacin, like other fluoroquinolones, exerts its antibacterial effects through inhibition of deoxyribonucleic acid (DNA) gyrase, a type II topoisomerase.[4,6-8] DNA topoisomerases are a class of enzymes that control the supercoiling of DNA. The DNA gyrase enzyme consists of 2 A subunits and 2 B subunits. The A subunits carry out 2 activities: introduction of single-strand breaks on the bacterial chromosome, then resealing of the chromosome strands after supercoiling. The 2 B subunits are ATP hydrolysis–dependent and introduce negative supercoils into the DNA strand after the initial strand incisions of the A subunits. The principle bactericidal actions of the fluoroquinolones result from inhibition of the A subunits of DNA gyrase following supercoiling, causing inhibition of bac-

Table I. Representative *in vitro* antibacterial activities of levofloxacin compared with ofloxacin and ciprofloxacin against selected organisms. All values obtained from studies using clinical isolates, broth or agar dilution techniques, and inoculum sizes of 10^4 to 10^6 colony-forming units/ml (after Davis & Bryson,[1] and Imamura et al.[4])

Organism	Mean MIC_{90} (mg/L)		
	levofloxacin (range)	ofloxacin	ciprofloxacin
Gram-positive aerobic bacteria			
Streptococcus pneumoniae	1.56 (0.78-12.5)	3.13	1.56
S. pyogenes	1.56 (0.39-3.13)	3.13	1.56
Staphylococcus aureus (MSSA)	0.39 (0.10-0.78)	0.78	0.39
S. aureus (MRSA)	3.13 (0.2-12.5)	6.25	6.25
S. epidermidis	0.42 (0.42-0.68)	0.83	0.68
Enterococcus faecalis	1.56 (0.78-6.25)	1.56	3.13
E. faecium	3.13 (3.13-6.25)	6.25	5.29
Gram-negative aerobic bacteria			
Escherichia coli	0.20 (≤0.05-0.78)	0.39	0.10
Proteus mirabilis	0.10 (≤0.05-0.20)	0.20	≤0.05
P. vulgaris	0.20 (≤0.05-4.0)	0.39	0.10
Klebsiella pneumoniae	0.10 (≤0.05-3.13)	0.20	≤0.05
Enterobacter cloacae	0.10 (≤0.05-0.78)	0.20	≤0.05
Morganella morganii	6.25 (≤0.05-6.25)	12.50	6.25
Citrobacter freundii	1.56 (≤0.05-50)	3.13	0.78
Acinetobacter anitratus	0.20 (≤0.05-1.56)	0.39	0.20
Salmonella spp.	0.09	0.17	0.03
Shigella spp.	0.05	0.21	0.025
Campylobacter jejuni	0.58	0.78	0.78
Providencia stuartii	0.22	0.68	0.17
P. rettgeri	2.26 (2.26-4.99)	4.99	3.77
Pseudomonas aeruginosa	6.25 (0.10-50)	12.5	1.56
Haemophilus influenzae	≤0.025 (≤0.05-0.05)	0.05	≤0.025
Moraxella catarrhalis	0.10 (0.05-0.39)	0.20	0.05
Neisseria gonorrhoeae	0.03 (0.02-0.11)	0.07	0.02
Anaerobic bacteria			
Bacteroides fragilis	3.52 (3.52-6.53)	6.53	14.99
Clostridium perfringens	0.75	1.20	2.48
C. difficile	5.00	12.5	14.39
Peptostreptococcus spp.	4.62 (0.39-8)	9.36	5.56

Abbreviations: MIC_{90} = minimum concentration at which 90% of tested strains are inhibited; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

terial DNA replication and transcription. Mechanisms other than inhibition of DNA gyrase may also be involved in the antibacterial actions of the fluoroquinolones.[9]

2. Analytical Methods

Both high-performance liquid chromatography (HPLC) and microbiological assay systems have been described for determination of levofloxacin concentrations in plasma, urine, other biological fluids and faeces. A chiral HPLC method involves liquid phase extraction of the drug from the sample matrix (plasma or urine) and a 2-step chemical reaction forming L-leucinamide salts which enable resolution of ofloxacin isomers.[10-12] This is followed by reverse phase chromatography with fluorescence detection at 298nm (excitation) and 458nm (emission). The analytical range for detection of levofloxacin using this HPLC method is

approximately 0.03 to 10 mg/L in plasma and 0.3 to 1132 mg/L in urine. Both ranges are linear and specific for detection of levofloxacin.

An HPLC method utilising ultraviolet (UV) detection has also been developed and extensively used.[13] The method involves a single-step liquid-liquid extraction of levofloxacin from the sample matrix, followed by reverse phase chromatography with UV detection at a wavelength of 330nm. Stereospecificity is achieved by the incorporation of chiral reagents directly into the assay mobile phase. The analytical range for detection of levofloxacin using this HPLC method is approximately 0.08 to 5.18 mg/L in plasma and 23 to 1464 mg/L in urine. Both ranges are linear and specific for detection of levofloxacin. Microbiological assays using disc diffusion techniques have also been utilised for quantification of levofloxacin concentrations in plasma, urine or faeces.[12,14]

3. Pharmacokinetic Profile

Published studies which evaluated the pharmacokinetic profile of oral levofloxacin have been conducted primarily in Japan and the US. These studies included healthy volunteers, volunteers with impaired renal function and patients with a variety of bacterial infections. The pharmacokinetic profile of levofloxacin has been demonstrated to be very similar to that of the racemic mixture ofloxacin.[4,6]

The enantioselective disposition of levofloxacin was studied in 5 healthy volunteers following a single 200mg dose of levofloxacin.[2] Concentrations of levofloxacin and its enantiomer, *d*-ofloxacin, in serum and urine were measured using a stereospecific HPLC method. Results showed that levofloxacin was stereochemically stable in body fluids and did not metabolically invert to *d*-ofloxacin.

3.1 Absorption and Distribution

The oral bioavailability of levofloxacin is similar to that of ofloxacin and approaches 100%.[6,15] The absolute bioavailability of an oral dose of levofloxacin 500mg is approximately 99%.[2] Levofloxacin is rapidly absorbed from the gastrointestinal tract with the time to maximum plasma concentrations (t_{max}) ranging from 0.8 to 2.4 hours after the administration of levofloxacin 50 to 1000mg with or without food (table II). Because oral absorption of levofloxacin is rapid and essentially complete, plasma concentration versus time profiles following the administration of levofloxacin 500mg either orally or intravenously (infused over 60 minutes) are very similar (fig. 2).[2] Therefore, the oral and intravenous routes of levofloxacin administration can be considered interchangeable.

Administration of levofloxacin with food apparently has little effect on drug absorption. The effect of food on levofloxacin absorption was examined in a single oral 500mg dose crossover study in 24 healthy volunteers (12 males and 12 females). Administration of the drug with a high fat meal slightly prolonged the t_{max} by approximately 1 hour (mean t_{max} increased from 1.5 to 2.4 hours in fasting and nonfasting individuals, respectively) and slightly decreased the C_{max} by approximately 14% (mean C_{max} decreased from 5.93 to 5.09 mg/L in fasting and nonfasting individuals, respectively). The extent of levofloxacin absorbed was not affected.[21] Similar results were observed in 5 healthy individuals following a 100mg dose of levofloxacin when administered orally with or without food.[12] The changes in levofloxacin absorption are not likely to be clinically significant. Therefore, levofloxacin can be administered orally without regard to food.

The disposition of levofloxacin is best described by a linear, 2-compartment open model characterised by first-order elimination.[14,17,19] Levofloxacin pharmacokinetic parameters derived from single-dose and multiple-dose studies in healthy volunteers are presented in table II. Following the administration of single oral doses of levofloxacin 50 to 1000mg to healthy volunteers, C_{max} ranged from 0.6 to 9.4 mg/L and increased in a linear, dose-proportional fashion (fig. 3). The area under the plasma concentration-time curve (AUC) of levofloxacin ranged from 4.7 to 108 mg • h/L has also been demonstrated to increase in a linear, dose-proportional manner (fig. 4).[2]

Table II. Mean levofloxacin pharmacokinetic parameters following administration to healthy volunteers

No. of volunteers	Dose (mg)	C_{max} (mg/L)	t_{max} (h)	V_β (L/kg)	$t_{½\beta}$ (h)	AUC (mg/L • h)[a]	CL/F (L/h)	f_e (%)	Reference
Single oral doses									
5[b]	100	1.35	1.80	1.26	6.93	11.66	8.51		11
5[b]	50	0.57	2.41	1.09	4.34	4.70	10.64	86	12
5[b]	100	1.22	0.92	1.19	3.96	7.46	13.40	80	12
5[c]	100	1.36	0.82	1.10	5.12	10.42	9.60	82	12
5[b]	200	2.04	1.48	1.25	5.97	19.88	10.06	80	12
8[c]	100	1.13	1.04		7.12	10.46	9.56		16
8[b]	100	0.86	1.88		6.51	8.74	11.44		16
10[c,d]	350	4.79	1.00	1.31	5.66	29.94	12.3	79	17
10	500	5.20	1.30	1.28	6.50	47.70	10.5		18
24	500	5.09	2.00	0.99	6.45	45.60	11.1	69	18
10[c]	750	7.13	1.9		7.7	82	9.42	75	19
10[c]	1000	8.85	1.7		7.9	111	9.36	73	19
Multiple oral doses									
10	500 qd	5.70	1.10	1.37	6.80	47.50	10.50	67	18
20	500 bd	7.80	1.30	1.34	8.40	59.00	8.60	72	18
10[b]	750 qd	8.60	1.4	1.29	8.8	91	8.58	79	19
10[b]	1000 qd	11.8	1.7	1.35	8.9	118	8.76	71	19
Single intravenous doses									
10	500	6.30	1.00	1.19	6.60	55.30	9.40	61	20
Multiple intravenous doses									
10	500 qd[e]	6.40	1.00	1.22	6.80	64.6	9.50	62	20
10	500 bd[e]	7.90	1.00	1.47	7.60	49.6	10.20	68	20

a AUC = 0 – ∞ for single doses, 0 to 24 hours for multiple once-daily doses, and 0 to 12 hours for multiple twice-daily doses.

b Nonfasting volunteers.

c Fasting volunteers.

d Fasting patients with asymptomatic HIV infection. Pharmacokinetic parameters were not significantly different from healthy volunteers in other studies.

e Multiple-dose regimens were administered for 7 days.

Abbreviations: AUC = area under the plasma concentration-time curve; bd = twice daily; C_{max} = peak plasma drug concentration; CL/F = total drug clearance; f_e = fraction of drug excreted unchanged in the urine; qd = once daily; $t_{½\beta}$ = terminal elimination half-life in plasma; t_{max} = time to C_{max}; V_β = volume of distribution during the terminal elimination phase.

The pharmacokinetics of levofloxacin have also been evaluated following multiple-dose intravenous administration (table II).[20] Levofloxacin was administered to 40 healthy male volunteers as single intravenous and multiple doses of 500mg once or twice daily for 7 days. At steady-state, mean C_{max} and trough plasma drug concentration (C_{min}) values following once-daily administration were 6.4 mg/L and 0.58 mg/L, respectively. These and other pharmacokinetic parameters were not significantly different from those observed following single doses. Twice-daily administration resulted in mean C_{max} values of 7.9 mg/L at steady-state. Although modest accumulation of levofloxacin was observed as a result of the administration of multiple doses at shortened intervals, other pharmacokinetic parameters were not significantly different from those observed after single-dose administration.

The pharmacokinetics of levofloxacin remain linear and predictable following various multiple once-daily, twice-daily, or 3 times daily administration regimens taken orally or intravenously. The degrees of accumulation at steady-state are all in good agreement with the theoretical values predicted from single dose data.[17,19] Levofloxacin accumu-

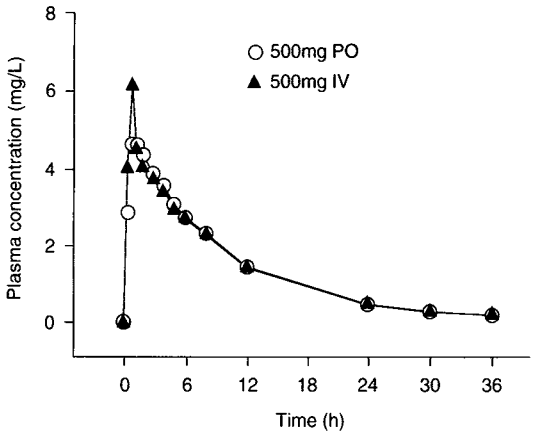

Fig. 2. Mean plasma levofloxacin concentrations after a single dose of levofloxacin 500mg administered orally (PO) or intravenously (1-hour infusion) to 23 healthy volunteers.[2]

lates minimally following a once-daily administration regimen. Steady-state is reached within 48 hours of levofloxacin 500mg once-daily orally or as an intravenous dose; C_{max} values attained are approximately 5.7 and 6.4 mg/L, respectively.[18,20] The plasma concentrations are generally well in excess of the MIC values for Gram-positive and Gram-negative bacteria within the spectrum of activity of levofloxacin.

In vitro, over a clinically relevant range (1 to 10 mg/L) of levofloxacin concentrations, serum protein binding is approximately 24 to 38% across all species studied (rats, dogs, monkeys and humans) as determined by the equilibrium dialysis method.[2] The results indicate that levofloxacin is only moderately bound by serum proteins (mainly bound to serum albumin in humans) and that this binding is not concentration-dependent.

The mean volume of distribution (Vd) of levofloxacin ranged from 1.09 to 1.26 L/kg (89 to 112L) after single and multiple doses of levofloxacin 50 to 500mg (table II). This large Vd is consistent with the extensive tissue distribution of the drug.

Levofloxacin concentrations in many tissues and body fluids after oral administration are similar to, or substantially higher than, those observed in plasma (table III). The extensive penetration of levofloxacin into tissues and fluids results in drug concentrations which are often many times higher than the MIC of bacterial pathogens commonly found at these sites (table I). High concentration : MIC ratios are achieved particularly against common Gram-negative organisms, as well as for many Gram-positive ones. High drug concentrations (35 to 100 mg/L) were also found in the faeces of healthy volunteers after oral administration of levofloxacin 100 to 200mg 3 times daily for 3 to 7 days.[37,38]

As ofloxacin efficiently penetrates into breast milk and crosses the placenta (100% of plasma concentrations),[39] levofloxacin is anticipated to have similar characteristics due to its other pharmacokinetic similarities to ofloxacin. Two important exceptions to the generally excellent fluid penetration of levofloxacin are cerebrospinal fluid and aqueous humor. The concentrations of drug in these fluids reach only 16 to 20% of simultaneous plasma concentrations; this may indicate a limited role for levofloxacin (similar to other fluoroquinolones) in the treatment of central nervous system or intraocular infections.

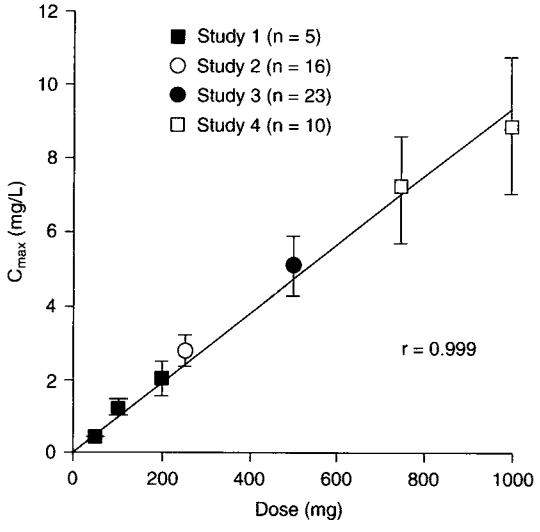

Fig. 3. Relationship between dose and peak plasma concentrations (mean ± SD) of levofloxacin following single oral doses to healthy individuals. Data were compiled from 4 separate studies (total n = 54) examining levofloxacin pharmacokinetics at varying doses ranging from 50 to 1000mg.[2]

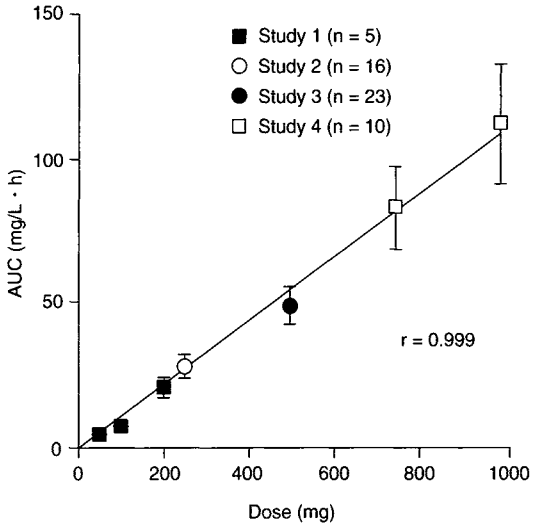

Fig. 4. Relationship between dose and area under the plasma concentration-time curve (AUC) of levofloxacin following single oral doses to healthy individuals. Data were compiled from 4 separate studies (total n = 54) examining levofloxacin pharmacokinetics at varying doses ranging from 50 to 1000mg.[2]

Levofloxacin, like other fluoroquinolones, actively penetrates into phagocytic cells *in vitro*, which has significant implications for activity against intracellular pathogens.[40-42] Significant accumulation of levofloxacin in phagocytic cells as well as other tissues contributes to the large Vd observed. The mean intracellular/extracellular concentration ratio of levofloxacin in neutrophils ranged from 8.8 to 9.8 mg/L following exposure to drug concentrations of 5 and 50 mg/L.[43,44] Other fluoroquinolones achieve similarly high intracellular/extracellular concentrations in macrophages.[45]

This uptake of fluoroquinolones, as well as macrolide antibiotics, into phagocytic cells has been postulated to enhance drug concentrations at the site of infection through phagocytic delivery mechanisms involving chemotaxis and phagocyte migration. Macrolide antibiotics have been observed to accumulate in infected or inflamed tissues and fluids to significantly higher concentrations than those observed in normal tissues.[46,47] The accumulation of levofloxacin and other fluoroquinolones within phagocytic cells may enhance not only their activity against intracellular pathogens, but also their activity against extracellular pathogens, by maintaining high, sustained concentrations of drug within tissues and fluids at the site of infection. The clinical relevance of the intracellular accumulation of levofloxacin in human neutrophils and macrophages has yet to be fully elucidated.

3.2 Metabolism and Excretion

Three metabolites of levofloxacin have been identified at low concentrations in rats, dogs, monkeys and/or humans.[2] These metabolites are levofloxacin-β-D-glucuronide (M1), desmethyllevofloxacin (M2), and levofloxacin-*N*-oxide (M3). Only the M2 and M3 metabolites have been identified in humans. Levofloxacin undergoes limited metabolism in humans and is mainly excreted unchanged in the urine (fig. 5). Following the administration of a single oral dose of levofloxacin, less than 5% of levofloxacin was excreted in the urine as metabolites in 24 hours (M2 and M3 accounted for approximately 1.75 and 1.63% of the dose, respectively), whereas approximately 79.6% of the dose was recovered in urine as unchanged drug in the following 24 hours.[2] The above metabolic profiles of levofloxacin in humans are similar to those reported for ofloxacin.[48,49] As formation of the metabolites is negligible, they have little relevant pharmacological activity.

At the usual 250 and 500mg therapeutic doses of levofloxacin, the mean plasma terminal elimination half-life ($t_{½β}$) of levofloxacin generally ranges from 6 to 8 hours.[2] This is consistent regardless of single or multiple doses, or the route of administration. The mean apparent total body clearance (CL/F) and renal clearance (CL_R) range from approximately 8.64 to 13.56 L/h and 5.76 to 8.52 L/h, respectively,[2] indicating a small degree of nonrenal clearance. The CL_R of levofloxacin after a single 200mg dose to 5 healthy volunteers was approximately 60% greater than creatinine clearance (mean 7.14 L/h/1.73m^2 versus 4.46 L/h/1.73m^2, respectively), indicating that both glomerular filtration and tubular secretion are important in the excretion of the drug.[11]

Table III. Mean levofloxacin concentrations in various tissues and body fluids following administration of single oral doses to patients or healthy volunteers

Body fluid/tissue	Dose (mg)	No. of study individuals or samples	Postdose sampling time (h)	Mean C_f (mg/L) or C_t (μg/g)	Mean C_p (mg/L)	Mean $C_f : C_p$ or $C_t : C_p$	Reference
Cerebrospinal fluid	200	10	3	0.36	2.31	0.16	22
Aqueous humour	100	20	2-9	0.22	1.10	0.20	23
	200	22	2-9	0.68	2.62	0.26	
Lacrimal fluid	100	13	2	0.61	1.05	0.58	24
Otic tissue	200	1	2	1.01	0.37	2.73	25
Maxillary sinus	100	41	1-8	0.67	0.45	1.15	26
Ethmoid sinus	100	2	1	0.67	0.84	0.63	25
Parotid gland	100	8	2-5	0.33	0.25	1.32	25
Palatine tonsil	100	26	1-6	1.25	0.62	2.02	25
	200	48	1-9	3.75	1.80	2.08	
Submandibular gland	100	5	2-8	1.03	0.64	1.61	25
Saliva	100	5	2	0.72	0.98	0.73	12
Sputum	100	2	4	1.27	1.10	1.15	26
	200	2	4	4.36	2.74	1.59	
Lung	500	5	2-3	7.74	4.12	2.02	2
	500	3	4-6	11.28	2.93	5.02	
	500	5	10-17	9.16	2.06	5.13	
	500	3	21-25	2.43	0.72	4.13	
Bronchial lavage fluid	200	7	1-3	0.12	2.52	0.06	27
Bronchoalveolar lavage fluid	200	8	1-3	0.209	2.52	0.10	27
Gall bladder	100	6	2.2-2.9	0.94	0.73	1.29	28
	100	4	2-6	2.47	1.53	1.61	29,30
Bile	100	6	2.2-2.9	6.58	0.73	9.01	28
	100	4	2-6	1.96	1.53	1.28	29,30
Skin	200	39	0.8-4.0	1.85	1.73	1.14	31
	100[a]	1	3	2.06	1.19	1.73	31
Blister fluid	500[b]	6	0.5-24	4.7	5.0	0.94	14
	500[c]	6	0.5-24	2.3	2.2	1.04	
Urine	200	5	2-4	286	1.01	283	11
	250	16	0-12	108			2
	250	16	12-24	63			
	500	10	0-12	343			2
	500	10	12-24	128			
	500[d]	10	0-12	309			2
	500[d]	10	12-24	131			
Epididymis	200	4	2	3.40	2.85	1.22	32,33
Testis	200	4	2	4.73	2.85	1.63	32,33
Semen	100[e]	5	7 days	1.19	1.09	1.12	32,33
	100[e]	5	13 days	1.32	1.04	1.26	32,33
Prostate gland	100	23	1-6	1.15	0.90	1.28	34
Female genital tissues	100	3	2.3-4.2	1.38		>1.0	35
	200	5	2.3-4.2	2.82		>1.0	
	200	42	2.9-3.2	3.01	2.33	1.29	36

a Samples obtained after final dose of multiple-dose regimen: 100mg 3 times daily for 7 days.

b Samples obtained after final dose of multiple-dose regimen: 500mg twice daily for 5 doses.

c Samples obtained after final dose of multiple-dose regimen: 500mg once daily for 3 doses.

d Dose administered intravenously.

e Samples obtained after final dose of multiple-dose regimen: 100mg 3 times daily for either 7 or 13 days.

Abbreviations: C_f = concentration of drug in fluids; C_p = concentration of drug in plasma; C_t = concentration of drug in tissue.

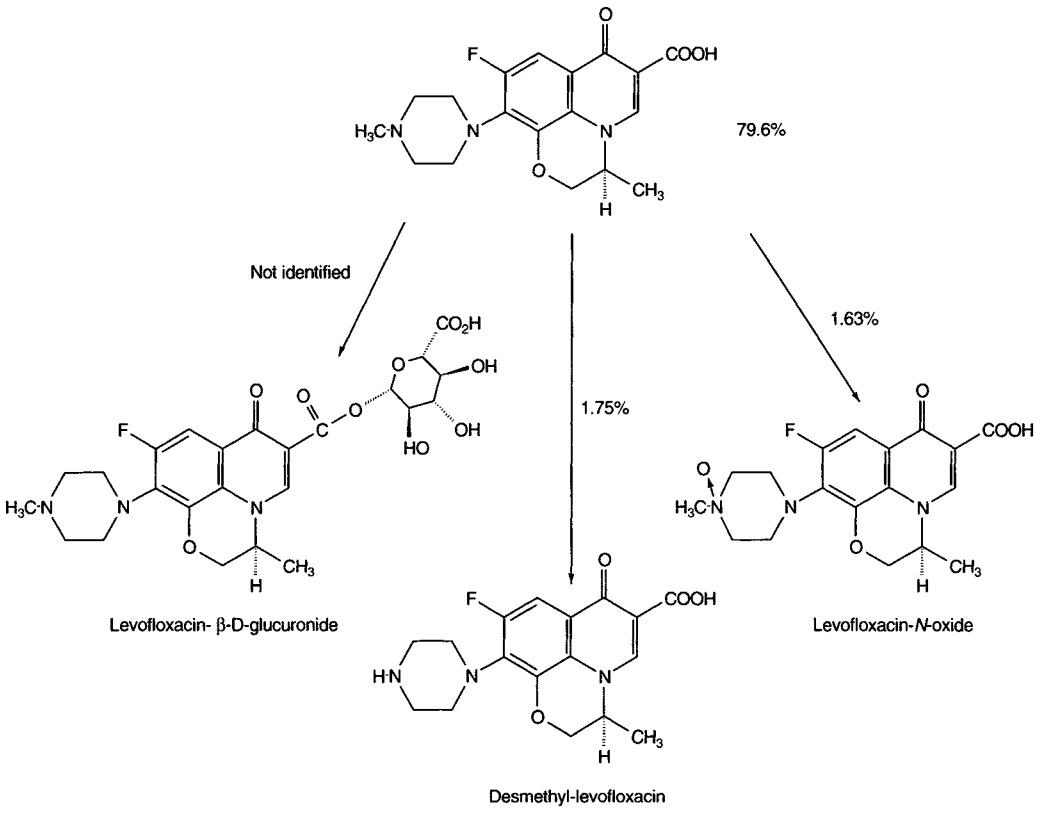

Fig. 5. Metabolism and excretion of levofloxacin after administration of a single 200mg oral dose to humans. Numbers indicate the approximate percentage of the total levofloxacin dose detected in the urine (24-hour urinary excretion) as levofloxacin and its principal metabolites, levofloxacin-β-D-glucuronide (M1), desmethyl-levofloxacin (M2) and levofloxacin-*N*-oxide (M3).[2,48]

Studies have also demonstrated significant alterations in CL_R of levofloxacin after concomitant administration of either cimetidine or probenecid, further illustrating the importance of tubular secretory mechanisms in renal excretion of the drug.[50] Levofloxacin is excreted largely unchanged in the urine. Following a single or once-daily 500mg oral or intravenous dose of levofloxacin to healthy volunteers, mean peak concentrations of levofloxacin ranging from 521 to 771 mg/L were measured in the urine.[2] Mean levofloxacin concentrations in urine of 108 and 63 mg/L were measured in healthy individuals after an oral dose of levofloxacin 250mg over the 0 to 12 and 12 to 24 hour collection intervals, respectively.[2] These urinary concentrations of levofloxacin are many times greater than MIC_{90} values for usual pathogens. Urine from individuals receiving oral levofloxacin 500mg twice daily was examined microscopically for the presence of levofloxacin crystals; no crystals were detected in any samples at urinary levofloxacin concentrations of 60 to 1100 mg/L.[2]

4. Pharmacokinetics in Special Populations

4.1 Effects of Age

The pharmacokinetics of levofloxacin in children have not been studied. The influence of advancing age on the pharmacokinetics of levoflox-

acin in adults was examined in a single oral 500mg dose study with 24 healthy individuals (12 individuals 65 years of age or greater, and 12 less than 65 years of age).[51] Levofloxacin mean $t_{1/2\beta}$ was increased by approximately 1.6 hours and the apparent Vd was decreased by 18% in elderly individuals. This change in the Vd was consistent with a decline in lean body mass with advancing age. Differences in C_{max}, AUC, CL/F, and CL_R became statistically insignificant when the individuals' CL_{CR} were included in a multivariate analysis. This is further confirmed by a covariate analysis of pooled data from 72 individuals (12 individuals 65 years of age or greater, 60 individuals <65 years of age) in 4 different pharmacokinetic studies.[20,51-53] The differences in levofloxacin pharmacokinetics in elderly individuals are limited and are primarily related to age-related changes in renal function. Levofloxacin dosage adjustment based solely on age is not necessary and should be individualised on the basis of the CL_{CR}.

4.2 Effects of Gender

Levofloxacin pharmacokinetics are not significantly changed in men compared with women when differences in renal function are taken into account.[54] Although the apparent Vd is approximately 15% lower in women, this difference is consistent with the lower total bodyweight and higher percentage of bodyweight as fat in the former. Covariate analysis of pooled data from 72 individuals (36 men and 36 women) also demonstrated that slight apparent differences in other pharmacokinetic parameters (C_{max}, CL/F and $t_{1/2\beta}$) were insignificant when the CL_{CR} of the individuals was incorporated in the statistical analysis. Dosage adjustment of levofloxacin on the basis of gender alone is not necessary.[54]

4.3 Effects of Race

The effects of race on levofloxacin pharmacokinetics were evaluated through covariate statistical analysis of data from 72 individuals (48 White, 24 non-White) pooled from 4 clinical studies.[52-55] No apparent differences in levofloxacin pharmacokinetic parameters were found and no dosage adjustment based only on race is required.[2]

4.4 Effects of Renal Dysfunction

Levofloxacin pharmacokinetic alterations in the presence of significant renal impairment were studied in 25 individuals with varying degrees of renal dysfunction.[51] These individuals received a single oral dose of levofloxacin 500mg and were divided into 5 groups according to varying degrees of renal impairment and CL_{CR}: Group I, CL_{CR} 3 to 4.8 L/h (50 to 80 ml/min) [n = 3]; Group II, CL_{CR} 1.2 to 2.94 L/h (20 to 49 ml/min) [n = 8]; Group III, CL_{CR} <1.2 L/h (<20 ml/min) [n = 6]; Group IV, haemodialysis (n = 4); and Group V, continuous ambulatory peritoneal dialysis (CAPD) [n = 4]. Individuals with increasing renal impairment demonstrated decreased CL_R and increased AUC and $t_{1/2}$ (9.09, 26.57, 34.83, 76.05 and 50.68 hours in Groups I to V, respectively). There were no significant differences between groups in C_{max} or t_{max}. Neither haemodialysis nor CAPD were found to be effective in the removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following either of these procedures.

Similar results were obtained in a study comparing 23 patients with varying degrees of renal impairment [CL_{CR} ranging from 4.2 to <1.2 L/h (70 to <20 ml/min)] with 5 healthy volunteers with normal renal function.[56] Both groups of patients received single oral doses of levofloxacin 100mg. Compared with the healthy volunteers, levofloxacin CL_R decreased and C_{max}, AUC and $t_{1/2\beta}$ increased in patients with renal impairment. A significant correlation was observed between $t_{1/2\beta}$ and CL_{CR}.

Another study examined the pharmacokinetics of levofloxacin in 11 elderly patients (mean age 71.5 years) with varying degrees of renal function.[57] Patients received a single oral dose of levofloxacin 100mg and were divided into 3 groups according to CL_{CR}: Group I, 4.2 L/h (70 ml/min; n = 1); Group II, 2.4 to 4.2 L/h (40 to 70 ml/min; n = 4); and Group III <2.4 L/h (<40

ml/min: n = 6). Levofloxacin C_{max} was similar among the 3 groups, but mean $t_{½\beta}$ (4.54, 4.83 and 9.86 hours in Groups I, II and III, respectively) and 72-hour urinary excretion (91, 85 and 60% of the dose in Groups I, II and III, respectively) were altered in relation to the degree of renal dysfunction.

A linear relationship between the CL/F and the CL_R was demonstrated across nearly the total range of renal function by pooling the data obtained from a study conducted with renally impaired patients[56] and an age- and gender-effect study conducted with healthy individuals.[51] The combined data set consisted of 41 individuals (none on dialysis treatment) who received a single dose of levofloxacin 500mg. 23 individuals were females and 18 were males, ranging from 22 to 80 years of age, 47 to 113kg in bodyweight, 0.6 to 7.02 L/h (10 to 117 ml/min) in CL_{CR}, and with CL/F ranging from 1.26 to 13.8 L/h (21 to 230 ml/min). As shown in figure 6, a significant relationship between CL/F and CL_{CR} was determined (correlation coefficient, r = 0.92), confirming good predictability of levofloxacin disposition kinetics based on the renal function status of the individuals as estimated by CL_{CR}. Dosage adjustment of levofloxacin administration is necessary in patients with impairment of renal function to avoid significant accumulation.

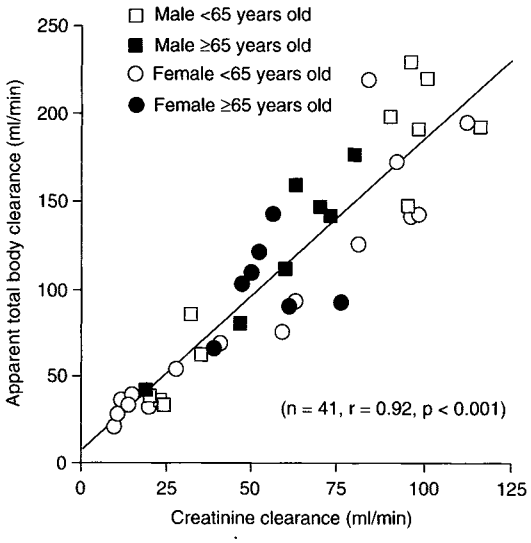

Fig. 6. Relationship between creatinine clearance (CL_{CR}) and apparent total body clearance of levofloxacin following single 500mg oral doses to 41 patients with varying degrees of renal function. Patients are further divided by age and gender. Degree of renal function was generally grouped as follows: CL_{CR} >4.8 L/h (>80 ml/min) [n = 12]; CL_{CR} = 3 to 4.8 L/h (50 to 80 ml/min) [n = 12]; CL_{CR} = 1.2 to 2.94 L/h (20 to 49 ml/min) [n = 11]; and CL_{CR} <1.2 L/h (<20 ml/min) [n = 6].[51,56]

4.5 Effects of Hepatic Dysfunction

The pharmacokinetic disposition of levofloxacin in patients with impaired hepatic function has not been studied. Because the total systemic clearance of levofloxacin has been shown to be highly correlated with CL_{CR} and only limited metabolism occurs, levofloxacin pharmacokinetics are not expected to be significantly affected by hepatic dysfunction.

4.6 Effects of Human Immunodeficiency Virus (HIV) Infection

Levofloxacin has potent *in vitro* activity against many pathogens common in human immunodeficiency virus (HIV)-infected patients. These patients are also known to have gastrointestinal infections or alterations in gastrointestinal function which may affect drug absorption. The pharmacokinetics of levofloxacin after single and multiple 350mg doses 3 times daily were therefore evaluated in 10 asymptomatic HIV-infected men (CD4+ lymphocyte count of 17 to 772 cells/μl).[17,58] Single-dose pharmacokinetic parameters were not significantly different from those obtained during multiple-dose administration, with the exception of C_{max} (4.79 mg/L after single doses and 6.92 mg/L after multiple doses); this degree of drug accumulation was consistent with that expected from the multiple-dose regimen. Levofloxacin disposition was very uniform throughout the study period, and the pharmacokinetics of the drug were similar to those obtained from healthy, non-HIV-infected individuals in other studies (table II).[11-15]

Similar results were observed in another double-blind, placebo-controlled trial in 16 males with HIV receiving multiple oral doses of levofloxacin 350mg thrice daily and concomitant zidovudine (AZT) treatment.[59] The pharmacokinetics and

safety of high-dose oral levofloxacin were also studied in 31 patients with symptomatic HIV-infection in a double-blind, placebo controlled trial (CD4+ cell count of 17 to 772 cells/μl).[60] Levofloxacin was administered initially in doses of 750mg daily for 14 days, then either 750 or 1000mg 3 times weekly for an additional 14 days. Mean C_{max} following 750mg daily, 750mg 3 times weekly and 1000mg 3 times weekly were 11.1, 10.3 and 11.2 mg/L, respectively. Serum half-life was similar among dosage groups. These values were comparable to those observed in healthy individuals receiving similar administration regimens (table II). These 3 dosage regimens were also well tolerated.

4.7 Effects of Bacterial Infections

The pharmacokinetics of levofloxacin in patients with serious community-acquired infections (skin, respiratory tract or urinary tract) were examined in a clinical trial.[62] Plasma concentrations of levofloxacin at specified times, guided by optimal sampling theory, were obtained from 272 patients received intravenous levofloxacin 500mg once daily (or 250mg once daily for the treatment of complicated urinary tract infection) treatment. A 2-compartment distribution model was utilised for the population analysis. Mean clearance and Vd of the central compartment were approximately 9.27 L/h and 0.84 L/kg, respectively, demonstrating that the pharmacokinetics of levofloxacin in patients with serious community-acquired infections are highly consistent with those observed in healthy individuals (table II).

5. Drug Interactions

Several well known and important interactions exist between fluoroquinolones and other drugs.[59] These interactions include those resulting in altered fluoroquinolone absorption (antacids, sucralfate, nutritional supplements); altered metabolism of the fluoroquinolone or the other agent (theophylline, caffeine, warfarin, histamine H_2 receptor antagonists); altered renal excretion (probenecid, azlocillin); and increased central nervous system toxicity (nonsteroidal anti-inflammatory agents, metronidazole). A number of studies have specifically evaluated the potential for significant drug interactions involving levofloxacin. These studies are summarised below.

5.1 Theophylline

Two studies in healthy volunteers have demonstrated that oral levofloxacin 100mg 3 times daily has only minor effects on the steady-state pharmacokinetics of theophylline.[61,63] Increases in serum theophylline C_{max} and AUC ranged from 2 to 11%, and the CL/F of theophylline was decreased from 2 to 17%. This contrasts with reported increases in C_{max} and AUC of 17 to 87% with ciprofloxacin, 5 to 11% with norfloxacin, 2 to 10% with ofloxacin and up to 240% with enoxacin.[59,64]

A randomised, double-blind, 2-way crossover study also evaluated the pharmacokinetic interaction between levofloxacin and theophylline.[65] Levofloxacin 500mg or placebo was administered orally twice daily for 9 doses to 14 healthy male volunteers; crossover study periods were separated by a 7-day washout period. A single intravenous dose of theophylline was administered immediately following the sixth dose of levofloxacin or placebo. Serum theophylline C_{max} increased by a mean of 6% and CL/F by a mean of approximately 3%; mean theophylline AUC was decreased by approximately 2%. The pharmacokinetic disposition of levofloxacin was not affected by theophylline.

Levofloxacin appears to have only minor potential for clinically significant drug interactions with theophylline (and presumably other xanthines such as caffeine). However, the magnitude of alterations in total clearance, C_{max} and AUC may vary considerably between individuals. Patients receiving these drugs concomitantly should be monitored for signs of theophylline toxicity.[1]

5.2 Antacids

Antacids containing divalent or trivalent metal cations (aluminium, magnesium, calcium) are recognised for their potential to cause decreased bioavailability of oral fluoroquinolones. Considerable evidence suggests that the formation of non-

absorbable metal-quinolone chelates in the stomach and/or small intestine is the mechanism responsible for impaired absorption.[59,66] Depending on the proximity of administration of the fluoroquinolone and antacids, C_{max} may be decreased by 30 to 94% with ciprofloxacin and >90% with norfloxacin.[67]

Concomitant administration of single doses of levofloxacin 100mg with aluminium hydroxide or magnesium oxide was studied in 18 healthy volunteers.[68] Individuals were given either levofloxacin plus aluminium or magnesium, or levofloxacin alone. When levofloxacin was administered with aluminium or magnesium, the extent of its absorption was reduced to 56 and 78%, respectively, of that for the drug alone. Levofloxacin C_{max} and AUC were decreased by 65% and 44%, respectively, when it was administered with aluminium, and by 37% and 22%, respectively, when administered with magnesium. Concurrent administration of levofloxacin with antacids containing aluminium or magnesium should therefore be avoided. Patients requiring both levofloxacin and such antacids should separate the doses by as large an interval as possible. Aluminium- or magnesium-containing antacids should not be administered within 2 hours before or after levofloxacin administration, if possible. Neither the rate nor the extent of levofloxacin absorption, nor its AUC, was significantly influenced by the concurrent administration of calcium carbonate, although t_{max} was slightly delayed and C_{max} was decreased by approximately 22%.[68]

5.3 Ferrous Sulfate

As was the case with aluminium- or magnesium-containing antacids, concurrent administration of ferrous sulfate has been shown to significantly reduce the bioavailability of ciprofloxacin and ofloxacin.[59,69] Concurrent oral administration of levofloxacin 100mg and ferrous sulfate 160mg resulted in a 45% reduction in C_{max} and a 19% reduction in AUC of levofloxacin relative to those obtained when the drug was administered alone.[68] Concurrent administration of levofloxacin and iron-containing products should be avoided. As with magnesium or aluminium antacid products, iron-containing products should not be administered within 2 hours before or after levofloxacin administration.

5.4 Ranitidine

Histamine H_2 receptor antagonists have been reported to alter the hepatic elimination of fluoroquinolones to varying degrees. Enoxacin clearance was significantly decreased by intravenous administration of ranitidine, while no pharmacokinetic changes were noted following concurrent administration of ranitidine and ciprofloxacin or ofloxacin.[59] Simultaneous administration of single doses of levofloxacin 100mg and ranitidine 150mg resulted in no alterations in the rate or extent of levofloxacin absorption.[68] The effects of long term ranitidine administration on levofloxacin pharmacokinetics have not been studied. However, from the results of such a study involving ofloxacin,[70] no significant alterations in levofloxacin disposition would be expected. Ranitidine and levofloxacin may be administered concomitantly without dosage adjustments.

5.5 Cimetidine and Probenecid

The ability of cimetidine and probenecid to compete with levofloxacin for renal tubular secretion through cationic and anionic pathways was evaluated in a randomised, 3-way crossover study in 12 healthy male individuals.[50] The absorption of a single oral dose of levofloxacin 500mg was unchanged. However, levofloxacin elimination was shown to be significantly affected by both of these drugs. Coadministration of cimetidine and probenecid each resulted in increases in mean $t_{1/2}$ of levofloxacin by approximately 30% (from 8.3 to 11 hours) and in mean AUC by 27 and 38% (from 53 to 68 and 74 mg • h/L), respectively. Cimetidine reduced mean levofloxacin CL_R and CL/F by 24% [from 7.14 to 5.46 L/h (119 to 91 ml/min)] and 21% [from 9.54 to 7.5 L/h (159 to 125 ml/min)], respectively. Probenecid reduced levofloxacin CL_R and CL/F by 35% [from 7.14 to 4.62 L/h (119 to 77 ml/min)] and 28% [from 9.54 to 6.84 L/h (159 to

114 ml/min)], respectively. Although CL_R was significantly reduced, the total 72-hour urinary excretion of levofloxacin was not significantly changed compared with levofloxacin alone. Although concomitant administration of levofloxacin with either cimetidine or probenecid resulted in statistically significant decreases in CL_R and CL/F, these interactions are unlikely to be of clinical significance except in the presence of concurrent renal impairment.

5.6 Cyclosporin

A double-blind, randomised, 2-way crossover study evaluated the effect of levofloxacin on the pharmacokinetics of cyclosporin.[55] Concomitant administration of multiple doses of oral levofloxacin 500mg twice daily for 6 days and a single oral dose of cyclosporin 10 mg/kg resulted in a mean cyclosporin t_{max} prolonged by 33% (from 1.8 to 2.4 hours) and a mean $t_{1/2}$ increased by 37% (from 6.4 to 8.8 hours). Other cyclosporin pharmacokinetic parameters were affected by less than 10%, and no changes were statistically significant compared with cyclosporin plus placebo. Levofloxacin pharmacokinetics were not affected by cyclosporin. Concurrent administration of these 2 drugs apparently requires no dosage adjustments for either.

5.7 Other Drugs

The potential for drug interactions between levofloxacin and warfarin, digoxin, zidovudine and sucralfate have also been evaluated in randomised studies. A randomised, double-blind, placebo-controlled, crossover study in 15 healthy male individuals evaluated the single-dose administration of warfarin 30mg (racemic) concurrently with levofloxacin 500mg twice daily for 9 days.[71] In a randomised, placebo-controlled, crossover study, digoxin 0.4mg was administered as a single dose to 12 healthy individuals receiving either levofloxacin 500mg or placebo twice daily for 5 days.[52] Zidovudine 100mg was evaluated in 16 HIV-infected men in a placebo-controlled study; pharmacokinetic interactions were studied following either single or multiple 3 times daily doses of levofloxacin 350mg.[58,72] Sucralfate was studied in a crossover fashion with levofloxacin administered 2 hours after that agent under fasting conditions.[53] The pharmacokinetic parameters of levofloxacin were not affected by concurrent administration of any of the other drugs (or 2 hours after for sucralfate) and dosage adjustments for levofloxacin are not required with any of these drugs. Similarly, the absorption and elimination pharmacokinetics of these other medications were not significantly altered by the concurrent administration of levofloxacin. With warfarin in particular, there were no pharmacokinetic alterations detected for either the *R*- or *S*-enantiomers of warfarin and no significant differences in prothrombin times were noted. Levofloxacin may be safely administered concurrently with warfarin, digoxin or zidovudine, and 2 hours before or 2 hours after sucralfate without dosage changes for either levofloxacin or the other agents. However, as with antacids, it is advisable not to administer sucralfate within 2 hours before or after levofloxacin, if possible.[53]

6. Pharmacokinetic/ Pharmacodynamic Considerations

Clinical failures and the development of resistance during fluoroquinolone therapy have been recognised to occur most frequently during treatment of infections caused by organisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, those which show only moderate susceptibility to currently available agents. Efforts to characterise useful pharmacodynamic parameters predictive of drug efficacy have clearly demonstrated that the fluoroquinolones exhibit concentration-dependent bacterial killing both *in vitro* and *in vivo*.[21,73-75] Recent *in vitro* data specifically evaluating levofloxacin pharmacodynamics are consistent with published work concerning other fluoroquinolones. An *in vitro* model of endocarditis demonstrated that simulated administration of levofloxacin 800mg daily in 1 or 2 doses was significantly better than either vancomycin monotherapy or vancomycin plus rifampicin (rifampin)

in the killing of *S. aureus* within infected platelet-fibrin clots.[76] The killing activity of levofloxacin was shown to be best correlated with the ratio of its C_{max} to the MIC (peak : MIC ratio) for *S. aureus* strains tested. It was further demonstrated that levofloxacin administered as a single daily dose, rather than in divided doses, resulted in more rapid bactericidal activity; this finding is consistent with the greater peak : MIC ratios achieved by the single large dose. Although the ratio of AUC to MIC (referred to as the area under the inhibitory time curve, or AUIC) was retrospectively shown to be the best predictor of favourable clinical response in efficacy trials involving ciprofloxacin,[77] this was not confirmed by the *in vitro* levofloxacin study.

A recent trial set out to prospectively develop a model which would predict successful clinical and microbiological response to levofloxacin therapy based on pharmacodynamic parameters.[78] Pharmacokinetic sampling was performed in 313 patients entered into a study evaluating the clinical efficacy of levofloxacin in the treatment of bacterial infections of the respiratory tract, skin or urinary tract. Population pharmacokinetic analysis was performed to determine levofloxacin parameters, and pharmacodynamic variables subsequently examined by logistic regression analysis in order to determine possible relationships between these variables and successful clinical and microbiological outcome. Of the patients entered into the study, 272 patients were included in the pharmacokinetic evaluation, 134 were finally included in the clinical outcome analysis with 116 in the microbiological outcome analysis. Although the AUC : MIC ratio (or AUIC) was associated with favourable response to levofloxacin therapy univariately, only the peak : MIC ratio was significantly associated with both favourable clinical and microbiological responses in the final logistic regression model. The specific breakpoint which defined patients with a high probability of favourable response to therapy was a levofloxacin peak : MIC ratio of 12.2. Although the occurrence of adverse effects was also examined in relation to pharmacodynamic variables, no association of adverse effects with degree of levofloxacin exposure was found.

Although prospective data specifically concerning levofloxacin are only recently becoming available, such findings are extremely promising for defining predictors of clinical outcome and therefore helping to establish rational pharmacodynamic-based therapeutic goals. It is anticipated that such data derived from future studies of levofloxacin, as well as other fluoroquinolones, will be directly applicable to maximising the therapeutic response achieved during clinical use of these agents.

7. Dosage Recommendations

In the US, the usual dose of levofloxacin is 500mg every 24 hours (administered orally or intravenously by slow infusion over 60 minutes). Dosage regimens for various treatment indications (due to the designated pathogens) are shown in table IV. These proposals are based on levofloxacin clinical pharmacokinetics, *in vitro* microbiological activity, NCCLS-approved MIC break-points, data from levofloxacin clinical efficacy trials, and apply to patients with normal renal function [CL_{CR} >4.8 L/h (80 ml/min)].

Dosage adjustments in patients with renal impairment [CL_{CR} ≤4.8 L/h (80 ml/min)] are shown in table V. Further dosage adjustments based on age, gender, or race are not necessary.

Table IV. Dosage recommendations for therapeutic use of levofloxacin[2]

Infection type	Dose (mg)	Dosage interval (h)	Duration of therapy (days)
Acute maxillary sinusitis	500	24	10-14
Acute bacterial exacerbation of chronic bronchitis	500	24	7
Community-acquired pneumonia	500	24	7-14
Uncomplicated skin and skin structure infections	500	24	7-10
Complicated urinary tract infection/acute pyelonephritis	250	24	10

Table V. Recommended levofloxacin dosage regimens for oral or intravenous administration in patients with impaired renal function as estimated by creatinine clearance (CL_{CR})[2]

CL_{CR} (L/h) [ml/min]	Complicated urinary tract infection/acute pyelonephritis	Other systemic infections
≥3 [≥50]	No dosage adjustment required	No dosage adjustment required
1.2-2.94 [20-49]	No dosage adjustment required	500 initially (1), then 250 q24h
0.6-1.14 [10-19]	250 q48h	500 initially (1), then 250 q48h
0 [0] haemodialysis or CAPD	Not applicable	500 initially (1), then 250 q48h

Abbreviations: CAPD = continuous ambulatory peritoneal dialysis; qxh = every x hours.

8. Conclusions

Levofloxacin is a fluoroquinolone with desirable pharmacokinetic characteristics. It is rapidly and essentially 100% bioavailable following oral administration. Therefore, the oral and intravenous routes of administration can be considered interchangeable. Levofloxacin is distributed throughout the body and achieves concentrations in many tissues and fluids which usually exceed those observed in plasma. The drug is also primarily excreted unchanged in the urine, with negligible metabolites formed and a relatively long plasma half-life of 6 to 8 hours. Concentrations of levofloxacin in tissues and biological fluids are relatively high compared with MIC values of the pathogens. These features allow the use of the drug in once-daily dose administration.

Levofloxacin has minimal potential for significant interactions with other drugs, including theophylline and warfarin. Similar to other fluoroquinolones, however, it has significant drug interactions with aluminum- or magnesium-containing antacids and ferrous sulfate. These agents should not be taken within a 2-hour period before or after levofloxacin administration. Minimal drug interaction potential makes levofloxacin useful in patients with complicated medication regimens.

Other favourable characteristics of levofloxacin include its broad *in vitro* antimicrobial spectrum of activity and its good tolerability during clinical use. Levofloxacin promises to be a useful agent in the treatment of a variety of infections.

References

1. Davis R, Bryson HM. Levofloxacin: a review of its antibacterial activity, pharmacokinetics and therapeutic efficacy. Drugs 1994; 47: 677-700
2. R.W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey, USA. Data on file
3. Hayakawa I, Atarashi S, Yokohama S, et al. Synthesis and antimicrobial activities of optically active ofloxacin. Antimicrob Agents Chemother 1986; 29: 163-4
4. Hooper DC, Wolfson JS. The fluoroquinolones: pharmacology, clinical uses, and toxicities in humans. Antimicrob Agents Chemother 1985; 28: 716-21
5. Imamura M, Shibamura S, Hayakawa I, et al. Inhibition of DNA gyrase by optically active ofloxacin. Antimicrob Agents Chemother 1987; 31: 325-7
6. Tanaka K-I, Iwamoto M, Maesaki S, et al. Basic and clinical studies on levofloxacin in the treatment of respiratory infections. Jpn J Antibiot 1992; 45: 548-55
7. Shen LL, Pernet AG. Mechanism of inhibition of DNA gyrase by analogues of nalidixic acid: the target of the drugs is DNA. Proc Natl Acad Sci USA 1985; 82: 307-11
8. Smith JT. The mode of action of 4-quinolones and possible mechanisms of resistance. J Antimicrob Chemother 1986; 18 Suppl. D: 21-9
9. Fu KP, Grace ME, McCloud SJ, et al. Discrepancy between the antibacterial activities and the inhibitory effects of *Micrococcus luteus* DNA gyrase of 13 quinolones. Chemotherapy 1986; 29: 494-8
10. Lehr K-H, Damm P. Quantification of the enantiomers of ofloxacin in biological fluids by high-performance liquid chromatography. J Chromatogr 1988; 425: 153-61
11. Okazaki O, Kojima C, Hakusui H, et al. Enantioselective disposition of ofloxacin in humans. Antimicrob Agents Chemother 1991; 35: 2106-9
12. Nakashima M, Uematsu T, Kanamaru M, et al. Phase I study of levofloxacin, (S)-(−)-ofloxacin. Jpn J Clin Pharmacol Ther 1992; 23: 515-20
13. Wong FA, Juzwin SJ, Flor SC. Rapid stereospecific high-performance liquid chromatogrphic determination of levofloxacin in human plasma and urine. J Pharm Biomed Analysis 1997. In press
14. Child J, Mortiboy D, Andrews JM, et al. Open-label crossover study to determine the pharmacokinetics and penetration of two dose regimens of levofloxacin into inflammatory fluid. Antimicrob Agents Chemother 1995; 39: 2749-51
15. Lode H, Höffken G, Olschewski P, et al. Pharmacokinetics of ofloxacin after oral and parenteral administration. Antimicrob Agents Chemother 1987; 31: 1338-42
16. Sasaki J, Morishima T, Shiiki K, et al. Clinical study of levofloxacin in treatment of odontogenic infections. Chemotherapy 1992; 40 Suppl. 3: 379-91
17. Goodwin SD, Gallis HA, Chow AT, et al. Pharmacokinetics and safety of levofloxacin in patients with human immunodeficiency virus infection. Antimicrob Agents Chemother 1994; 38: 799-804
18. Holland ML, Chien S-C, Corrado ML, et al. The pharmacokinetic profile of levofloxacin following once- or twice-daily 500mg oral administration of levofloxacin hemihydrate [ab-

stract]. 5th International Symposium on New Quinolones; 1994 Aug 25-27: Singapore
19. Chein SC, Chow AT, Fowler CL, et al. Double-blind evaluation of the safety and pharmacokinetics of multiple oral once-daily 750mg and 1g doses of levofloxacin in healthy volunteers [abstract A14]. American Society of Mircobiology: Abstracts of the 36th Interscience Conference on antimicrobial Agents and Chemotherapy; 1996 Sep 15-18; New Orleans, 3
20. Holland ML, Chien S-C, Corrado ML, et al. The pharmacokinetic profile of intravenous levofloxacin following once- or twice-daily 500mg administration [abstract]. 5th International Symposium on New Quinolones; 1994 Aug 25-27: Singapore
21. Dudley MN, Blaser J, Gilbert D, et al. Bactericidal activity of ciprofloxacin against *Ps. aeruginosa* and other bacteria in an *in vitro* capillary model. Rev Infect Dis 1988; 10: S34-5
22. Ohi Y, Goto T, Kawahara K, et al. Penetration of fluoroquinolones into human spinal fluid. Chemotherapy 1992; 40: 469-73
23. Inoue S, Misaki M, Matsumura K. Intraocular penetration of DR-3355. Atarashii Ganka [J Eye] 1992; 9: 487-90
24. Tomii T, Fukuda M, Sasaki K. Penetration of *l*-ofloxacin (DR-3355) into the lacrimal fluid. Jpn J Clin Ophthalmol 1991; 45: 1607-10
25. Baba S, Miyamoto N, Yanai O, et al. Study on the penetration of levofloxacin (DR-3355) into the otorhinolaryngeal tissues and discharges in patients. Chemotherapy 1992; 40 Suppl. 3: 326-33
26. Nakamori Y, Tsuboi E, Narui K, et al. Sputum penetration of levofloxacin and its clinical efficacy in patients with chronic lower respiratory tract infections. Jpn J Antibiot 1992; 45: 539-47
27. Nagai H, Yamasaki T, Masuda M, et al. Penetration of levofloxacin into bronchoalveolar lavage fluid. Drugs 1993; 45 Suppl. 3: 259
28. Hukagawa H, Noga K. A study on the concentration of levofloxacin in the gallbladder tissue and bile of patients. Jpn J Antibiot 1992; 45: 253-7
29. Ohnishi H, Tanimura H, Ichimaya G, et al. Excretion of levofloxacin into bile and gallbladder tissue. Drugs 1993; 45 Suppl. 3: 260-1
30. Tanimura H, Ohnishi H, Okamura T, et al. Chemotherapy of biliary tract infections (XXXVII): excretion into bile and gallbladder tissue levels of levofloxacin and its clinical effect in biliary tract infections. Jpn J Antibiot 1992; 45: 557-68
31. Takahashi H, Mogi S, Kobayashi M, et al. Assay of skin level and clinical investigation of levofloxacin in the treatment of skin infections. Chemotherapy 1992; 40 Suppl. 3: 286-305
32. Saito I, Suzuki A, Saiko Y, et al. Acute nongonococcal epididymitis: aetiology and levofloxacin therapy. Drugs 1993; 45 Suppl. 3: 379
33. Saito I, Suzuki A, Saiko Y, et al. Acute nongonococcal epididymitis: pharmacological and therapeutic aspects of levofloxacin. Acta Urol Jpn 1992; 38: 623-8
34. Yamashita M, Sawada K, Chokyu H, et al. Prostatic tissue levels of levofloxacin. Chemotherapy 1992; 40 Suppl. 3: 203-9
35. Soyama Y, Mizuhara H, Iwata Y. Fundamental study on levofloxacin in the field of obstetrics and gynecology. Jpn J Antibiot 1992; 45: 265-9
36. Ito K, Mikamo H, Izumi K, et al. Penetration of levofloxacin into gynecological tissues. Chemotherapy 1992; 40 Suppl. 3: 306-10
37. Inagaki Y, Nakaya R, Chida T, et al. The effect of levofloxacin, an optically-active isomer of ofloxacin, on fecal microflora in human volunteers. Jpn J Antibiot 1992; 45: 241-52
38. Murata M, Ohnishi K, Irimajiri S, et al. Clinical trial of levofloxacin (DR-3355) and fecal drug concentration and change in the fecal microflora in infectious enteritis. Chemotherapy (Tokyo) 1992; 40 Suppl. 3: 170-87
39. Giamarellou H, Kolokythas E, Petrikkos G, et al. Pharmacokinetics of three newer quinolones in pregnant and lactating women. Am J Med 1989; 87 Suppl. 5A: 49-51
40. Nozaki-Renard J, Iino T, Sato Y, et al. Fluoroquinolones protect the human lymphocyte CEM cell line from HIV-1 mediated cytotoxicity. Cell Struct Funct 1990; 15: 295-9
41. Pascual A, Garcia I, Perea EJ. Uptake and intracellular activity of an optically active ofloxacin isomer in human neutrophils and tissue culture cells. Antimicrob Agents Chemother 1990; 34: 277-80
42. Pascual A, Garcia I, Conejo MC, et al. Fluorometric and high-performance liquid chromatographic measurement of quinolone uptake by human neutrophils. Eur J Clin Microbiol Infect Dis 1991; 10: 969-71
43. Gaja M, Higa F, Yamashiro T, et al. Penetration of levofloxacin, a new quinolone antibacterial agent, into human neutrophils. Chemotherapy 1992; 40 Suppl. 3: 64-7
44. Taira K, Koga H, Kohno S. Accumulation of a newly developed fluoroquinolone, OPC-17116, by human polymorphonuclear leukocytes. Antimicrob Agents Chemother 1993; 37: 1877-81
45. Perea EJ, Garcia I, Pascual A. Comparative penetration of lomefloxacin and other quinolones into human phagocytes. Am J Med 1992; 92 Suppl. 4A: 48S-51S
46. Gladue RP, Bright GM, Isaacson RE, et al. In vitro and in vivo uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. Antimicrob Agents Chemother 1989; 33: 277-82
47. Carbon C. Clinical relevance of intracellular and extracellular concentrations of macrolides. Infection 1995; 23 Suppl. 1: S10-4
48. Borner K, Lode H. Biotransformation of certain gyrase inhibitors. Infection 1986; 14 Suppl. 1: S54-9
49. Monk JP, Campoli-Richards DM. Ofloxacin: a review. Drugs 1987; 33: 346-91
50. Gaitonde MD, Mendes P, House ESA, et al. The effects of cimetidine and probenecid on the pharmacokinetics of levofloxacin [abstract no. A41]. American Society for Microbiology: Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17-29: San Francisco, 8
51. Gisclon LG, Curtin CR, Williams RR, et al. The pharmacokinetics of levofloxacin in subjects with renal impairment, and in subjects receiving hemodialysis or continuous ambulatory peritoneal dialysis [abstract no. A13]. American Society for Microbiology: Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15-18; New Orleans, 3
52. Chien SC, Chow AT, Williams R, et al. Absence of an effect of levofloxacin on digoxin pharmacokinetics [abstract]. American Academy of Pharmaceutical Scientists: Annual Meeting Program Supplement; 1995 Jun 5-6: New Brunswick
53. Lee L-J, Hafkin B, Lee I-D, et al. Effect of food and sucralfate on levofloxacin after a single oral dose of 500 mg in male and female subjects [abstract no. A40]. American Society for Microbiology: Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17-29: San Francisco, 8

54. Rogge MC, Chien S-C, Wong F, et al. Single-dose pharmacokinetics of levofloxacin: influence of age and gender [abstract]. 5th International Symposium on New Quinolones; 1994 Aug 25-27: Singapore
55. Doose DR, Walker SA, Chien SC, et al. Absence of an effect of levofloxacin on cyclosporine pharmacokinetics in healthy adult volunteers [abstract]. American Academy of Pharmaceutical Scientists: Annual Meeting Program Supplement; 1995 Jun 5-6: New Brunswick
56. Saito A, Oguchi K, Harada Y, et al. Pharmacokinetics of levofloxacin in patients with impaired renal function. Chemotherapy 1992; 40 Suppl. 3: 188-95
57. Aoki N, Usuda Y, Koda Y, et al. Clinical pharmacology and efficacy of levofloxacin in elderly patients. Jpn J Antibiot 1992; 45: 530-8
58. Chien SC, Chow AT, Hendrix C, et al. The pharmacokinetics and safety of oral levofloxacin in HIV-infected individuals receiving concomitant zidovudine [abstract no. A33]. American Society for Microbiology: Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17-29: San Francisco, 7
59. Radandt JM, Marchbanks CR, Dudley MN. Interactions of fluoroquinolones with other drugs: mechanisms, variability, clinical significance, and management. Clin Infect Dis 1992; 14: 272-84
60. Spooner KM, Baird BF, Davey RT, et al. Evaluation of the pharmacokinetics and safety of single and multiple high dose regimens of levofloxacin in HIV seropositive subjects [abstract no. LM32]. American Society for Microbiology: Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17-29; San Francisco, 332
61. Niki Y, Hashiguchi K, Okimoto N, et al. Quinolone antimicrobial agents and theophylline [letter]. Chest 1992; 101: 881
62. Preston SL, Drusano GL, Berman AL, et al. Levofloxacin population pharmacokinetics and creation of a demographics model for prediction of individual drug clearance in patients with serious community-aquired infection [abstract A12]. American Society for Microbiology: Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15-18; New Orleans, 2
63. Okimoto N, Niki Y, Soejima R. Effect of levofloxacin on serum concentration of theophylline. Chemotherapy 1992; 40 Suppl. 3: 68-74
64. Beckmann J, Elsässer W, Gundert-Remy U, et al. Enoxacin: a potent inhibitor of theophylline metabolism. Eur J Clin Pharmacol 1987; 33: 227-30
65. Gisclon LG, Curtin CR, Fowler CL, et al. Absence of a pharmacokinetic interaction between intravenous theophylline and orally administered levofloxacin [abstract no. A39]. American Society for Microbiology: Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17-29: San Francisco, 8
66. Tanaka M, Kurata T, Fujisawa C, et al. Mechanistic study of inhibition of levofloxacin absorption by aluminum hydroxide. Antimicrob Agents Chemother 1993; 37: 2173-8
67. Nix DE, Wilton JH, Schentag JJ, et al. Inhibition of norfloxacin absorption by antacids and sucralfate. Rev Infect Dis 1989; 11 Suppl. 5: S1096-8
68. Shiba K, Sakai O, Shimada J, et al. Effect of antacids, ferrous sulfate, and ranitidine on absorption of DR-3355 in humans. Antimicrob Agents Chemother 1992; 36: 2270-4
69. Polk RE, Healy DP, Sahai J, et al. Effect of ferrous sulfate and multivitamins with zinc on absorption of ciprofloxacin in normal volunteers. Antimicrob Agents Chemother 1989; 33: 1841-4
70. Höffken G, Lode H, Wiley R, et al. Pharmacokinetics and bioavailability of ciprofloxacin and ofloxacin: effect of food and antacid intake. Rev Infect Dis 1988; 10 Suppl. 1: S138-9
71. Liao S, Palmer M, Fowler CL, et al. Absence of the effect of levofloxacin on warfarin pharmacokinetics and anticoagulation in male volunteers [abstract no. A42]. American Society for Microbiology: Abstracts of the 35th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1995 Sep 17-29: San Francisco, 8
72. Holland ML, Chow AT, Chien S-C, et al. The pharmacokinetics of oral levofloxacin in HIV-infected individuals with or without concomitant zidovudine [abstract]. 5th International Symposium on New Quinolones; 1994 Aug 25-27: Singapore
73. Chalkley LJ, Koornhof HJ. Antimicrobial activity of ciprofloxacin against *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus* determined by the killing curve method: antibiotic comparisons and synergistic interactions. Antimicrob Agents Chemother 1985; 28: 331-42
74. Peloquin CA, Cumbo TJ, Nix DE, et al. Intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections: impact of plasma concentrations, organism MIC, and clinical condition on bacterial eradication. Arch Intern Med 1989; 149: 2269-73
75. Maderas-Kelly KJ, Ostergaard BE, Hovde LB, et al. Twenty-four-hour area under the concentration-time curve/MIC ratio as a generic predictor or fluoroquinolone antimicrobial effect by using three strains of *Pseudomonas aeruginosa* and an in vitro pharmacodynamic model. Antimicrob Agents Chemother 1996; 40: 627-32
76. Palmer SM, Rybak MJ. Pharmacodynamics of once- or twice-daily levofloxacin versus vancomycin, with or without rifampin, against *Staphylococcus aureus* in an in vitro model with infected platelet-fibrin clots. Antimicrob Agents Chemother 1996; 40: 701-5
77. Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in severely ill patients. Antimicrob Agents Chemother 1993; 37: 1073-81
78. Preston SL, Drusano GL, Berman AL, et al. Prospective development of pharmacodynamic relationships between measures of levofloxacin exposure and measures of patient outcome [abstract no. A98]. American Society for Microbiology: Abstracts of the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy; 1996 Sep 15-18: New Orleans, 19

Correspondence and reprints: Dr *Douglas N. Fish*, Department of Pharmacy Practice, School of Pharmacy, University of Colorado Health Sciences Center, Campus Box C-238, 4200 East Ninth Avenue, Denver, CO 80262, USA.