REVIEW ARTICLE

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Pharmacokinetics and Pharmacodynamics of Fluoroquinolones

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Abstract

The fluoroquinolones have moderate to excellent bioavailability, moderate to long elimination half-lives (50 to 98%) and volumes of distribution >1.5 L/kg. There is considerable variation in elimination pattern between fluoroquinolone agents, ranging from predominant renal excretion to extensive hepatic metabolism. Protein binding also varies between agents. Tissue concentrations often exceed plasma concentrations, while concentrations in CSF are modest in the presence of inflammation. Fluoroquinolones show concentration-dependent killing *in vitro*, and animal models have demonstrated the 24-hour AUC/MIC (area under the concentration-time curve/minimum inhibitory concentration) ratio to be the best predictor of bacterial killing *in vivo*, with the peak plasma concentration (C_{max})/MIC ratio being important for some bacteria, to prevent the emergence of resistance during treatment. Animal models and human studies with ciprofloxacin, grepafloxacin and levofloxacin show that a 24-hour AUC/MIC ratio of about 100, or a C_{max}/MIC ratio of about 10 gives maximum clinical and bacteriological efficacy. These values can be used to predict the efficacy of different agents against different pathogens, and to define pharmacodynamic 'breakpoints'.

1. Pharmacokinetics

1.1 Common Features

The pharmacokinetic features of fluoroquinolones have been summarised in recent times.[1] They have moderate to excellent oral absorption and bioavailability, which are only marginally affected by food. Absorption is generally rapid, with peak plasma concentrations (C_{max}) achieved within 1 to 2 hours (table I). Absorption is reduced by divalent cations, including Al^{+++}, Mg^{++}, Ca^{++} and Fe^{++}, that are frequently found in antacids and other medications, as well as in dairy products.[13] Most drugs have moderate clearance and elimination half-lives (4 to 10 hours) while volumes of distribution exceed 1.5 L/kg, consistent with significant distribution into tissues and cells.

1.2 Variable Features

The predominant route of elimination varies widely between fluoroquinolones. Ofloxacin and its *l*-isomer, levofloxacin, lomefloxacin, rufloxacin and gatifloxacin have predominant renal excretion and minimal metabolism (<10%). In contrast nalidixic acid, pefloxacin, sparfloxacin and grepafloxacin undergo extensive hepatic metabolism (>35%). The other drugs undergo modest metabolism but have significant levels of renal excretion as well.

Protein binding also varies to some extent, with norfloxacin, lomefloxacin and gatifloxacin having the lowest, and clinafloxacin, rufloxacin and trovafloxacin the highest, degree of binding.

1.3 Tissue Penetration

For most fluoroquinolones, tissue concentrations are usually higher than plasma concentrations. This tissue penetration is not related to lipid solubility. In contrast, fluoroquinolones have relatively poor CSF penetration into uninflamed meninges, but at least 4 agents – ciprofloxacin, pefloxacin, ofloxacin and trovafloxacin – are known to penetrate to a moderate extent in the presence of inflammation.[1]

Table I. Pharmacokinetic properties of fluoroquinolones

Agent	Usual dosage schedule	% Oral bioavailability[a]	C_{max} (mg/L)[b]	$t_{½β}$ (h)	AUC_{24} (mg/L • h)[c]	Volume of distribution (L/kg)[d]	Protein binding (%)	% Metabolised[a,e]	Reference
Balofloxacin	200mg daily	NA	2.2	7.8	17.1	2.0	NA	NA	2
Ciprofloxacin	500mg bid	70-85	2.5	4.0	25.8	3.4	35	10	3
Ciprofloxacin	750mg bid	70-85	3.3	4.2	35.2	3.7	35	10	3
Clinafloxacin	200mg daily	80-98	1.3	5.7	9.9	2.1	50-60	NA	4
Difloxacin	400mg daily	NA	4.1	27.1	165.6	8.0	42	20	5
Enoxacin	400mg bid	90	2.7	5.2	32.2	2.7	43	15	6
Fleroxacin	400mg daily	96	5.1	9.2	59.6	1.3	23	10	7
Gatifloxacin	400mg daily	NA	3.4	8.4	32.4	2.2	20	<1	8
Grepafloxacin	400mg daily	90	0.9	11.7	11.4	7.5	50	60	9
Grepafloxacin	600mg daily	90	1.4	12.7	19.8	7.0	50	60	9
Levofloxacin	500mg daily	85-95	5.2	7.4	61.1	1.5	24-38	5	10
Lomefloxacin	400mg daily	95	2.9	6.7	24.9	2.1	10	5-8	11
Moxifloxacin	400mg daily	86	2.5	13.1	26.9	3.5	30-45	10	12
Norfloxacin	400mg bid	80	1.3	5.1	14.8	6.1	15	10-20	13,14
Ofloxacin	200mg bid	85-95	2.2	5.6	29.2	1.6	8-30	5-10	17
Ofloxacin	400mg bid	85-95	4.5	4.6	55.3	1.3	8-30	5-10	18
Pefloxacin	400mg bid	83	5.1	10.6	113.0	1.5	25	55-85	15
Rufloxacin	400mg daily	50	4.3	29.8	154.0	1.6	60	2-4	16
Sitafloxacin	100mg bid	NA	1.0	5.0	11.1	2.0	NA	NA	19
Sparfloxacin	400mg loading, 200mg daily	40-60	0.6	3.8	16.4	8.3	45	40	20
Tosufloxacin	102mg tid[f]	NA	0.4	2.3	8.4	2.3	NA	NA	21
Trovafloxacin	200mg daily	70-90	2.2	11.3	30.4	1.4	70	>11	22

a From Bergen.[1]

b For first dose.

c AUC_{24} at steady state calculated as equivalent to AUC_{∞} for single dose multiplied by number of daily doses.

d Vd calculated from other data by formula: $Vd = dose \bullet t_{½}/Ln(2)/AUC_{\infty}$.

e As estimated by percentage of metabolites excreted in urine.

f As tosufloxacin tosilate 150mg.

AUC_{24} = area under the concentration-time curve from 0 to 24 hours postdose; **C_{max}** = maximum plasma concentrations; **bid** = twice daily; **NA** = data not available; **$t_{½β}$** = elimination half-life; **tid** = 3 times daily.

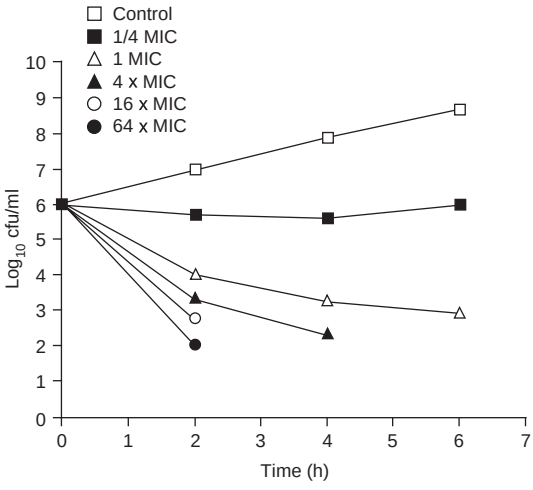

Fig. 1. Killing curves for ciprofloxacin at increasing concentrations against *Pseudomonas aeruginosa*. **cfu** = colony forming units; **MIC** = minimum inhibitory concentration.[23]

2. Pharmacodynamics

2.1 *In Vitro*

The key pharmacodynamic features of fluoroquinolones are similar to those of aminoglycosides and include concentration-dependent killing (fig. 1) and a moderate postantibiotic effect.[23] They also share with aminoglycosides the propensity to select for resistant mutants, especially in *Pseudomonas aeruginosa*, a property that has been well characterised in an *in vitro* pharmacodynamic model.[24] In this model, bacteria are exposed to the same pharmacokinetic profile of changing drug concentrations as found *in vivo*. This is shown in figure 2, with the demonstration of a significant increase in the concentration required to achieve a 50% reduction of bacterial numbers at 24 hours versus at 4 hours. The pharmacodynamic model has also demonstrated that optimum eradication requires C_{max}/MIC (minimum inhibitory concentration) ratios >10 (fig. 2).[24] Dose (concentration) dependency has also been demonstrated readily in the *in vitro* pharmacodynamic model with higher doses giving more rapid elimination.[5]

2.2 Animal Models

Animal models have shown that the principal predictors of *in vivo* killing are the 24-hour AUC (area under the plasma concentration-time curve)/MIC ratio (AUC_{24}/MIC) and the C_{max}/MIC ratio.[25,26] The AUC_{24}/MIC ratio appears to be important for killing, whereas the C_{max}/MIC ratio is important to prevent the selection of resistant mutants during treatment. In the mouse thigh infection model, bacteriostasis is achieved with an AUC_{24}/MIC ratio of around 35,[27] while in a variety of animal models mortality is completely prevented once the ratio reaches 100.[25]

2.3 Human Studies

Of all groups of antimicrobials, the fluoroquinolones have been the one group where the *in vitro* and animal predictors of efficacy have been critically examined in humans. Two clinical studies have examined the clinical and bacteriological outcomes of treatment against a range of pharmacodynamic parameters.[28,29] Forrest et al.[28] conducted a retrospective analysis of studies of ciprofloxacin in the treatment of nosocomial lower respiratory tract infection in intubated patients. Each of the patients in the study had plasma drug concentrations measured and daily endotracheal cultures performed. Of 7 different pharmacodynamic parameters measured that might predict outcome, only the AUC_{24}/MIC ratio was significant in multivariate analysis. Clinical and bacteriological efficacy were only 42 and 26%, respectively, when the AUC_{24}/MIC ratio was <125, while for all ratios >125

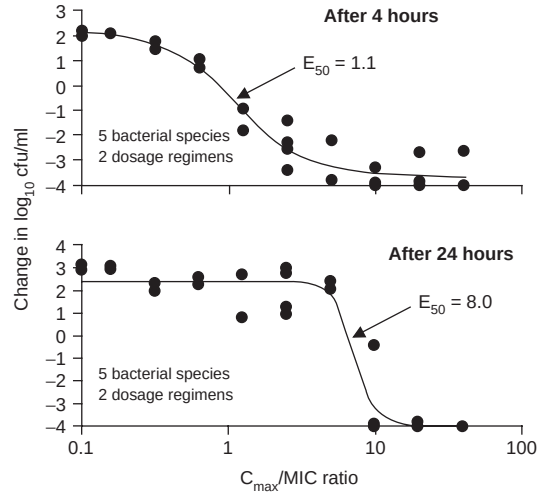

Fig. 2. Killing by enoxacin at 4 and 24 hours using different dosage regimens in an *in vitro* pharmacodynamic model. **cfu** = colony forming units; **C_{max}** = maximum plasma concentrations; **MIC** = minimum inhibitory concentration.[24]

Table II. MIC_{90} values (minimum concentrations which inhibit 90% of tested strains) of various fluoroquinolones against key pathogens

Agent	MIC_{90} (mg/L)				Reference
	Streptococcus pneumoniae	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	
Balofloxacin	0.39	0.2	0.2	12.5	31
Ciprofloxacin	2	0.5	0.03	4	32
Clinafloxacin	0.06	0.03	0.015	1	33
Difloxacin	2	0.5	0.5	16	34
Enoxacin	16	1	0.25	4	35
Fleroxacin	8	1	0.125	8	36
Gatifloxacin	0.39	0.1	0.1	6.25	37
Grepafloxacin	0.39	0.1	0.1	50	38
Levofloxacin	1.56	0.4	0.1	3.13	39
Lomefloxacin	16	2	0.5	32	40
Moxifloxacin	0.25	0.06	0.06	8	41
Norfloxacin	16	1	0.125	2	35
Pefloxacin	8	0.5	0.5	8	42
Rufloxacin	16	1	0.5	16	43
Ofloxacin	2	0.5	0.125	16	32
Sitafloxacin	0.05	0.025	0.025	0.078	44
Sparfloxacin	0.5	0.125	0.125	16	39
Tosufloxacin	0.39	0.1	0.05	0.78	31
Trovafloxacin	0.25	0.03	0.03	2	32

both clinical and bacteriological efficacy were maximal and >70%. Ratios >250 resulted in the most rapid elimination of the pathogen. A similar analysis was conducted by Preston et al.[29] on a prospective study of levofloxacin in pulmonary, skin and soft tissue and urinary tract infections. Using multivariate analysis, the C_{max}/MIC ratio proved to be the best predictor of outcome, but this was highly correlated with the AUC/MIC ratio. C_{max}/MIC ratios >12.2 produced the best rates of clinical and bacteriological cure (99 and 100%, respectively). Forrest et al.[30] have also examined the efficacy of grepafloxacin in the treatment of acute exacerbations of chronic bronchitis in terms of the AUC_{24}/MIC ratio. Maximum clinical efficacy was achieved when the AUC_{24}/MIC ratio exceeded 50, while maximum bacteriological efficacy was achieved when the ratio exceeded 100. The most rapid eradication was achieved when the ratio exceeded 190.

Thus, clinical studies have substantiated *in vitro* and animal model data, providing us with a reasonable guide as to how dosages of fluoroquinolones might be optimised. Ideally, an AUC_{24}/MIC ratio of around 100 and a C_{max}/MIC ratio of about 10 should be achieved in order to optimise clinical efficacy and bacterial eradication. It is interesting that these values, which are based on AUC values achieved in plasma, consistently hold true for all fluoroquinolones, despite significant differences in distribution between the agents.

3. Pharmacodynamic Comparison of Available Fluoroquinolones

An understanding of the key pharmacodynamic parameters of the fluoroquinolones, and the values of these parameters required for optimum efficacy, allows for direct comparison between agents against pathogens of interest. Figures 3 and 4 compare AUC_{24}/MIC_{90} ratios achieved (for both unbound and bound drug) against 4 pathogens of interest with conventional doses of widely available fluoroquinolones. AUC_{24} and protein binding data are taken from table I and MIC_{90} data from table II. In the choice of values, account is taken of the fact that AUC_{∞} for the first dose multiplied by the number of doses given in 24 hours is equivalent to AUC_{24} at steady state.

It must be stressed that although this is a quantitative comparison, there are known variations in the numerator and the denominator. AUC_{∞} varies between studies, in disease states and with age, and most importantly between individuals; the values chosen are mean values from a single study, in this instance the most recently published. AUC_{∞} will also vary with dose and schedule. Where 2 dosage schedules have been widely recommended, these have been included (ofloxacin and grepafloxacin). MIC values also vary between studies and a single 2-fold dilution difference in MIC_{90} will have a significant effect on the ratio, either halving it or doubling it. Thus, at best the comparison must be considered semi-quantitative. With few exceptions, the comparisons of C_{max}/MIC_{90} ratios look very similar. With an optimum AUC/MIC_{90} ratio of 100 it is clear that the vast majority of currently available fluoroquinolones achieve this ratio against *Escherichia coli*. The conclusion is the same for other Enterobacteriaceae, which tend to have MIC values not too dissimilar to *E. coli*. By contrast, none of the agents, even at the higher recommended doses, reach the optimum ratio against *P. aeruginosa*. Overall,

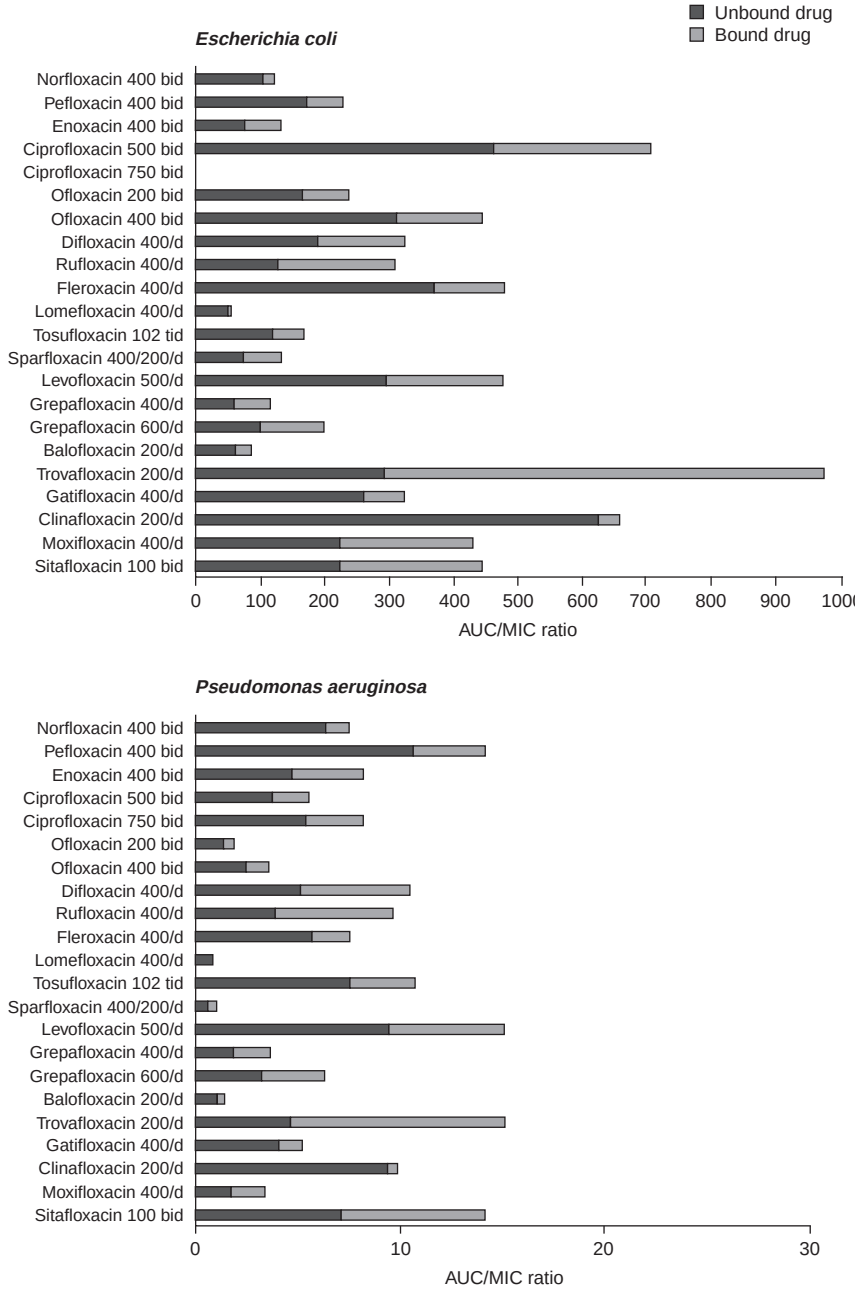

Fig. 3. Ratios of area under concentration-time curve from 0 to 24 hours/minimum concentrations inhibiting 90% of tested strains (AUC_{24})/MIC_{90}) for fluoroquinolones at common dosage schedules against *Escherichia coli* and *Pseudomonas aeruginosa*. Protein binding values are from table I, apart from levofloxacin and ofloxacin, for which the highest reported values were used, and tosufloxacin and balofloxacin, which were assigned values of 30% (in the absence of published data) for the purpose of calculation.

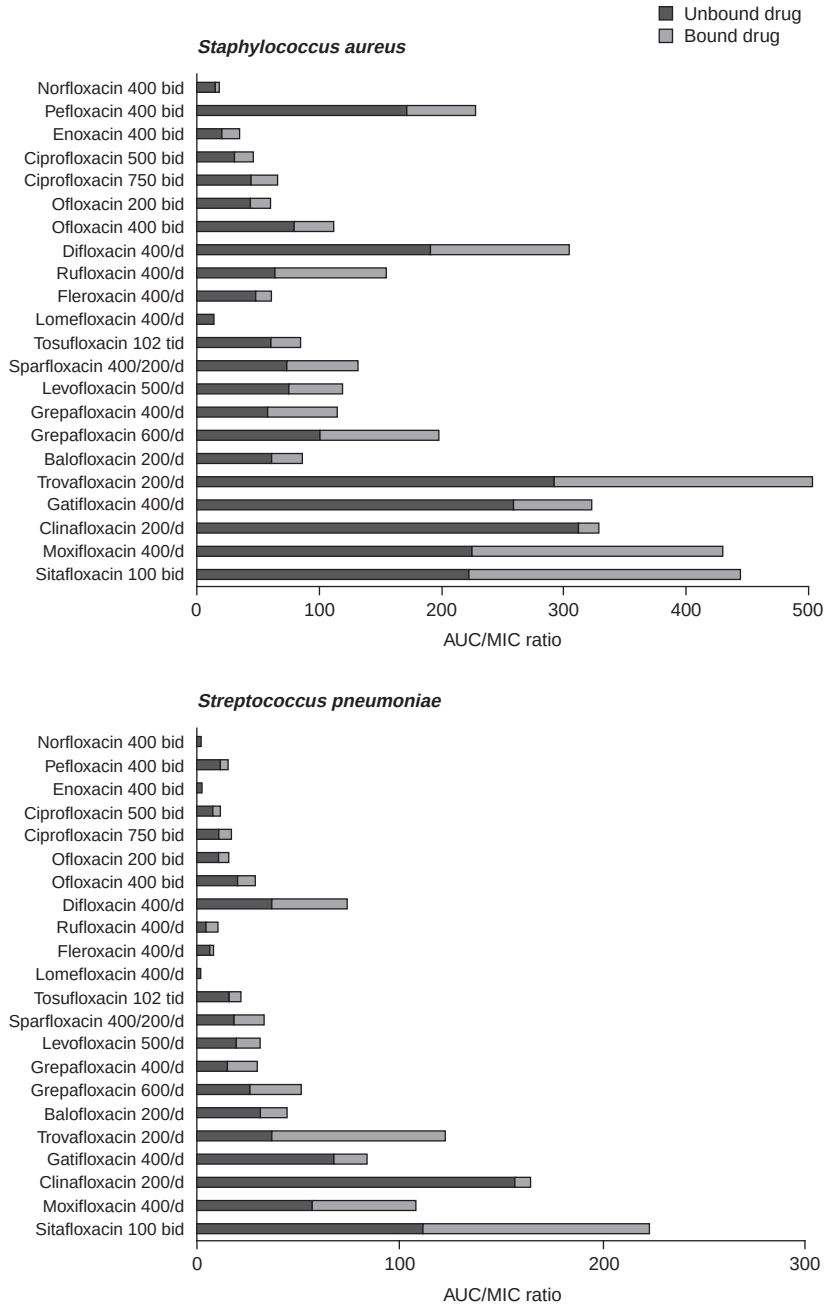

Fig. 4. Ratios of area under concentration-time curve from 0 to 24 hours/minimum concentrations inhibiting 90% of tested strains (AUC_{24}/MIC_{90}) for fluoroquinolones at common dosage schedules against *Staphylococcus aureus* and *Streptococcus pneumoniae*. Protein binding values are from table I, apart from levofloxacin and ofloxacin, for which the highest reported values were used, and tosufloxacin and balofloxacin, which were assigned values of 30% (in the absence of published data) for the purpose of calculation.

Table III. Pharmacodynamic 'breakpoints' for fluoroquinolones

Agent	Dosage schedule	Pharmacodynamic 'breakpoint'[a] (mg/L)	NCCLS breakpoint for susceptibility (mg/L)
Balofloxacin	200mg daily	0.25	ns
Ciprofloxacin	500mg bid	0.5	1
Ciprofloxacin	750mg bid	0.5	1
Clinafloxacin	200mg daily	0.25	ns
Difloxacin	400mg daily	0.5	ns
Enoxacin	400mg bid	0.5	2
Fleroxacin	400mg daily	1	2
Gatifloxacin	400mg daily	0.5	ns
Grepafloxacin	400mg daily	0.125	1
Grepafloxacin	600mg daily	0.25	1
Levofloxacin	500mg daily	1	2
Lomefloxacin	400mg daily	0.5	2
Moxifloxacin	500mg daily	2	ns
Norfloxacin	400mg bid	0.5	4[b]
Rufloxacin	400mg bid	0.25	ns
Ofloxacin	400mg daily	0.5	2
Ofloxacin	200mg bid	1	2
Pefloxacin	400mg bid	2	ns
Sitafloxacin	100mg bid	0.125	ns
Sparfloxacin	200mg daily	0.25	0.25-0.5
Tosufloxacin	102mg tid[c]	0.125	ns
Trovafloxacin	200mg daily	0.5	1

a Determined as the highest value for peak plasma concentration (C_{max})/10 or area under the concentration-time curve AUC/100, rounded to the next highest 2-fold dilution.

b For urinary infection only where drug levels are higher.

c As tosufloxacin tosilate 150mg.

bid = twice daily; **NCCLS** = National Committee for Clinical Laboratory Standards (USA); breakpoint values can vary for different pathogens or pathogen groups; **ns** = not set; **tid** = three times daily.

ciprofloxacin remains the most active agent against Gram-negative pathogens and is as active as, or more active, based on these ratios, than the newer agents and/or those with long elimination half-lives.

The superiority of the new generation of fluoroquinolones against Gram-positive bacteria is obvious when examining the AUC_{24}/MIC_{90} ratios against *Staphylococcus aureus* and *Streptococcus pneumoniae*. Some of the older agents (pefloxacin, ofloxacin in higher doses, difloxacin and rufloxacin) achieve the optimum ratio against *S. aureus*, while the newer agents such as sparfloxacin, levofloxacin and grepafloxacin are adequate. Trovafloxacin and the fluoroquinolones under development reach AUC/MIC ratios that are significantly higher than other agents.

A pattern similar to that of *S. aureus* is seen with *S. pneumoniae*, except that fewer agents reach the optimum ratio of 100. Indeed only trovafloxacin, clinafloxacin, moxifloxacin and sitafloxacin reach this value.

4. Dose Optimisation

The calculation of AUC_{24}/MIC_{90} ratios cannot be applied easily to predictions in individual patients. As Forrest et al.[28,30] have shown with both ciprofloxacin and grepafloxacin, there is substantial intersubject variation in pharmacokinetic parameters, including AUC_{24}, in the clinical setting. For example, while there was only a 3-fold variation in dosages in these studies, AUC_{24} values varied over about a 25-fold range. In addition MIC data for the infecting pathogen must be available for each patient. Nevertheless, it has been recently shown for 1 agent with predominantly renal elimination, levofloxacin, that individual variation in kinetics can be predicted largely by calculated creatinine clearance.[45] Such strategies may be used in the future to optimise dosages and AUC_{24}/MIC_{90} ratios.

5. Pharmacodynamic MIC 'Breakpoints'

Schentag[46] has shown that it is possible using AUC_{24}/MIC ratios to calculate MIC 'breakpoints' for clinical effectiveness, analogous to those used to interpret susceptibility testing results. Again using an optimum AUC_{24}/MIC ratio of 100, such MIC 'breakpoints' for the common agents are shown in table III. In general, these calculated values are lower than those recommended in standardised susceptibility testing methods such as those of the National Committee

for Clinical Laboratory Standards. However, these values must clearly be considered in the patient with more serious infection, given the strong support from the clinical studies of the importance of the AUC_{24}/MIC ratio.

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