What Have We Learned from Pharmacokinetic and Pharmacodynamic Theories?

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Pharmacokinetic characteristics and pharmacodynamic properties dictate antimicrobial response and, along with natural immune responses, clinical outcomes. As new agents are developed with long half-lives, we will lose the ability to differentiate between concentration-dependent and time-dependent properties. The area under the inhibitory concentration curve (AUIC) defines drug regimens as a ratio of drug exposure to minimum inhibitory concentration (MIC) and allows them to be compared with each other. With AUIC and agents with long half-lives, these comparisons are possible regardless of chemical classification or concentration or time-dependent activity. Historical examples of reduced drug exposure from decreased doses (i.e., cefaclor, clarithromycin, and ciprofloxacin), and thus low AUIC values, directly correlate with drug resistance. In the face of rising MICs (as is occurring worldwide with *Streptococcus pneumoniae*), close attention to appropriate dosing and concentration above the MIC may delay and potentially even prevent antibiotic resistance. Creating selective pressure on reliable antibiotics by inappropriately reducing their doses will undoubtedly challenge these agents and may destroy entire drug classes with similar mechanisms of action or resistance.

The rationale for the link between dosing, activity, and antibiotic efficacy has evolved from the expansion and application of pharmacokinetic characteristics and pharmacodynamic properties. Years of clinical study of antibiotics have shown that adherence to antibiotic class-specific pharmacokinetic principles predicts optimal antimicrobial effect, or pharmacodynamic response. For example, the pharmacodynamic response of antibiotics exhibiting concentration-dependent pharmacodynamics traditionally has been described by measuring peak concentration (C_{max}) to MIC, or C_{max}/MIC. Time-dependent agents have been evaluated by time above the MIC, percentage of day, or percentage of dosing interval greater than the MIC [1, 2].

Area under the inhibitory curve (AUIC) is the newest pharmacological measure that integrates the principles of pharmacokinetics and pharmacodynamics. AUIC represents the ratio of the antibiotic area under the concentration-time curve (AUC_{24}) to the organism's MIC, or AUC_{24}/MIC (figure 1). Although these are seemingly diverse, few examples demonstrating differences between these pharmacodynamic measures (such as AUIC, time > MIC, and peak/MIC) are reported in the literature. Of those reported, most examples are in animals receiving antibiotics with short half-lives [3, 4]. As antibiotics with extended half-lives are developed, the importance and ability of differentiating between these parameters diminishes. Here we discuss what we have learned as a result of the evolution of these parameters and what we currently understand about pharmacokinetics and pharmacodynamics.

GENERAL PHARMACODYNAMICS

Antibiotics are categorized as concentration-dependent or time-dependent agents on the basis of the pharmacokinetic principles dictating their mechanism of action. Application of these pharmacokinetic principles results in pharmacodynamic measures of response. General

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Clinical Infectious Diseases 2001; 32(Suppl 1):S39–46

1058-4838/2001/3206S1-0007$03.00

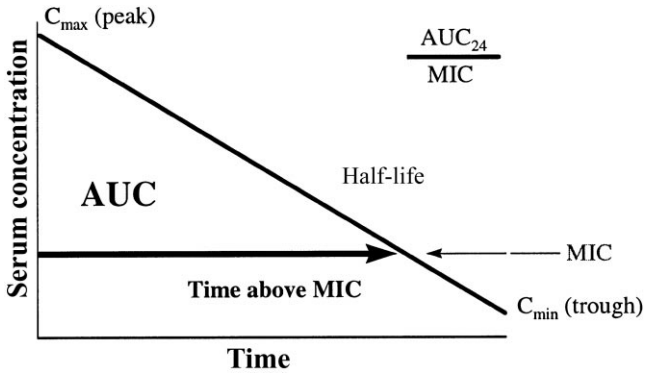

Figure 1. Serum concentration versus time graphic depiction of area under the inhibitory curve: the ratio of the area under the curve (AUC) to MIC. C_{max}, peak concentration; C_{min}, trough concentration.

pharmacodynamic principles, independent of antibiotic class, correlate C_{max}/MIC >8–10 with antimicrobial efficacy, although this is ascribed mostly to representative concentration-dependent agents, such as the aminoglycosides and fluoroquinolones. Clearly, as shown in figure 1, where the MIC line intersects the AUC makes a great deal of difference. For example, maximum rate of bacterial killing is reported at ratios >25:1, and selection of resistance during therapy is observed at most values <3:1 [5]. Similarly, an AUIC value may predict killing and resistance rates with values closely linked to peak/MIC ratios. An AUIC of at least 125 SIT (serum inhibitory titer)$^{-1}$ should be targeted (which represents ~80% of the entire AUC above the MIC) because values <100 have been associated with resistance development [6]. (AUIC values are presented hereafter as ratios.)

Organisms at or near the MIC breakpoint, already marginally susceptible, are generally the first to express resistance. It is assumed that the MIC is reflective of growth inhibition independent of the species of bacteria and remains unchanged. Therefore, when MICs rise or doses are lowered, concentrations below the MIC are the result. In either case, a low AUIC ratio is produced and the emergence of resistance is predictable. Which AUC/MIC ratio value is the optimal breakpoint for all antibiotics to differentiate clinical success or failure seems to be controversial. The bottom line is that dosing with particular attention to the MIC will dictate the AUIC ratio. With sensitive organisms (low MICs), clinical success is likely. However, by lowering doses for economic benefits or misguided perceptions of pharmacokinetics and pharmacodynamics, AUIC values are decreased, creating more selective pressure on the antibiotic classes that we rely on so heavily.

We partially lower this risk with increased reliance on combination therapy; many antibiotic regimens now include 2 or more agents. The overall success of the regimen, or patient's pharmacodynamic response, may be assessed in terms of a total AUIC value, which is the sum of the partial AUIC values [7]. Thus, the additivity feature is a unique quality of this pharmacokinetic and pharmacodynamic measure and may further justify its designation as the preferred parameter.

AUIC VALUES: HOW WAS 125 DETERMINED AS A BREAKPOINT?

A study evaluating tobramycin, cefmenoxime, and ciprofloxacin adjusted for a patient weighing 70 kg with a 70-mL/min creatinine clearance was conducted by Schentag and colleagues to assess AUIC values over MICs of 0.005–100 μg/mL [8]. Serum concentrations fell below the MIC at the point at which ~80% of the achievable AUC was above the MIC. As shown in table 1, tobramycin AUC/MIC was 80% ([(36.8 μg·h/mL)/46.1 μg·h/mL)] × 100 = 80%). The AUIC value of 125 was achievable for cefmenoxime (short half-life and time-dependent killing agent) as well as for ciprofloxacin (longer

Table 1. Calculated values for AUC above MIC and time above MIC for 3 antibiotics at a range of MICs.

	Tobramycin		Cefmenoxine		Ciprofloxacin	
MIC, μg/mL	AUC above MIC	t > MIC, h/24 h	AUC above MIC	t > MIC, h/24 h	AUC above MIC	t > MIC, h/24 h
0.005	46.1	24	540.1	24	29.3	24
0.05	45	24	539	24	28.3	24
0.10	43.8	24	537.8	24	27.1	24
0.25	40.2	24	534	24	**23.5**	**24**
0.39	**36.8**	**24**	530.8	24	20.1	23.8
0.5	34.3	22.2	528.2	24	17.6	21
4	1.5	2.6	444.4	23.9	0	0
4.5	0.5	0.7	**432.3**	**23.4**	0	0

NOTE. AUC, area under the curve; t, time. Bold values indicate AUC above MIC at 24 h for each agent. Data from [8].

Table 2. Calculated values for AUIC for 3 antibiotics at a range of MICs.

MIC, μg/mL	AUIC		
	Tobramycin	Cefmenoxine	Ciprofloxacin
0.24	192	2254	**125**
0.25	185	2161	118
0.37	**125**	1460	80
0.50	91	1080	56
4	3	135	0
4.3	2	**125**	0

NOTE. AUIC, area under the inhibitory concentration curve; *t*, time. MIC at t >MIC 24 h for each antibiotic corresponds to an AUIC value of 125 *(bold)*. Data from [8].

half-life and concentration-dependent killing representative) where 80% of all AUC was above the MIC. This defined the breakpoint between success and failure.

Time above the MIC at the point where time became <24 h defined the expected threshold point of antibiotic failure (table 2). The AUC and MIC at that time point corresponded with an AUIC of 125 and thus the breakpoint currently separating success and failure for gram-negative organisms. A true MIC versus the breakpoint would only increase precision of a calculated AUIC because National Committee for Clinical Laboratory Standards breakpoints are higher than the true MIC [9]. This illustrates the close linkage between time above the MIC and 80% of the AUC above the MIC.

LOWER RESPIRATORY TRACT INFECTION MANAGEMENT: INFECTION AND AUIC

Although 125 is the AUIC breakpoint most commonly referred to, it is easy to justify an AUC/MIC >250 for fluoroquinolones on the basis of the ability to achieve rapid eradication of the pathogen with these agents. By day 7 of treatment with ciprofloxacin, only 30% of patients studied with nosocomial lower respiratory tract infections eradicated the pathogen when AUIC values were <125. With these lower AUIC values, 70% of patients had persistently positive cultures with stepwise increases in resistance inversely related to AUIC values, as occurs in the test tube. With AUIC values of 125–250, 50% of patients achieved bacterial eradication by day 6 of antimicrobial therapy. However, the most rapid sterilization of infection sites occurred when AUIC values >250 were attained. In fact, 60% of patients were culture negative on day 1 of therapy.

Although this study was conducted in the hospital setting, this finding also can be replicated in the outpatient environment, as shown in a study of patients with bronchitis. A study conducted with clarithromycin and ciprofloxacin in the treatment of *Haemophilus influenzae* bronchitis correlated AUIC values with the percentage of outpatients who remained culture positive at the end of therapy [10]. Clarithromycin, a marginal anti-*Haemophilus* agent with high MICs of 4–8 μg/mL and AUIC values of ~40, revealed that 80% of patients remained culture positive after 10 days of treatment. Patients who received ciprofloxacin achieved significantly greater AUIC values of 1600 and attained microbiologic cure after 1 day of fluoroquinolone therapy, as shown in figure 2 [10].

Despite the abundance of available antimicrobial agents useful in the treatment of lower respiratory tract infections, few are ideal. Agents are even less ideal, however, when there is a high likelihood for persistence of positive cultures as demonstrated with clarithromycin [10, 11]. Opportunities for therapeutic improvement include optimizing dosing, keeping in mind pharmacokinetics, pharmacodynamics, and AUIC values, along with a focus on resistance prevention in exposed organisms, especially in reservoir populations.

RESISTANCE AND AUC/MIC

A study at Millard Fillmore Hospital of 107 patients evaluated factors associated with the development of bacterial resistance in acutely ill patients during therapy [12]. Patients had AUC/MIC ratios derived from measured or calculated AUC values by use of precise MICs, and all organisms were initially shown to be susceptible to the antibiotics they were receiving. Organisms were primarily gram negative (29% *Pseudomonas aeruginosa*, 11% *Escherichia coli*, and 37% *Klebsiella pneumoniae*), with some gram positive (4% *Staphylococcus aureus* and 1 isolate *Streptococcus pneumoniae*) and 19% others. With AUIC values <100 after 5 days of therapy, there was a 50% probability that the organism remained susceptible. Overall, 83% of the

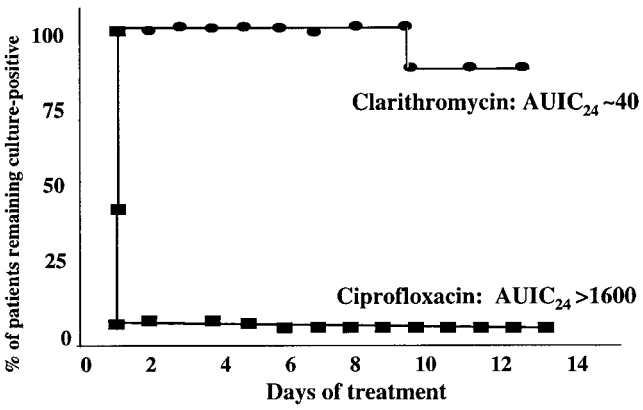

Figure 2. *Haemophilus* eradication in bronchitis patients and 24-h area under the inhibitory curve ($AUIC_{24}$). Eighty percent of clarithromycin-treated patients remained culture positive after 10 d of treatment. Ciprofloxacin-treated patients achieved AUIC values >1600 and microbiologic cure after 1 day of therapy. Data from [10].

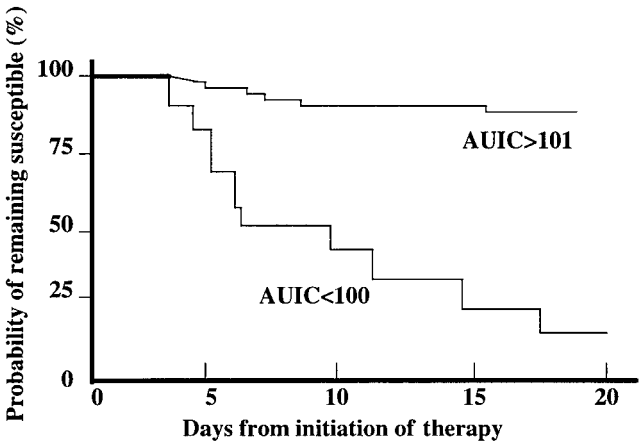

Figure 3. Area under the inhibitory curve (AUIC) and organism resistance at Millard Fillmore Hospital. At AUIC values >101, only 9% patients developed resistant organisms. At AUIC values <100, 50% organisms remained susceptible after 5 d of therapy. Selective pressure leads to resistance when antibiotic doses are lowered below the organism's MIC. Data from [12].

organisms developed resistance via some mechanism, primarily believed to be selection of a subpopulation. However, if initial AUIC values were >101, only 9% of patients with similar organisms developed resistance [12] (figure 3). It is evident from these data that the emergence of resistance is predictable when dosing is lowered below the organism's MIC, which implies that selective pressure is the primary mode of resistance expression.

COMMUNITY INFECTIONS AND RESISTANCE

Resistance issues that exist in the hospital setting are also prevalent in the community, as modeled by clarithromycin in bronchitis therapy. Another example pertains to the use of cefaclor for the treatment of otitis media caused by *S. pneumoniae* [13–15]. Microbiologic failure, rather than primary clinical failure, is of paramount importance regarding *S. pneumoniae* resistance in these patients because otitis media will clinically improve even when the organism persists. However, resistance can occur later. Because cefaclor MICs have increased for *S. pneumoniae* throughout the 1980s and early 1990s and now average 1.0 μg/mL, AUIC values are virtually always below the desired 125 threshold for this organism, as shown in figure 4. In fact, cefaclor doses of 250–500 mg every 8 h underexpose *S. pneumoniae* every time this agent is used. It is clear that underexposure, defined by low AUIC values, predisposes to β-lactam resistance [12]. A major concern exists with the emergence of rapid class resistance and cross-resistance within cephalosporins and macrolides.

S. pneumoniae is also reported to have developing resistance against fluoroquinolones [16], although not through the same mechanism. Low AUIC values of 30–40 may be achieved, and if the patient is not ill, they may be associated with clinical cure even with resistant organism colonization. However, as MICs increase, AUIC values will decrease, with resultant underexposure of agents in the treatment of *S. pneumoniae,* and there will be some clinical failures. Microbiologic eradication will not occur, and resistance can be selected.

LEVOFLOXACIN AND AUIC VALUES <125 FOR RESPIRATORY PATHOGENS

With rising *S. pneumoniae* MICs to the fluoroquinolones, low AUIC values are typically the outcome of treatment with once-daily 500-mg doses of levofloxacin. Steady state dosing of levofloxacin, 500 mg daily, yields a peak concentration averaging 5.7 μg/mL and an AUIC value of 96, 48, and 24 if the pathogen MIC_{90} is 0.5, 1.0, and 2.0, respectively, as shown in figure 5. Acceptance of lower AUIC values (30–40) was proposed, presumably on the premise that successful clinical outcomes would continue even with low AUIC values.

To prospectively quantify the relationship between plasma concentrations of levofloxacin and successful clinical or microbiologic outcomes, a study was conducted in the early 1990s in 313 patients. Of 313 patients, 134 had a pathogen recovered from the primary infection site and had an MIC of the pathogen to levofloxacin determined; only 7 were deemed to have clinically failed to respond to treatment. The clinical outcome was predicted by the peak/MIC ratio, as was microbiologic eradi-

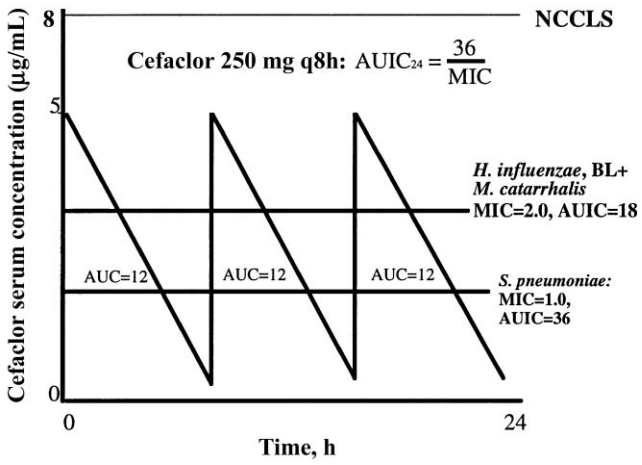

Figure 4. Cefaclor serum concentration versus time. Cefaclor MICs of 1.0 and 2.0 μg/mL to *Streptococcus pneumoniae* and *Haemophilus influenzae/Moraxella catarrhalis,* respectively, consistently achieve area under the inhibitory curve (AUIC) values below the desired 125 with regimens of 250–500 mg every 8 h. The line at 8.0 indicates the breakpoint for susceptibility. BL, β-lactamase; NCCLS, National Committee for Clinical Laboratory Standards.

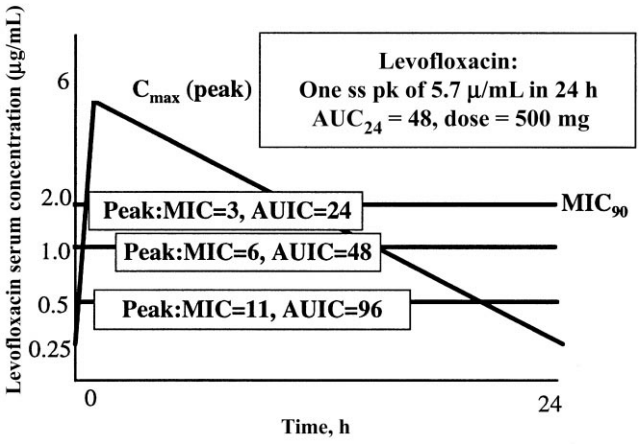

Figure 5. Levofloxacin serum concentration versus time. Levofloxacin, 500 mg, with resulting area under the inhibitory curve (AUIC) values below the desired 125 for organism MICs of 0.5, 1.0, and 2.0 μg/mL. The relationship of area under the curve (AUC)/MIC and peak/MIC change maintains identical relative values. C_{max}, peak concentration; C_{min}, trough concentration; MIC_{90}, 90% MIC; pk, peak; ss, steady state.

cation. A peak/MIC ratio >12.2 was predictive of a favorable clinical and microbiologic outcome. AUC/MIC was also a significant predictor of outcome, as originally found in the study by Forrest and colleagues [5, 17].

In 20 patients with *S. pneumoniae,* 17 patients achieved AUIC values ⩾50; 11 patients, ⩾75; and 9 patients, ⩾100 [18]. Analysis of these data supports the argument that higher AUIC values were effective, but the study data did not allow definition of the low AUIC threshold because there were no well-documented microbiologic failures. This study had 116 evaluable patients, and patients were probably enrolled around 1992–1993. Eradication, as in most trials of this type, was presumed when clinical response was defined as cure. Eighty percent of patients had peak/MIC ratios >10:1, with the mean being 13.4:1 for *S. pneumoniae.* AUIC mean values were 112.8, a value much higher than the minimum AUC/MIC of 25.7, which occurs if MICs are 1–2 μg/mL. The lower fluoroquinolone MICs in the early 1990s probably explain why there were no AUIC values of 30 in this trial. Because this study was conducted in the early 1990s, the impact of an increased frequency of fluoroquinolone-resistant mutations in new populations of *S. pneumoniae* was not studied, but now it must be considered.

The MICs are rising to fluoroquinolones, but in most cases, the high laboratory breakpoints obscure the rise below it, and we are not yet seeing many isolates with MICs above the high breakpoint for the fluoroquinolones. If we continue to challenge these antibiotics inappropriately with low doses and low AUIC values against *S. pneumoniae* (values ~30), we can predict that further selection will occur and the entire population of these organisms will become less susceptible to this class of antibiotics. Early fluoroquinolone resistance may already be linked to low AUIC values in the community. Most likely the majority of *S. pneumoniae* MICs of 1–2 μg/mL will result in clinical improvement; however, microbiologic colonization with less susceptible mutants may still occur. Eradication is not guaranteed, and microbiologic cure is what we need to avoid resistance.

SHOULD AUIC VALUES FOR GRAM-POSITIVE AND GRAM-NEGATIVE ORGANISMS DIFFER?

AUIC is the most important predictor of fluoroquinolone pharmacodynamics, specifically characterized for ciprofloxacin and grepafloxacin [5, 17]. With these data, an AUIC value of 125, as previously stated, has been proposed to be the breakpoint differentiating clinical success and failure. However, the theory that different target AUIC values should be defined for gram-positive and gram-negative organisms has been advanced by in vitro data [19]. Specifically, for gram-positive organisms only (i.e., *S. pneumoniae*), a breakpoint AUIC as low as 30 has been proposed [19]. Although most patients in the levofloxacin study were above AUIC values of 50, the authors still maintain that an AUIC value of 30 is sufficient presumably on the basis of in vitro studies [18]. Certainly, the concentration-dependent killing characteristic of these drugs argue for target AUIC values of 250, and there is no support for deliberately lowering the targets. Rather, the question of low-end adequacy persists.

Published clinical trials lag behind the reality of a fast-moving resistance problem. For example, in the study of Preston and colleagues [18], the problem was that there were few *S. pneumoniae* isolates with MICs to fluoroquinolones higher than 1–2 μg/mL at the time the study was conducted. This is no longer the case as the MICs of *S. pneumoniae* are increasing and now are typically 1–2 μg/mL to levofloxacin. Unattainable breakpoints of 2.0 μg/mL have prevented the detection of this problem, but it is our belief that the likely development of resistance will follow once-daily use of low-potency fluoroquinolones and that this practice should not be advocated even if there is no immediate evidence of harm. In essence, with the recommendation to aim for a lower drug exposure level, we must rely on decreasing renal function in order to increase the drug exposure, or AUC, as MICs increase. Usual values of 20–40 need to be higher (at 80–90 μg·h/mL) if levofloxacin is to succeed against MICs of 2.0 μg/mL. Underdosing a new antibiotic created needless selective pressure. Experience in the microbiology laboratory proves that cross-resistance occurs within the fluoroquinolone class. Newer agents within this class may or may not follow the exact mechanisms of resistance, but inadvertently fostering class resistance by dosing weaker fluoroquinolones to low AUIC values in an attempt to save money is unacceptable.

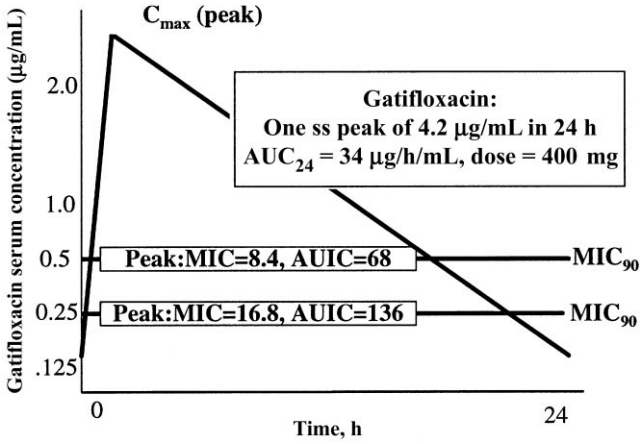

Figure 6. Gatifloxacin serum concentration versus time. Gatifloxacin, 400 mg, with area under the inhibitory curve (AUIC) values of 68 and 136 at MICs of 0.5 and 0.25 µg/mL, respectively. If MICs rise above these values secondary to selective pressure, an AUIC target of 125 will be not attainable. C_{max}, peak concentration; MIC_{90}, 90% MIC; ss, steady state.

RESISTANCE AND NEW FLUOROQUINOLONES

Fluoroquinolones act by inhibiting the action of DNA gyrase (topoisomerase II), resulting in inhibition of bacterial replication and ultimately cell death. Topoisomerase IV is a second target of fluoroquinolones, primarily seen in gram-positive organisms [20]. Mutations involving either of these topoisomerases (DNA gyrase or topoisomerase IV) lead to resistant strains. As the antimicrobial spectrum of new fluoroquinolones includes gram-positive organisms, studies linking topoisomerase IV with cross-resistance are in progress. Because of this unique mechanism of action, however, cross-resistance to this class of antimicrobials from others is thus far limited. Older quinolone agents exhibit direct cross-resistance to each other with mutations leading to reduced susceptibility, whereas the newer quinolone agents exhibit a lower risk of this phenomenon [20–22].

With favorable pharmacokinetics and potent in vitro microbiologic profiles, these new agents show enhanced activity against a wide spectrum of gram-positive, gram-negative, and atypical organisms, including respiratory tract pathogens. Activity is maintained against resistant strains [23–26]. A steady state peak serum concentration of 4.2 µg/mL and an average AUC of 34 µg·h/mL are produced from a dose of gatifloxacin, 400 mg daily (figure 6). These parameters and an MIC_{90} of 0.5 µg/mL yield an AUIC value of 68. Compared with levofloxacin (MIC_{90}, 2.0 µg/mL and corresponding AUIC of 24), gatifloxacin is more active. If levofloxacin continues to exert selective pressure on the *S. pneumoniae* population, this difference will narrow and may easily compromise gatifloxacin activity.

By use of moxifloxacin pharmacokinetic data such as C_{max} and AUC with the knowledge of MICs of target pathogens, an array of AUIC values may be calculated, as shown in figure 7. One steady state peak of 4.5 µg/mL and an average AUC of 48 µg·h/mL are produced from a dose of moxifloxacin, 400 mg daily. These parameters and an MIC_{90} of 0.125 µg/mL yield an AUC/MIC of 384. To achieve an AUIC value of 250 targeted for more rapid microbiologic cure, an MIC of 0.16 µg/mL or lower is required, and 0.125 is the 90% MIC in some studies. The majority of reported 50% MICs for moxifloxacin are low; thus an AUIC of 250 is feasible. However, local susceptibility patterns must always be reviewed when deciding on antibiotics and then dosages. In a bimodal MIC population, regimens designed to address the high-end 90% MICs use doses that will not reach the 125 target for fluoroquinolones, as shown clearly for levofloxacin.

NEWER FLUOROQUINOLONES

Moxifloxacin and gatifloxacin, as well as clinafloxacin, sparfloxacin, and trovafloxacin, show enhanced gram-positive bacterial activity against *S. pneumoniae* [26–28]. Moxifloxacin is a methoxy fluoroquinolone that was approved for use in the United States on 10 December 1999. Studies of healthy volunteer subjects reveal moxifloxacin to display linear pharmacokinetics after a 400-mg dose with a half-life ($t_{1/2}$) ~8 h (when administered orally or iv), supporting the use of moxifloxacin at once-daily dosing [29–31] (table 3).

Maximum concentrations in plasma after oral and iv administration were similar, and both were in the range of ~2.5–5 µg/mL, with the time to C_{max} occurring 1–2 h after an oral dose and at the end of an iv infusion. AUC_{24} values of 35–48 µg·h/

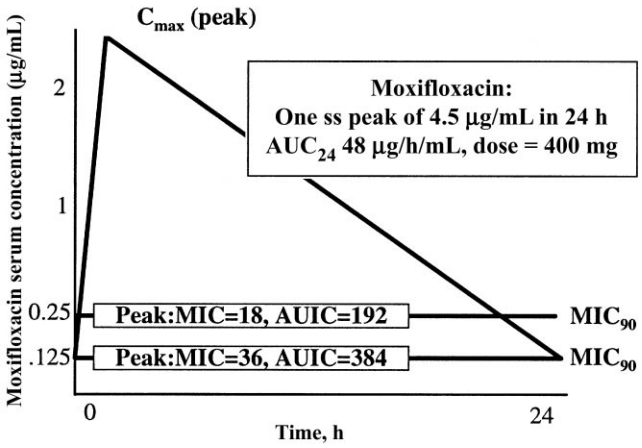

Figure 7. Moxifloxacin serum concentration versus time. Moxifloxacin, 400 mg, with area under the inhibitory curve (AUIC) values of 192 and 384 at MICs of 0.25 and 0.125 µg/mL, respectively. Appropriate dosing will secure breakpoint MICs at 0.125–0.25 µg/mL while maintaining effective antimicrobial activity (AUIC values >125–250). C_{max}, peak concentration; MIC_{90}, 90% MIC; ss, steady state.

Table 3. Pharmacokinetic characteristics of newer fluoroquinolones indicating that lower MICs to *Streptococcus pneumoniae* correspond with increased susceptibility to these agents.

Agent	Unit dose, mg	C_{max}, mg/L	AUC, μg·h/L	$t_{1/2}$, h	Urinary recovery, %	*S. pneumoniae* 90% MIC, μg/mL
Gatifloxacin	400	4.2	34	8.4	>80	0.5
Levofloxacin	500	5.7	48	6.3	>80	2
Moxifloxacin	40	4.5	48	12	~20	0.125
Sparfloxacin	400	1.6	32	18	~45	0.25
Trovafloxacin	200	1.4	23	9.6	6	0.25

NOTE. AUC, area under the curve; C_{max}, peak concentration; $t_{1/2}$, half-life. From [21, 28, 30].

mL were achieved for 400-mg doses of both oral and iv formulations. Moxifloxacin penetration into inflammatory fluids occurred in ~4 h for oral administration and 2.4 h for iv administration, achieving concentrations of 2.6 and 3.2 μg/mL, respectively. Both C_{max} and $t_{1/2}$ in inflammatory fluid were significantly less than values reported in plasma.

Moxifloxacin showed a greater bactericidal effect than other fluoroquinolones against gram-positive and gram-negative organisms in a postantibiotic effect evaluation study of *Streptococcus pyogenes, H. influenzae, S. aureus,* and *E. coli* [32]. A postantibiotic effect of $\geq$1 h against these strains was also observed. A direct association with concentration and postantibiotic effect was demonstrated. Extent of bioavailability of the oral formulation was reported to be nearly complete, which facilitates sequential iv-to-oral administration.

CONCLUSION

By use of principles of pharmacokinetics and pharmacodynamics, the development of resistance should be predictable and therefore widely monitored. The killing rate of organisms follows the relationships shown in vitro, and thus it is important to accurately dose antibiotics such as moxifloxacin and other newer active quinolones in the treatment of infecting pathogens on the first attempt. Attention to MICs and potential use of computer program aids to dosing will successfully target pharmacodynamic measures. As newer antimicrobial agents are developed with longer half-lives, allowing once-daily administration, the division that has existed for many years between concentration and time-dependent agents will become less important.

We have learned that newer indexes of pharmacodynamic response, such as AUIC, seem appropriate in predicting clinical outcomes, despite some debate over the exact AUIC breakpoints to use as targets. It is certain that if we underdose patients with new antimicrobial agents in relation to the organisms' MICs, we are creating additional selective pressure and MICs will increase. Resistance will eliminate the entire class, so we need to increase the fluoroquinolone AUIC values overall against *S. pneumoniae* by increasing the doses of most members of this class. The dose needs to be correct initially to achieve minimal AUIC values of 100 to control resistance; however, values of 250 are preferable to kill the pathogen on day 1 of therapy. Ultimately, if we utilize these pharmacokinetic and pharmacodynamic principles correctly, patients will benefit from this attempt at strategic dosing. Years of resistance-free or low-frequency resistance to newer agents will likely result.

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