

# Comparative Pharmacokinetics and Pharmacodynamics of the Newer Fluoroquinolone Antibacterials

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## Abstract

A number of new fluoroquinolone antibacterials have been released for clinical use in recent years. These new agents exhibit enhanced activity against Gram-positive organisms while retaining much of the Gram-negative activity of the earlier agents within the same class. The pharmacokinetics of most of these agents are well described including serum pharmacokinetics, tissue and fluid distribution, and pharmacokinetics in renal and hepatic disease. When compared with earlier agents within this class (i.e. ciprofloxacin), the newer agents retain the wide distribution characteristics; however, they exhibit a more prolonged elimination, which, in part, supports single daily administration for these agents. Based on their predominant renal elimination, dosage adjustment is necessary in the presence of renal disease for ciprofloxacin, levofloxacin, gatifloxacin and sitafloxacin.

Drug interactions, particularly with multivalent cations (calcium/aluminium-containing antacids and iron products), remain a problem for the newer agents,

resulting in reduced absorption requiring separate administration times to maximise bioavailability. However, the newer agents do not appear to interfere significantly with the cytochrome P450 system, thus minimising the potential for interactions with other drugs metabolised by this system.

The pharmacodynamic properties of the fluoroquinolones have been well described. The bactericidal activity is maximised when the ratios of peak plasma drug concentration ( $C_{\max}$ ) : minimum inhibitory concentrations (MIC) or area under the concentration-time curve (AUC) : MIC exceed specific threshold values. Knowledge of the pharmacodynamic relationships allows for appropriate drug selection and enables design of dosage regimens to maximise the bactericidal activity. Therapeutic drug monitoring of the fluoroquinolones may provide a means of optimising the dosage regimen in certain clinical situations (that is, meningitis and hospitalised pneumonias) with the goals of achieving a more predictable therapeutic response and minimising the potential for the development of resistance.

A number of new fluoroquinolone agents have become available for use worldwide since the initial introduction of ciprofloxacin in the late 1980s. Compared with the earlier fluoroquinolones such as ciprofloxacin and ofloxacin, the newer agents have enhanced activity against several important pathogens, as well as improved pharmacokinetic properties. The newer agents include gatifloxacin, gemifloxacin, levofloxacin, moxifloxacin, rufloxacin, sitafloxacin and sparfloxacin. Rufloxacin and sitafloxacin are available for use outside of the US. Almost all of the fluoroquinolones are US Food and Drug Administration (FDA)-approved for use in the treatment of patients with respiratory tract and urinary tract infections. Additional indications for selected agents include bone and joint infections, skin and skin structure infections, and sexually transmitted infections. The purpose of this paper is to compare and contrast the pharmacokinetic and pharmacodynamic properties of the newer fluoroquinolones. Ciprofloxacin will be used as a basis for comparison between the early and the newer agents.

### 1. Single and Multiple Dose Pharmacokinetics

A number of studies have examined the single dose pharmacokinetics of the newer fluoroquinolones (see table I). While many of the newer quinolones exhibit similar pharmacokinetic properties as

the older agents (i.e. absorption, clearance and volume of distribution), important differences do exist between the individual compounds. The volumes of distribution of the newer agents range from 1.2 to 5.5 L/kg, compared to about 3 L/kg for ciprofloxacin. The half-lives of the newer agents are all prolonged compared with ciprofloxacin, with values ranging from between 5 and 83 hours. Based on those values, the area under the concentration curve (AUC) of each of the newer fluoroquinolones are significantly higher than that of ciprofloxacin, which may have clinical implications depending on the minimum inhibitory concentration (MIC) of the organism in question.

The pharmacokinetic properties of the newer fluoroquinolones are influenced minimally by multiple dose administration. Pharmacokinetic parameter values such as peak plasma drug concentration ( $C_{\max}$ ), time to  $C_{\max}$  ( $t_{\max}$ ), half-life ( $t_{1/2}$ ), total body clearance (CL) and the AUC change little after single and multiple doses. This suggests that the frequency of administration does not affect the rate of elimination, decreasing the possibility of drug accumulation over time.

Tables I and II summarise the representative pharmacokinetic parameters of the fluoroquinolones. Pharmacokinetic data were obtained from studies involving healthy volunteers. Due to the extensive literature available on earlier fluoroquinolone agents

**Table I.** Single dose pharmacokinetics of fluoroquinolones

Reference	Dose (mg)	C <sub>max</sub> (mg/L)	t <sub>max</sub> (min)	Vd (L/kg)	CL (L/h)	t <sub>1/2β</sub> (h)	AUC <sub>∞</sub> (mg/L • h)	F (%)	f <sub>e</sub> (%)
<b>Ciprofloxacin</b>									
Keller et al. <sup>[1]</sup>	250 PO	1.5 ± 0.4	47 ± 20			5.3 ± 0.8	5.8 ± 1.3		42.1 ± 7.2
LeBel et al. <sup>[2]</sup>	500 PO	2.26	80	3.76 <sup>a</sup>	54.5 <sup>b</sup>	3.69	10	55.6	
Hoffken et al. <sup>[3]</sup>	750 PO	2.65	66	3.53 <sup>c</sup>	61.5 <sup>b</sup>	4.75	12.2		33
Drusano et al. <sup>[4]</sup>	200 IV	3.8		1.90 <sup>a</sup>	25.2	4.4	7.2		60
Gonzalez et al. <sup>[5]</sup>	400 IV	4.5 ± 0.8			34.4	3.4 ± 0.5	12 ± 1.8		
<b>Gatifloxacin</b>									
Keller et al. <sup>[1]</sup>	400 PO	3.4 ± 0.7	89 ± 39			6.5 ± 0.8	30 ± 4		77 ± 5.6
Nakashima et al. <sup>[6]</sup>	400 PO	3.3 ± 0.5	118 ± 39	2.2 <sup>d</sup>	10.4 <sup>b</sup>	8.4 ± 2.2	32.4 ± 4.1		83 ± 4
Data on file <sup>[7]</sup>	400 PO	3.8 ± 1.0	60		12.6 <sup>b</sup>	7.8 ± 1.3	33 ± 6.2	96	72 ± 18
	400 IV	5.5 ± 1.0		1.5 <sup>a</sup>	11.7	7.4 ± 1.6	35.1 ± 6.7		62 ± 17
<b>Gemifloxacin</b>									
Allen et al. <sup>[8]</sup>	320 PO	1.5 ± 0.4	60	4.9	9.1 <sup>b,e</sup>	6.6 ± 1.3	9.8 ± 2.7		27.5 ± 6.4
	600 PO	3.8 ± 1.1	60	4.1	8.5 <sup>b,e</sup>	8.3 ± 0.8	24.4 ± 7.1		32 ± 7.2
	800 PO	4.3 ± 0.6	60	4.2	10.5 <sup>b,e</sup>	8.0 ± 0.7	31.4 ± 7.6		39.4 ± 7.9
Pay et al. <sup>[9]</sup>	320 PO	2.0 ± 0.3	50		12.3 <sup>e</sup>	8.2 ± 0.9	9.3 ± 1.6		33 ± 4.6
<b>Levofloxacin</b>									
Keller et al. <sup>[1]</sup>	500 PO	6.2 ± 1.3	48 ± 23			6.9 ± 0.8	45 ± 4.4		76 ± 12
Data on file <sup>[10]</sup>	250 PO	2.8 ± 0.4	100 ± 60		9.3 ± 1.2 <sup>b</sup>	7.3 ± 0.9	27.2 ± 3.9	99	
Holland et al. <sup>[11]</sup>	500 PO	5.2	78 ± 30	1.3 <sup>d</sup>	10.5 <sup>b</sup>	6.5	47.7		69
Holland et al. <sup>[12]</sup>	500 IV	6.3		1.2	9.4	6.6	55.3		61
<b>Moxifloxacin</b>									
Keller et al. <sup>[1]</sup>	400 PO	4.3 ± 1.6	62 ± 45			9.1 ± 1.6	39 ± 5.4		20 ± 4.6
Stass et al. <sup>[13,14]</sup>	400 PO	2.5	90	3.5 <sup>c</sup>	14.9 <sup>b</sup>	13.1	26.9	86.2	
Stass et al. <sup>[15]</sup>	400 PO	2.5	120	3.1 <sup>a</sup>	11.6 <sup>b</sup>	15.6	29.8	86.2	19.3
	400 IV	3.6		2.1 <sup>a</sup>	11.6	15.4	34.6		22.1
<b>Rufloxacin</b>									
Segre et al. <sup>[16]</sup>	200 PO	1.0 ± 0.3	240			70.4 ± 19	48 ± 12 <sup>f</sup>		53 ± 13
	400 PO	1.0 ± 0.3	342			83 ± 46	47 ± 13 <sup>f</sup>		49 ± 8.9
Imbimbo et al. <sup>[17]</sup>	400 PO	2.7 ± 0.6	230	2.1 <sup>c</sup>	3.2 <sup>b</sup>	39 ± 20	143 ± 57		21 ± 7.8
<b>Sitafloxacin</b>									
Nakashima et al. <sup>[18]</sup>	100 PO	1.0 ± 0.1	72	1.8 <sup>a</sup>	18.8 <sup>b</sup>	5.0 ± 1.9	5.5 ± 1.2		
	200 PO	1.8 ± 0.4	60	1.8 <sup>a</sup>	17.6 <sup>b</sup>	4.6 ± 0.8	12 ± 3.2		
<b>Sparfloxacin</b>									
Sakashita et al. <sup>[19]</sup>	200 PO	0.6	210	5.5 <sup>c</sup>	15.3 <sup>b</sup>	15.8	14.7		
Sakashita et al. <sup>[19]</sup>	400 PO	1.4	258	4.6 <sup>c</sup>	12.1 <sup>b</sup>	16.9	34.7		
Montay et al. <sup>[20-22]</sup>	400 PO	1.2	300		12.7 <sup>b</sup>	18.2	32.7		9.5 ± 2.1

a V<sub>ss</sub>/F.

b CL/F.

c Vd/F.

d V<sub>β</sub>/F.

e Renal clearance.

f AUC to 96 hours postdose.

AUC<sub>∞</sub> = area under the concentration-time curve to infinity; CL = total body clearance; C<sub>max</sub> = peak plasma drug concentration; F = bioavailability; f<sub>e</sub> = fraction of unchanged drug excreted in the urine; IV = intravenous; PO = oral; t<sub>1/2β</sub> = elimination half-life; t<sub>max</sub> = time to peak drug plasma concentration; V<sub>β</sub> = volume of distribution determined during the β-elimination phase in a two-compartment model; Vd = volume of distribution; V<sub>ss</sub> = volume of distribution at steady state.

**Table II.** Multidose pharmacokinetics of fluoroquinolones

Reference	Dose (mg)	C <sub>max</sub> (mg/L)	t <sub>max</sub> (min)	Vd (L/kg)	CL (L/h)	t <sub>1/2β</sub> (h)	AUC <sub>24</sub> (mg/L • h)	f <sub>e</sub> (%)
<b>Ciprofloxacin</b>								
Bergan et al. <sup>[23]</sup>	500 PO	2.3	90	1.78 <sup>a</sup>	52.1 <sup>b</sup>	2.5	9.6 <sup>e</sup>	42.5
Sorgel et al. <sup>[24]</sup>	500 PO	3.5 ± 0.3	60 ± 25		29 <sup>b</sup> ± 12	4.7 ± 1.2	13.9 <sup>e</sup> ± 5.3	
	200 IV	4.9 ± 1.0			29 ± 3.8	3.6 ± 0.6	6.9 <sup>e</sup> ± 0.9	
Gonzalez et al. <sup>[5]</sup>	400 IV	4.6 ± 0.7			32 ± 5.2	3.5 ± 0.7	12.9 <sup>e</sup> ± 2.1	
<b>Gatifloxacin</b>								
Data on file <sup>[7]</sup>	400 PO	4.2 ± 1.3	60		12 <sup>b</sup> ± 1.8	7.1 ± 0.6	34.4 ± 5.7	80 ± 12
	200 IV	2.4 ± 0.4		2.0 <sup>a</sup>	12 ± 2.6	12 ± 4.6	18.8 ± 3.6	72 ± 16.4
	400 IV	4.6 ± 0.6		1.6 <sup>a</sup>	11 ± 1.4	14 ± 3.9	35.4 ± 4.6	83 ± 13.8
<b>Gemifloxacin</b>								
Allen et al. <sup>[25]</sup>	320 PO	1.8 ± 0.4	48			10 ± 1.3	9.0 ± 2.2	22 ± 6.0
	640 PO	2.8 ± 0.4	90			8.6 ± 1.5	20.1 ± 3.7	27 ± 3.0
Pay et al. <sup>[9]</sup>	320 PO	2.0 ± .2	46		15.8	10 ± 1.7	8.6 ± 0.8	45 ± 4.8
<b>Levofloxacin</b>								
Holland et al. <sup>[11]</sup>	500 PO	5.7	66	1.37 <sup>c</sup>	10.5 <sup>b</sup>	6.8	47.5	67
Chen et al. <sup>[26]</sup>	750 PO	8.6	84	1.29 <sup>c</sup>	8.6 <sup>b</sup>	8.8	91	79
Holland et al. <sup>[12]</sup>	500 IV	6.4		1.22 <sup>c</sup>	9.5	6.8	64.6	62
<b>Moxifloxacin</b>								
Sullivan et al. <sup>[27]</sup>	400 PO	4.5				12.0	48	
<b>Rufloxacin</b>								
Segre et al. <sup>[16]</sup>	200 PO	6.2 ± 1.8	480			36.2 ± 21	92.2 ± 32	
Kisicki et al. <sup>[28]</sup>	400 PO	7.2 ± 0.3	168	1.8 <sup>d</sup>	2.2 <sup>b</sup> ± 0.1	44 ± 1.3	87.0 ± 3.1	51.1 ± 2.1
<b>Sparfloxacin</b>								
Montay et al. <sup>[21]</sup>	200 PO	1.4 ± 0.4	210		10 <sup>b</sup> ± 2.0	20 ± 1.9	20.4 ± 4.6	
	400 PO	2.9 ± 0.6	222		9.5 <sup>b</sup> ± 2.7	18 ± 1.3	45.3 ± 13.8	

a V<sub>ss</sub>/F.

b CL/F.

c V<sub>β</sub>/F.

d Vd/F.

e AUC<sub>12</sub>.

AUC<sub>∞</sub> = area under the concentration-time curve to infinity; CL = total body clearance; C<sub>max</sub> = peak plasma drug concentration; F = bioavailability; f<sub>e</sub> = fraction of unchanged drug excreted in the urine; IV = intravenous; PO = oral; t<sub>1/2β</sub> = elimination half-life; t<sub>max</sub> = time to peak drug plasma concentration; V<sub>β</sub> = volume of distribution determined during the β-elimination phase in a two-component model; Vd = volume of distribution; V<sub>ss</sub> = volume of distribution at steady state.

(i.e. ciprofloxacin), representative studies were chosen based on the number of patients evaluated and completeness of the pharmacokinetic analysis.

### 1.1 Absorption

The newer quinolones, such as sparfloxacin and levofloxacin, readily dissolve in the gastrointestinal (GI) tract and are absorbed throughout the duodenum and jejunum.<sup>[29]</sup> However, the bioavailability and t<sub>max</sub> vary between the different agents. All of the

newer fluoroquinolones have equal or greater bioavailability compared with ciprofloxacin, which varies between 55 to 88%.<sup>[2,30]</sup> Levofloxacin and gatifloxacin have excellent bioavailability (>95%) followed by sparfloxacin (92%) and moxifloxacin (86%).<sup>[31-34]</sup> Of note, sparfloxacin appears to be absorbed by both passive and carrier-mediated processes in the duodenum and colon. Thus, bioavailability is reduced at higher doses because of the decreased absorption.<sup>[35]</sup>

Limited data suggests that approximately 60% of rufloxacin and 70% of sitafloxacin and gemifloxacin are absorbed after an oral dose.<sup>[16,18,36]</sup> With the exception of rufloxacin and sparfloxacin, all other newer fluoroquinolones have  $t_{\max}$  values of approximately 1 to 2 hours.<sup>[1,6,18,29,37-40]</sup> Rufloxacin and sparfloxacin have demonstrated  $t_{\max}$  values ranging from 2 to 4 hours and 2.5 to 5 hours, respectively.<sup>[16,20,28,41-44]</sup> It has been suggested that this is because of delays in the dissolution and gastric emptying time of the rufloxacin capsule.<sup>[42]</sup> In addition, it has been demonstrated that the drug is absorbed more quickly in the lower dosage ranges. This is consistent with the need for a longer period of time for dissolution and gastric emptying of multiple rufloxacin capsules.<sup>[28]</sup>

## 1.2 Distribution

The newer fluoroquinolones demonstrate a linear increase in  $C_{\max}$  with increasing dosages. Plasma concentrations after oral and intravenous administration are very similar for levofloxacin and gatifloxacin given their high bioavailability. Many infections, however, are not limited to the blood or central compartment. The distribution characteristics of an antibacterial are therefore important to consider since they help determine the extent to which the drug penetrates the site of infection. Ciprofloxacin distributes well into various body tissues as reflected by its relatively large volume of distribution ( $V_d$ ), ranging from 1.7 to 2.5 L/kg.<sup>[4,45]</sup> The other fluoroquinolone agents exhibit a similar  $V_d$  with the exception of sparfloxacin, which ranges from 4.5 to 5.5 L/kg.<sup>[21,43]</sup>

A commonly employed method of assessing potential antimicrobial activity within various tissues is to compare their respective tissue-to-serum concentration ratios. While this method is useful to compare the relative tissue penetration, it does not necessarily guarantee that therapeutic concentrations are achieved at the site of infection. Ideally, knowledge of the tissue concentrations in relation to the sensitivity of the organism would provide the best indicator of potential efficacy of the antibacterial regimen.

Ciprofloxacin has a tissue-to-serum ratio of 1.6 in bronchial secretions, 2.1 in lung tissue, 1.2 in blister fluid, 13.3 in the kidneys and up to 30 in the bile.<sup>[46]</sup> In addition, the bronchial mucosa, epithelial lining fluid, and alveolar tissue to plasma concentrations for ciprofloxacin were reported in ratios of 1.7, 1.9 and 14.3, respectively.<sup>[47]</sup> Table III summarises the tissue and fluid penetration of the fluoroquinolone agents into the respiratory system, cerebrospinal fluid, prostate and skin, representing the common sites of infection where these agents might be considered. Based on this data, the fluoroquinolones penetrate well into respiratory tissues and fluids with concentrations typically well in excess of that of serum. This excellent penetration accounts for the success of this drug class in the treatment of patients with pneumonias and upper respiratory tract infections.

Penetration into skin and prostatic tissues and fluids results in concentrations similar to that of serum with the exception of ciprofloxacin, which exhibits greater penetration into prostatic tissue than other fluoroquinolones. In contrast, penetration into the cerebrospinal fluid (CSF) is lower for this class of agents with concentrations of 20 to 50% of serum in the absence of inflamed meninges. High dose ciprofloxacin has been used in the treatment of patients with multi-drug resistant Gram-negative meningitis with positive outcomes. However, the effectiveness of monotherapy with a fluoroquinolone under these circumstances depends on the MIC of the organism and the CSF penetration of the particular agent.<sup>[71]</sup> With enhanced activity against Gram-positive organisms and CSF penetration similar to ciprofloxacin, the newer fluoroquinolones would be expected to be effective in the treatment of these infections.

Another means of assessing the activity of antimicrobials in the treatment of infections is to compare their relative penetration into blister fluid. Agents that penetrate well into blister fluid would be expected to exhibit good activity against extracellular organisms. Table IV lists serum and blister fluid concentrations and their ratios. Based on these data, blister fluid concentrations approximate those

**Table III.** Mean fluoroquinolone concentrations in various tissues and body fluids

Reference	Tissue	Dose (mg)	Sampling time (h)	C <sub>s</sub> (mg/L)	C <sub>t</sub> (mg/L)	C <sub>t</sub> : C <sub>s</sub>
<b>Ciprofloxacin</b>						
Wolff et al. <sup>[48]</sup>	CSF (inflammatory)	200 IV <sup>a</sup>	2	1.4	0.6	0.4
	CSF (uninflammatory)	200 IV	NA	1.1	0.3	0.3
Baldwin et al. <sup>[49]</sup>	Bronchial mucosa	500 PO	4.8	1.2	1.8	1.5
	Epithelial lining fluid	500 PO	4.8	1.2	3.0	2.5
	Alveolar macrophages	500 PO	4.8	1.2	13.4	11.2
Honeybourne et al. <sup>[50]</sup>	Bronchial (biopsy)	500 PO <sup>a</sup>	NA	1.9-2	1.2-17.3	1.6
Hopf et al. <sup>[51]</sup>	Lung tissue	200 IV	1	1.1	2.3	2.1
Fraschini et al. <sup>[52]</sup>	Sputum	500 PO	NA	2.3	1.3	0.6
Grabe et al. <sup>[53]</sup>	Prostate (tissue)	500 PO <sup>a</sup>	1-2	1.1	3.3	3.0
Daschner et al. <sup>[54]</sup>	Skin	100 IV	2-3	0.3	0.2	0.7
<b>Gatifloxacin</b>						
Data on file <sup>[7]</sup>	CNS	150-200 PO <sup>a</sup>	NA	NA	NA	0.4
Naber et al. <sup>[55]</sup>	Prostatic fluid	400 PO	NA	1.9	2.1	1.1
<b>Gemifloxacin</b>						
Wise et al. <sup>[56]</sup>	Prostatic fluid	320 PO	4	0.5	0.3	0.6
<b>Levofloxacin</b>						
Ohi et al. <sup>[57]</sup>	CSF (uninflammatory)	200 PO	3	2.3	0.4	0.2
Nagai et al. <sup>[58]</sup>	Bronchoalveolar lavage fluid	200 PO	1-3	2.5	0.2	0.1
Fish and Chow <sup>[59]</sup>	Lung tissue	500 PO	2-3	4.1	7.7	1.9
Nakamori et al. <sup>[60]</sup>	Sputum	200 PO	4	2.7	4.4	1.6
Yamashita et al. <sup>[61]</sup>	Prostate gland	100 PO	1-6	0.9	1.1	1.2
Takahashi et al. <sup>[62]</sup>	Skin	200 PO	0.8-4.0	1.7	1.8	1.1
<b>Moxifloxacin</b>						
Andrews et al. <sup>[63]</sup>	Bronchial mucosa	400 PO	3-24	0.5-3.3	1.0-5.5	1.7
	Epithelial lining fluid	400 PO	3-24	0.5-3.3	3.5-24.4	7.0
	Alveolar macrophage	400 PO	3-24	0.5-3.3	38.6-113.6	
Muller et al. <sup>[64]</sup>	Skin (subcutaneous)	400 IV	0-12	3.7 <sup>b</sup>	1.0 <sup>b</sup>	0.3
<b>Rufloxacin</b>						
Wise et al. <sup>[65,66]</sup>	Bronchial mucosa	400 PO	4-12	3.6-1.2	5.4-2.9	1.7
	Epithelial lining	400 PO	4-12	3.6-1.2	25-6.1	6.7
<b>Sparfloxacin</b>						
Kawahara et al. <sup>[67]</sup>	CSF (uninflammatory)	200 PO	3	0.6	0.2	0.3
Nakatani et al. <sup>[68]</sup>	Sputum	300 PO	2	2.3	4.3	1.9
Takeuchi et al. <sup>[69]</sup>	Prostate (tissue)	200 PO	C <sub>max</sub> <sup>c</sup>	1.1	1.3	1.2
Tanimura et al. <sup>[70]</sup>	Skin	300 PO	2.5-7.5	1.2	1.7	1.4

a Multidose regimen.

b C<sub>max</sub>.

c Tissue sampling at maximum serum concentrations.

C<sub>max</sub> = peak serum drug concentration; C<sub>s</sub> = concentration of serum; CSF = cerebrospinal fluid; C<sub>t</sub> = concentration of tissue; NA = not available.

of serum with the exception of moxifloxacin and gemifloxacin, which are less than half.

### 1.2.1 Protein Binding

The newer fluoroquinolones vary widely with respect to their protein binding characteristics,

ranging from 20 to 80%. Similar to ciprofloxacin, levofloxacin and gatifloxacin are poorly bound to plasma proteins (i.e. 20 to 40%).<sup>[6,59,75,76]</sup> In contrast, moxifloxacin, sparfloxacin, sitafloxacin and rufloxacin bind more avidly to serum proteins (40 to 50%).<sup>[13,15,17-21,39,43,77]</sup> Gemifloxacin also appears

**Table IV.** Mean fluoroquinolone concentrations in blister fluid

Reference	Dose (mg)	Sampling time (h)	C <sub>s</sub> (mg/L)	C <sub>bf</sub> (mg/L)	C <sub>bf</sub> :C <sub>s</sub>
<b>Ciprofloxacin</b>					
LeBel et al. <sup>[2]</sup>	500 PO	6	2.3	1.7	0.7
<b>Gatifloxacin</b>					
Wise et al. <sup>[72]</sup>	400 PO	0-24	4.1 <sup>b</sup>	3.6 <sup>b</sup>	0.9
<b>Gemifloxacin</b>					
Wise et al. <sup>[56]</sup>	320 PO	0-24	2.3	0.7	0.3
<b>Levofloxacin</b>					
Child et al. <sup>[73]</sup>	500 PO <sup>a</sup>	0.5-24	5.0	4.7	0.9
<b>Moxifloxacin</b>					
Muller et al. <sup>[64]</sup>	400 IV	0-12	3.7 <sup>b</sup>	1.7 <sup>b</sup>	0.5
Wise et al. <sup>[74]</sup>	400 PO	0.5-24	4.9	2.6	0.5
<b>Rufloxacin</b>					
Wise et al. <sup>[65]</sup>	400 PO	0-12	4.4 <sup>b</sup>	3.2 <sup>b</sup>	0.7

a Multidose regimen.

b C<sub>max</sub>.

C<sub>max</sub> = peak drug serum concentration; C<sub>bf</sub> = concentrations in blister fluid; C<sub>s</sub> = concentrations in serum.

to be significantly bound with values ranging from 50 to 60%.<sup>[78]</sup> Rufloxacin appears to be the most extensively bound to proteins at 60 to 80%.

The most clinically significant aspect of protein binding involves its role in antimicrobial activity. Since only the unbound drug has activity, the more highly protein bound an antibacterial, the less free drug is available to exert its effect. Therefore, when comparing antimicrobial activity of these agents it is necessary to take protein binding into consideration (see fig. 1).

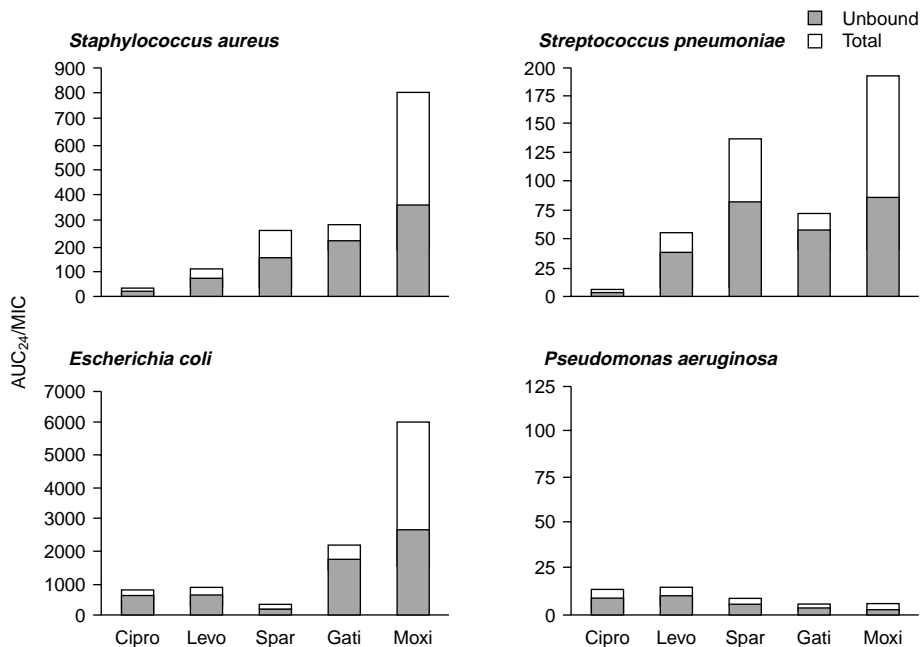
### 1.3 Elimination

All of the newer agents have longer elimination half-lives ( $t_{1/2\beta}$ ) when compared with ciprofloxacin, which contributes to their ability to be administered as a single daily dose (tables I and II). However, the susceptibility of target organisms also predicated dose frequency.

Fluoroquinolones, as a class, may be removed by renal and nonrenal routes of elimination. Nonrenal mechanisms of clearance account for approximately one-third of ciprofloxacin elimination.<sup>[46]</sup> Approximately 15% of a ciprofloxacin dose has been reported to be recovered in the faeces. This is because of elimination through the intestinal mucosa

combined with biliary excretion.<sup>[80]</sup> In addition, 4 separate metabolites of ciprofloxacin have been recovered in the urine and faeces, suggesting hepatic metabolism.<sup>[46]</sup> Two-thirds of a ciprofloxacin dose is eliminated by a combination of glomerular filtration and tubular secretion.<sup>[46]</sup> As a result of the combined clearances, ciprofloxacin has a relatively short  $t_{1/2\beta}$  when compared with other fluoroquinolones. Studies have reported a half-life ranging from between 3 and 5 hours.<sup>[1,3,24,46,80,81]</sup>

Levofloxacin, gatifloxacin and sitafloxacin are cleared predominately by renal elimination with approximately 60 to 80% of the dose recovered unchanged in the urine.<sup>[1,6,7,11,18,33,59,76,82]</sup> The renal clearance of levofloxacin is approximately 60% greater than creatinine clearance, suggesting elimination by both glomerular filtration and tubular secretion.<sup>[83]</sup> This was proven by a 24 to 35% decrease in renal clearance following doses of either probenecid or cimetidine, which inhibit renal tubular secretion.<sup>[10]</sup> Only 5% of a levofloxacin dose has been recovered in the urine as 3 metabolites over a 24-hour period.<sup>[59]</sup> Gatifloxacin is also converted into 4 metabolites and excreted in the urine in minimal amounts.<sup>[6]</sup> Cumulative faecal recovery of unchanged gatifloxacin and sitafloxacin



**Fig. 1.** Comparative pharmacodynamic activity of the newer fluoroquinolones against common pathogens. **AUC<sub>24</sub>** = area under the concentration-time curve over 24 hours; **Cipro** = ciprofloxacin; **Gati** = gatifloxacin; **Levo** = levofloxacin; **MIC** = minimum inhibitory concentration **Moxi** = moxifloxacin; **Spar** = sparfloxacin.<sup>[79]</sup>

are approximately 5%.<sup>[6,18]</sup> At the usual therapeutic doses, the reported mean values for  $t_{1/2\beta}$  range from 6 to 8 hours for levofloxacin and gatifloxacin, and nearly 5 hours for sitafloxacin.<sup>[1,6,11,12,16,18,33,59,76,84]</sup>

In contrast, moxifloxacin and sparfloxacin exhibit very little renal elimination. After a single oral dose, only 10 to 14% of a sparfloxacin dose and 20% of a moxifloxacin dose were recovered in the urine unchanged.<sup>[1,15,19,85]</sup> Renal clearance of moxifloxacin is lower than creatinine clearance, suggesting tubular reabsorption.<sup>[39]</sup> Up to 35% of the glucuronide metabolite of sparfloxacin was recovered in the urine, suggesting extensive metabolic biotransformation.<sup>[20,86]</sup> Similarly, 50% of a moxifloxacin dose is recovered in the urine and faeces as two primary metabolites, *N*-sulfate and acyl glucuronide.<sup>[15]</sup> Despite the large percentage of metabolism by the liver, moxifloxacin does not appear to be transformed by the cytochrome P450 (CYP) isoenzyme system, making it less susceptible to drug-drug interactions.<sup>[15,37]</sup> In addition, 50

to 56% of sparfloxacin and 25% of a moxifloxacin dose was recovered as unchanged drug in the faeces after a single oral dose. This represented partially unabsorbed drug, combined with biliary excretion of unchanged drug.<sup>[19,85]</sup> Sparfloxacin and moxifloxacin have relatively prolonged  $t_{1/2\beta}$  ranging from 15 to 24 hours for sparfloxacin and 9 to 15 hours for moxifloxacin following single oral doses.<sup>[13-15,19,20,22,37,85,87]</sup>

Similar to ciprofloxacin, the elimination of rufloxacin and gemifloxacin occurs through a combination of renal and nonrenal mechanisms. Approximately 21 to 53% of single doses of rufloxacin and 25 to 40% of gemifloxacin are excreted unchanged in the urine.<sup>[8,17,41,65]</sup> Renal clearance of gemifloxacin exceeds glomerular filtration, suggesting some degree of active tubular secretion. Only about 1% of rufloxacin is recovered in the bile 72 hours after the dose, and only 2% of the *N*-desmethyl metabolite is recovered in the plasma and bile.<sup>[41]</sup> However, the metabolic fate of the remaining portion is

currently unknown. The  $t_{1/2\beta}$  of rifloxacin and gemifloxacin is 28 and 7 hours, respectively.<sup>[8,16,17,28,42,65]</sup>

## 2. Interactions

### 2.1 Drug-Drug Interactions

Some of the drug interactions associated with ciprofloxacin can also occur with the newer agents, but typically to a lesser extent (table V). The formation of insoluble quinolone-multivalent cation chelates in the GI tract appears to occur with all agents in this class, resulting in significant decreases in bioavailability.<sup>[46,118]</sup> Concomitant oral administration of magnesium-, aluminum- and calcium-containing antacids and sucralfate have been reported to reduce ciprofloxacin bioavailability to 15%.<sup>[88-90]</sup> The newer agents are also affected by this interaction but typically to a lesser degree

(table V). The extent of the interaction diminishes when the interacting agent is administered at least 2 hours after the fluoroquinolone.<sup>[46,89,118]</sup>

In addition, studies have shown that concurrent administration of oral iron preparations and multivitamins with zinc have exhibited similar interactions with ciprofloxacin and newer agents such as levofloxacin, gatifloxacin, gemifloxacin and moxifloxacin.<sup>[31,76,91,95,96,100,104,105,107]</sup> H<sub>2</sub>-receptor antagonists, however, do not affect the absorption of newer fluoroquinolones.<sup>[75,104]</sup>

Interactions via the elimination or metabolic pathways have been reported with probenecid, cimetidine and theophylline. Ciprofloxacin and the newer fluoroquinolones do not interact significantly with H<sub>2</sub>-blockers, such as cimetidine or ranitidine, which can inhibit the CYP isoenzymes as well as increasing gastric pH.<sup>[119]</sup> Coadministra-

**Table V.** Pharmacokinetic drug interactions with the newer fluoroquinolones

Drug	Al <sup>+++</sup> /Mg <sup>++</sup> Antacids	Fe <sup>++</sup>	Sucralfate	Ca <sup>++</sup>	Probenecid	Theophylline	Warfarin	References
Ciprofloxacin	↓77-85F% <sup>a</sup>	↓AUC57% <sup>e</sup>	↓96%F <sup>e</sup> , ↓17%F <sup>a</sup>	↓40%F <sup>b</sup>	↓CL <sub>R</sub>	↓CL 30-113%	↑PT <sup>c</sup>	88-94
Gatifloxacin	↓64%AUC <sup>e</sup> ↓42%AUC <sup>f</sup> ↓18%AUC <sup>g</sup>	↓35%AUC <sup>e</sup>	Unknown	NE <sup>f,g</sup>	↑42%AUC	NE	NE	95-99
Gemifloxacin	↓85%AUC <sup>e</sup> ↑3%AUC <sup>f</sup> ↓15%AUC <sup>h</sup>	↓11%AUC <sup>i</sup>	↓53%AUC <sup>i</sup>	↓20%	Unknown	NE	NE	78, 100-103
Levofloxacin	↓56-78%F <sup>e</sup>	↓81%F <sup>e</sup>	NE <sup>g</sup>	NE	↓28% CL <sub>R</sub>	↓CL 2-17%	NE	104-106
Moxifloxacin	↓45%F <sup>a</sup>	↓39%AUC	Unknown	NE <sup>d</sup>	NE	NE	NE	107-111
Rufloxacin	Unknown	Unknown	Unknown	Unknown	Unknown	NE	Unknown	112
Sitafloxacin	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	
Sparfloxacin	↓23%AUC <sup>f</sup> ↓17%AUC <sup>g</sup> ↓5%AUC <sup>h</sup>	Unknown	↓44%F <sup>e</sup>	Unknown	NE	NE	NE	113-117

a 2 hours before or after dose.

b Relative bioavailability.

c Prothrombin time.

d With dairy products.

e Concomitant administration.

f 2 hours before dose.

g 2 hours after dose.

h >2 hour after dose.

i 3 hours before dose.

**AUC** = area under the concentration-time curve; **CL** = total body clearance; **CL<sub>R</sub>** = renal clearance; **F** = bioavailability; **NE** = no effect; **PT<sup>c</sup>** = prothrombin time.

tion with probenecid results in prolongation of the half-life for agents with significant renal elimination such as gatifloxacin, levofloxacin and ciprofloxacin, because of a competitive inhibition of the tubular secretion of these drugs.<sup>[120]</sup> Ciprofloxacin has been shown to inhibit the hepatic metabolism of coadministered methylxanthines, such as theophylline, through inhibition of CYP1A2.<sup>[45]</sup> However, negligible or no effect on theophylline metabolism has been noted for levofloxacin, sparfloxacin, gatifloxacin, gemifloxacin, moxifloxacin and rufloxacin.<sup>[97,98,101,108,112-114,121,122]</sup> Data on the interactions with sitafloxacin are currently unknown. Additionally, other case reports have documented ciprofloxacin-associated increases in prothrombin times in patients concurrently receiving warfarin;<sup>[92]</sup> no such effect was noted for levofloxacin, gatifloxacin, gemifloxacin or moxifloxacin.<sup>[37,102,106,123]</sup>

The lack of effect for the newer agents on theophylline and warfarin metabolism can be explained by the fact these agents do not depend on the CYP system for biotransformation, thus decreasing the probability of significant drug interactions with this enzyme system.<sup>[39]</sup>

## 2.2 Drug-Food Interactions

As a class, fluoroquinolones are not significantly affected by coadministration with food. Most studies have shown that the newer fluoroquinolones have slightly delayed  $t_{max}$  and lower  $C_{max}$  values, but overall the AUC and bioavailability is not clinically altered.<sup>[124]</sup>

Data from several studies investigating the effects of different enteral feeding supplements on the bioavailability of ciprofloxacin demonstrate mixed results. Three studies have shown that various enteral products can decrease ciprofloxacin  $C_{max}$  by 26 to 47% and AUC by 58 to 73%.<sup>[125-127]</sup> However, one study in 6 healthy volunteers found no statistically significant changes in AUC,  $C_{max}$  and  $t_{max}$  when ciprofloxacin was administered with enteral feeding.<sup>[128]</sup> The apparent discrepancy in results may be due to differing cation concentrations in the various enteral formulations. Whether

the same can be expected in critically ill patients is uncertain since these patients often have residual feedings which allow for a longer time for a physical interaction to occur in the GI tract. The potential interaction between enteral feeds and the newer fluoroquinolone agents has not been well studied.

## 3. Special Populations

### 3.1 Patients with Renal Impairment

As discussed in section 1.3, a number of the fluoroquinolones are eliminated predominantly by renal clearance mechanisms and will, therefore, have altered pharmacokinetics in the presence of renal impairment (table VI). Dosage adjustment guidelines according to the degree of renal insufficiency are summarised in table VII. The large  $V_d$  and relatively high intrinsic clearance of the fluoroquinolones mean that their removal during haemodialysis or peritoneal dialysis is not significant. Thus, no supplemental doses are necessary following these procedures.<sup>[129-131,133-136]</sup>

Ciprofloxacin, gemifloxacin and rufloxacin are eliminated by renal and extrarenal routes; therefore, significant accumulation does not occur until renal function is severely impaired (creatinine clearance  $<20$  to  $30$  ml/min).<sup>[132,135,139]</sup> Levofloxacin, sitafloxacin and gatifloxacin are primarily eliminated through renal mechanisms. As expected, clearance decreases and half-life increases as the degree of renal impairment increases for both levofloxacin and gatifloxacin. Data on the pharmacokinetics of sitafloxacin in renal disease are currently limited; however, since it is primarily excreted unchanged in the urine, it is most likely to require dosage reduction in patients with renal disease.

In contrast, dosage reduction for renal insufficiency is not currently indicated for either moxifloxacin or sparfloxacin since both drugs are cleared primarily by nonrenal mechanisms.<sup>[134,140]</sup> However, data from individual pharmacokinetic studies in patients with renal dysfunction have led to recommendations for dosage adjustment by various authors (table VII).

**Table VI.** Pharmacokinetics of selected fluoroquinolones in patients with renal impairment

Reference	Dose (mg)	CL <sub>CR</sub>	C <sub>max</sub> (mg/L)	t <sub>1/2β</sub> (h)	AUC <sub>24</sub> (mg/L • h)
<b>Ciprofloxacin</b>					
Drusano et al. <sup>[129]</sup>	200 IV	>100 ml/min/1.73m <sup>2</sup>	6.3 ± 1.8	4.3 ± 0.8	7.4 <sup>a</sup>
		60-99 ml/min/1.73m <sup>2</sup>	4.1 ± 1.1	6.1 ± 1.6	7.6 <sup>a</sup>
		10-59 ml/min/1.73m <sup>2</sup>	5.4 ± 0.8	7.7 ± 1.2	13.3 <sup>a</sup>
		<10 ml/min/1.73m <sup>2</sup>	5.4 ± 1.6	8.5 ± 3.3	12.9
Boelaert et al. <sup>[130]</sup>	250 PO	>60 ml/min/1.73m <sup>2</sup>	1.5 ± 0.2	4.4 ± 0.2	6.9 ± 0.9
		<20 ml/min/1.73m <sup>2</sup>	1.7 ± 0.4	8.7 ± 0.9	14.3 ± 3.4
		ESRD	2.1 ± 0.2	5.8 ± 0.9	15.8 ± 1.9
<b>Gatifloxacin</b>					
Kawada et al. <sup>[131]</sup>	100 PO	60-90 ml/min		8.9	13.2
		30-59 ml/min		16.5	20.6
		10-29 ml/min		29.6	47.9
<b>Gemifloxacin</b>					
Allen et al. <sup>[132]</sup>	160 PO	>100 ml/min	0.7 ± 0.3	6.7 ± 1.2	3.2 ± 0.8
		<20 ml/min	0.6 ± 0.3	14 ± 4.6	6.2 ± 3.5
		ESRD	0.7 ± 0.3	14 ± 3.2	6.8 ± 1.9
<b>Levofloxacin</b>					
Gisclon et al. <sup>[133]</sup>	500 PO	50-80 ml/min	7.8 ± 1.8	9 ± 0.9	96 ± 12
		20-49 ml/min	7.1 ± 3.1	27 ± 10	182 ± 63
		10-19 ml/min	8.2 ± 2.6	35 ± 5	263 ± 72
		Hemodialysis	5.7 ± 1.0	76 ± 41	NA
		CAPD	6.9 ± 2.3	51 ± 24	NA
<b>Moxifloxacin</b>					
Stass et al. <sup>[134]</sup>	400 PO	>90 ml/min/1.73m <sup>2</sup>	4.4 ± 1.4	14.9 ± 1.5	43.4 <sup>b</sup> ± 1.4
		60-89 ml/min/1.73m <sup>2</sup>	4.9 ± 1.3	15.1 ± 1.1	40.1 <sup>b</sup> ± 1.3
		30-59 ml/min/1.73m <sup>2</sup>	3.4 ± 1.5	16.2 ± 1.2	35.8 <sup>b</sup> ± 1.4
		<30 ml/min/1.73m <sup>2</sup>	3.1 ± 1.1	14.5 ± 1.2	44.0 <sup>b</sup> ± 1.3
<b>Rufloxacin</b>					
Perry et al. <sup>[135]</sup>	400 PO	>80 ml/min	4.3 ± 0.4	29.8 ± 3.2	154 <sup>c</sup> ± 10
		30-80 ml/min	4.6 ± 0.4	36.4 ± 4.9	199 <sup>c</sup> ± 13
		8-29 ml/min	4.3 ± 0.4	43.5 ± 2.9	243 <sup>c</sup> ± 26
		<8 ml/min <sup>c</sup>	6.8 ± 0.3	26.6 ± 3.9	219 <sup>c</sup> ± 34
<b>Sparfloxacin</b>					
Dorr et al. <sup>[136]</sup>	200 <sup>d</sup>	≥50 ml/min/1.73m <sup>2</sup>	0.8	18.7	11.5 <sup>e</sup>
		30-49 ml/min/1.73m <sup>2</sup>	1.5	27.7	25.4 <sup>e</sup>
		10-29 ml/min/1.73m <sup>2</sup>	0.8	20.4	19.2 <sup>e</sup>

a Normalised AUC/1.73m<sup>2</sup>.b AUC<sub>96</sub>.c AUC<sub>∞</sub>.

d Multiple dosages.

e AUC<sub>24</sub>.

**AUC<sub>t</sub>** = area under the concentration-time curve to time *t*; **CAPD** = continuous ambulatory preitoneal dialysis; **CL<sub>CR</sub>** = creatinine clearance; **C<sub>max</sub>** = peak serum drug concentration; **ESRD** = end-stage renal disease; **IV** = intravenous; **PO** = orally; **t<sub>1/2β</sub>** = elimination half-life.

### 3.2 Patients with Hepatic Disease

Similar to alterations in renal function, changes in hepatic function can potentially affect the dos-

age adjustments of fluoroquinolones, particularly those agents with significant nonrenal clearance mechanisms. Since only one-third of a ciprofloxacin dose is eliminated by nonrenal mechanisms, as

**Table VII.** Suggested dosage adjustments for patients with renal dysfunction

Drug	CL <sub>CR</sub> (ml/min)	Suggested dose
Ciprofloxacin <sup>[46]</sup>	>30	250-500mg q12h PO 200-400mg q12h IV
	<30	250mg q12h PO 200mg q12h IV
Gatifloxacin <sup>[137]</sup>	>30	400mg PO q24h
	<30	400mg load, 200mg q24h
Gemifloxacin <sup>[132]</sup>	>100	320mg PO q24h
	<20	160mg PO q24h
Levofloxacin <sup>[59]</sup>	>50	250-500mg PO/IV q24h
	20-49	500mg load, 250mg PO/IV q24h
	10-19	500mg load, 250mg PO/IV q48h
	<10	500mg load, 250mg PO/IV q48h
Moxifloxacin <sup>[134,138]</sup>	No dosage adjustment required	400mg q24h
Rufloxacin <sup>[135]</sup>	>30 ml/min/1.73m <sup>2</sup>	400mg load, 200mg q24h
	<30 ml/min/1.73m <sup>2</sup>	400mg load, 200mg q48h
Sparfloxacin <sup>[136]</sup>	>30 ml/min/1.73m <sup>2</sup>	400mg load, 200mg q24h
	<30 ml/min/1.73m <sup>2</sup>	400mg load, 200mg q48h

CL<sub>CR</sub> = creatinine clearance; IV = intravenously; PO = orally; q<sub>xh</sub> = every x hours.

expected, studies have not demonstrated any clinically significant alterations in ciprofloxacin pharmacokinetics in patients with cirrhosis when compared with healthy controls.<sup>[129]</sup> Thus, dosage adjustments are not necessary.<sup>[46]</sup>

In patients with mild to moderately impaired hepatic function, moxifloxacin exposure was approximately 23% higher when compared with healthy volunteers. The results, though statistically significant, did not appear clinically significant enough to warrant dose adjustments in patients with mild to moderate hepatic dysfunction.<sup>[138]</sup> Like moxifloxacin, sparfloxacin is primarily eliminated by nonrenal mechanisms. However, data thus far have not demonstrated significant changes in the presence of hepatic disease.<sup>[141]</sup> Thus, no dosage adjustments are currently recommended.

No significant alternations in the pharmacokinetics would be expected for levofloxacin or gatifloxacin in patients with hepatic dysfunction since these agents are predominately cleared renally. The pharmacokinetics of gatifloxacin were studied in 8 patients with moderate hepatic impairment. After a single oral dose of 400mg, C<sub>max</sub> and AUC values were 32% and 23% greater than that of healthy volunteers, respectively.<sup>[142]</sup> The manufacturer, however, recommends that no dosage adjustment is necessary in patients with moderate hepatic dysfunction.<sup>[7]</sup>

Data on rufloxacin and sitafloxacin are limited. However, dosage adjustments in hepatic dysfunction are not likely to be required as both drugs have other routes of elimination.

### 3.3 Other Populations

Studies of fluoroquinolone agents in the elderly have not demonstrated any clinically significant changes in pharmacokinetic parameters such as AUC, clearance and C<sub>max</sub>.<sup>[9,37,43,46,59,76,87,138,143]</sup>

The pharmacokinetics of drugs in patients may differ from that of controls because of the impact of their underlying disease state. In a study of patients with burns, ciprofloxacin clearance was increased in burn victims compared with controls.<sup>[144]</sup> However, the pharmacokinetics of gatifloxacin were not shown to be significantly different in patients with acute exacerbations of chronic bronchitis, compared with healthy controls.<sup>[145]</sup> Many of the newer fluoroquinolones have not yet been sufficiently studied in special populations.

## 4. Pharmacodynamics

Because of the differences in the pharmacokinetics and antimicrobial susceptibility between various fluoroquinolone agents, a pharmacodynamic comparison incorporating the variability in both of these factors has been proposed to determine the antimicrobial spectrum of activity of these agents. Several surrogate markers exist for assessing the clinical and microbiological efficacy of an antimicrobial agent. Markers such as time above the minimum inhibitory concentration (t>MIC), the

peak serum concentration-to-MIC ratio ( $C_{\max}/\text{MIC}$ ) and the ratio of the AUC to the MIC (AUC/MIC) explain the specific relationships between the pharmacokinetic and the pharmacodynamic interactions between the antibacterial and the infecting organism.<sup>[146]</sup> For antimicrobials such as  $\beta$ -lactams and glycopeptides, the  $t > \text{MIC}$  is the most important pharmacokinetic-pharmacodynamic marker as these drug classes exhibit time-dependent bactericidal activity.<sup>[146]</sup>

In contrast, aminoglycosides and fluoroquinolones exhibit concentration-dependent bactericidal activity. For this reason,  $C_{\max}/\text{MIC}$  and AUC/MIC appear to be the more important surrogate markers when attempting to optimise therapy.<sup>[146]</sup>

Forrest et al.<sup>[147]</sup> examined the pharmacodynamics of intravenous ciprofloxacin in 64 patients with nosocomial pneumonia. Analysis of the data revealed that AUC/MIC values were highly predictive of microbiological and clinical cures. Only 26% of patients with AUC/MIC values of  $<125$  achieved microbiological eradication, compared with 82% of patients with an AUC/MIC of  $>125$ . Clinically, 42% of patients with an AUC/MIC  $<125$  achieved clinical cures, when compared with a cure rate of 80% in patients with an AUC/MIC of  $>125$ .<sup>[147]</sup> Based on these data, a target AUC/MIC of  $>125$  has been suggested as the pharmacokinetic-pharmacodynamic goal in all patients for whom ciprofloxacin is prescribed for the treatment of pneumonia.<sup>[148]</sup>

As recommended by these investigators,<sup>[148]</sup> in patients with marginally-susceptible organisms causing severe infections (i.e. *Pseudomonas aeruginosa*) the use of ciprofloxacin every 8 hours should be considered. If the target AUC/MIC ratio cannot be achieved, consideration should be given to changing to another agent. Alternatively, combining with an agent from another class (e.g.  $\beta$ -lactams) may provide additive or synergistic effects.

The AUC/MIC can also be used to evaluate the probability of developing resistance to antimicrobial therapy. Thomas et al.<sup>[149]</sup> attempted to determine which surrogate marker best correlated with the development of bacterial resistance. Data from 107 patients with nosocomial pneumonias were

retrieved and analysed. Results showed that approximately 50% of isolated organisms acquired resistance within 4 days of initiating therapy when AUC/MIC was  $<100$ , regardless of the antimicrobial therapy used. AUC/MIC values of  $>100$ , on the other hand, were associated with an absence of antimicrobial resistance.<sup>[149]</sup> The analysis also demonstrated that, within the first 24 hours of therapy, a high AUC/MIC must be achieved for effective killing of the organisms to occur. Lower AUC/MIC ratios of 30 to 50 have been shown, however, to eradicate strains of *Streptococcus pneumoniae* without the development of resistance, both *in vitro* and in patients with community-acquired pneumonias.<sup>[150,151]</sup> It is, therefore, important to note that the AUC/MIC goals reflect a specific antibacterial against a specific organism. It would be inappropriate to extrapolate these goals to other antibacterial-organism combinations without confirming data.

The  $C_{\max}/\text{MIC}$  ratio also appears to correlate well with fluoroquinolone efficacy. Preston et al.<sup>[152]</sup> examined the probabilities of successful outcomes for levofloxacin at 3 different sites of infection. They found that the probabilities of clinical cure were dependent upon achievement of specific  $C_{\max}/\text{MIC}$  break-points which differed depending on the infectious site (e.g. skin and soft tissue, pulmonary, urinary tract).<sup>[152]</sup> For example, at a break-point of 12.2, there was almost a 100% probability of a urinary tract infection being cured. At the same break-point, pulmonary infections and skin and soft tissue infections had approximately a 93 and 80% probability of clinical cure, respectively.<sup>[152]</sup> These data demonstrates that the choice of a goal  $C_{\max}/\text{MIC}$  is dependent on the site of infection, as well as the clinician's definition of an acceptable failure rate.

The apparent discrepancy in terms of which pharmacodynamic indices (e.g.  $C_{\max}/\text{MIC}$  or AUC/MIC) are most predictive of clinical and microbiological outcomes is due in part to the fact that these indices are interrelated. Secondly, differences in the susceptibility of the infecting organism and site of infection between studies probably affect the

probability of achieving the desired pharmacodynamic goal. In the study by Preston et al.,<sup>[152]</sup> patients primarily had community-acquired infections with relatively susceptible organisms. The optimal  $C_{\max}/MIC$  ratio was more likely to be achieved when compared with the patients in the study by Forrest et al.<sup>[147]</sup> which included predominantly nosocomial acquired infections with less susceptible organisms. Therefore, it is possible that if the optimal  $C_{\max}/MIC$  ratio is not achieved ( $>10$ ), then the AUC/MIC ratio is the most predictive of clinical and microbiological outcomes.<sup>[152]</sup>

## 5. Discussion

A pharmacodynamic comparison of fluoroquinolone antibacterials takes into consideration both pharmacokinetic variability and antimicrobial susceptibility. When compared with ciprofloxacin, the newer fluoroquinolones generally retain wide distribution characteristics but longer half-lives which, combined with post-antibacterial effect, enables single daily administration. Based on the lower  $MIC_{90}$  values for Gram-positive organisms (i.e. *S. pneumoniae*) and improved pharmacokinetics, the newer quinolones are expected to provide a superior pharmacodynamic profile when compared with ciprofloxacin against these pathogens. This relationship is depicted in figure 1 which summarises the estimated  $AUC_{24}/MICs$  of 5 fluoroquinolones for selected pathogens.

Pickerill et al.<sup>[79]</sup> reported these values by using manufacturer suggested doses for each fluoroquinolone, combined with the population pharmacokinetic parameters and median  $MIC_{90}$  values for the selected pathogens. Based on these data, the strength of the new fluoroquinolones lies in their enhanced Gram-positive activity. Levofloxacin, sparfloxacin, gatifloxacin and moxifloxacin all have significantly greater activity against both *Staphylococcus aureus* and *S. pneumoniae* when compared with ciprofloxacin. While moxifloxacin appears to have the greatest activity against these organisms, its activity is similar to that of sparfloxacin and gatifloxacin when protein binding is taken into consideration.

Monte Carlo simulation has also been utilised to compare the relative activity of the fluoroquinolone agents against *S. pneumoniae*.<sup>[153]</sup> This technique takes pharmacokinetic variability and MICs into consideration, thus providing more information on the relative activity of the agents than single point estimates (i.e. median AUC and MIC values of each agent). All agents appear to have excellent activity against *Escherichia coli*, while none have sufficient activity against *P. aeruginosa*, indicating the need for higher doses and/or the addition of other agents in treating serious infections involving this organism. In addition, the newer agents appear to have enhanced activity against anaerobes compared with ciprofloxacin; however, the clinical significance is unknown.

Achievement of specific threshold values for the pharmacodynamic indices (i.e.  $C_{\max}/MIC > 10$  or  $AUC/MIC > 125$ ) are predictive of clinical and microbiological outcomes for ciprofloxacin in the treatment of lower respiratory tract infections and levofloxacin in the treatment of various community-acquired infections (i.e. respiratory tract, urinary tract and skin/skin structure infections). In addition, failure to achieve these goals has been shown to increase the likelihood for development of resistance to ciprofloxacin. Whether these goals hold true for the newer fluoroquinolones as well as in the treatment of infections involving other organisms (e.g. anaerobes) and other sites of infection requires further studies.

A potential role for therapeutic drug monitoring of the newer fluoroquinolones exists in the future as more data to delineate the pharmacodynamic relationships become available. As described in section 4, the microbiological and clinical outcomes with these agents appear to be linked to maximising the  $C_{\max}/MIC$  or AUC/MIC ratio. In order to achieve these goals, the correct dose of the drug needs to be administered to the patient at the appropriate interval. Although routine measurement of fluoroquinolone concentrations is currently impractical, they can be used to optimise therapy in selective situations (i.e. patients with nosocomial-acquired pneumonia, burns, meningitis).

Over the past decade, a number of pharmacokinetic tools, such as optimal sampling, population pharmacokinetic modelling and maximum a posteriori probability (MAP)-Bayesian modelling have provided the resources necessary to enable practitioners to control drug exposure in individual patients with the goal of achieving a more predictable therapeutic response.<sup>[152,154]</sup>

In order to use these tools, a compartmental pharmacokinetic model is necessary to describe the absorption, distribution, metabolism and elimination processes utilising pharmacokinetic parameters. The majority of the studies conducted to date evaluating the pharmacokinetics of fluoroquinolones have utilised noncompartmental analysis; however, a few compartmental pharmacokinetic analyses have been performed. The results of these studies indicate that the pharmacokinetics of ciprofloxacin, levofloxacin, moxifloxacin, sparfloxacin and gatifloxacin can best be described using a 2-compartmental model.<sup>[6,13,152,155]</sup>

Population-pharmacokinetic analysis programs such as NPEM (nonparametric expectation maximisation), NONMEM (nonlinear mixed effects modelling), NPML (nonparametric maximum likelihood) and IT2B (iterative 2-stage Bayesian) approaches provide powerful tools to perform compartmental pharmacokinetic analysis even with sparse sampling.<sup>[154]</sup>

Using an iterative IT2B approach, Forrest et al.<sup>[155]</sup> developed a model for individualising ciprofloxacin dosage to achieve the desired AUC/MIC ratio based on an estimate of the patient's creatinine clearance and the MIC. In selected patients in whom assurance of the optimal drug exposure is critical, obtaining appropriately timed serum drug concentrations may be beneficial. The optimal sampling strategy for serum concentrations has been examined by Forrest et al.<sup>[155]</sup> for ciprofloxacin in 74 patients following intravenous doses of 200, 300 or 400mg. The results indicate that 3 well-timed samples (at 15 to 30 minutes and 2.5 hours after the dose, and a trough concentration) provide accurate and precise estimates of clearance and  $V_d$ .<sup>[155]</sup> Analysis of these serum concentrations

using MAP-Bayesian software programs provides precise control of drug exposure designed to achieve specific pharmacodynamic end-points (i.e. specific AUC/MIC ratios).

Additional studies are necessary to more clearly define the pharmacodynamic relationships with the newer fluoroquinolone agents and to determine the outcomes associated with their clinical application. Prospective concentration-controlled trials are needed to compare outcomes between traditional fixed versus individualised dosage regimens.

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