Maximizing efficacy and reducing the emergence of resistance

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An understanding of the pharmacokinetic and pharmacodynamic properties of antimicrobial agents enables better choices to be made in the clinical situation. The fluoroquinolones share several useful pharmacokinetic properties, such as good bioavailability (in most cases >85%) and the ability to penetrate and concentrate intracellularly, giving them activity against pathogens such as *Legionella pneumophila* and *Listeria monocytogenes*. Nevertheless, there are some important differences between the fluoroquinolones, and even the newer fluoroquinolones demonstrate a range of pharmacodynamic properties. When considering the area under the inhibition curve (AUIC) and the \( C_{\text{max}}/\text{MIC} \), the comparative figures are: ciprofloxacin and ofloxacin (5–25, 1–5); levofloxacin, grepafloxacin and gatifloxacin (25–75, 5–10); trovafloxacin (75–250, 10–20) and moxifloxacin, clinafloxacin and gemifloxacin (>250, >20). The development of resistance is also a concern, and selecting an agent that reaches an adequate concentration above the MIC will reduce the opportunity for resistance to develop. These properties should be considered when selecting a fluoroquinolone either for inclusion in a formulary, or for use in an individual patient.

Keywords: fluoroquinolones, pharmacodynamics, resistance

Introduction

To be effective, antimicrobials need to be present in high concentrations (relative to the MIC for susceptible pathogens) at the infection site.\(^1,2\) The ability to reach this goal depends on the relationship between the pharmacokinetic and pharmacodynamic properties of the antimicrobial.

Pharmacokinetics describes the absorption, distribution, metabolism and excretion of an antimicrobial in a host.\(^3\) Simple pharmacokinetic parameters that are readily measured are the maximum serum concentration (\( C_{\text{max}} \) or peak) and minimum concentration (\( C_{\text{min}} \) or trough), and the time for the serum concentration to be reduced by half, i.e., the elimination half-life (\( t_{1/2} \)) (Figure 1).

During the development of the fluoroquinolones, considerable attention has been given to the study of pharmacodynamics; the inter-relationship between the concentration of an antimicrobial at an infection site and its activity against the microorganism involved.\(^3\) Pharmacodynamics includes the study of concentration–bactericidal effect relationships, post-antibiotic effect (PAE), animal or *in vitro* models and human studies. The most frequently used pharmacodynamic parameter for measuring the activity of an antimicrobial *in vitro* is the minimum inhibition concentration (MIC).\(^5\) However, *in vivo* efficacy cannot be predicted by *in vitro* MIC data alone, which are obtained by exposing bacteria to a constant antimicrobial concentration. *In vivo*, concentrations change according to the pharmacokinetics of the particular antimicrobial.\(^6,7\) Also the MIC does not represent the real pharmacodynamic activity, as the ability of the antimicrobial to kill or just to inhibit is neglected.

Predictors of clinical efficacy

The three main pharmacodynamic parameters are: the ratio of the maximum serum antimicrobial concentration (\( C_{\text{max}} \)) to the MIC (\( C_{\text{max}}/\text{MIC} \)); the time the serum antimicrobial concentration remains over the MIC (\( t > \text{MIC} \)); and the ratio of the area under the time-serum antimicrobial concentration curve over 24 h (AUC\(_{24}\)) to the MIC; and the area under the inhibition curve (AUC/MIC or AUIC) (Figure 1).\(^8\) These parameters have been measured and correlated with clinical outcome and the development of resistance as predictors of clinical efficacy.\(^9\) Other more subtle and complicated predictors of clinical efficacy include the area under the bactericidal kill...
R. Wise

Pharmacokinetics of fluoroquinolones

The major attribute of the fluoroquinolones is their high volume of distribution (~2 L/kg) and it is this that provides these agents with their pharmacokinetic opportunities, and in turn their clinical opportunities. They are rapidly and completely absorbed (bioavailability, mainly >85%) into the bloodstream from which they rapidly penetrate into interstitial fluid and are widely distributed around the body, with the exception of the CSF and fat tissue where penetration is fairly poor. However, penetration into the CSF is fairly rapid (levels in the CSF are 25–35% that of serum), and the half-life in CSF is similar to those in serum suggesting a ready transport between the two sites.

Fluoroquinolones are concentrated in phagocytic cells, (macrophages, particularly alveolar macrophages, and polymorphonuclear neutrophils) and the mucosae (urinary, gut and bronchial) of the body, the interface between the outside world and the body, where many infections occur. They accumulate in lung tissues to the extent that local concentrations usually exceed serum concentration by a ratio of greater than 2:1–3:1 in the bronchial mucosa, 8:1 in the epithelial lining fluid (ELF) of the terminal alveoli and >25:1 in alveolar macrophages.24,25 The respiratory concentrations of the new fluoroquinolone, moxifloxacin, compared with plasma levels, have been shown to be 2:1 (bronchial mucosa), 10:1 (ELF) and 50–70:1 (alveolar macrophages) and are considerably higher than the MIC90 for the most common respiratory pathogens, Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis.

Fluoroquinolones, tetracyclines and macrolides show good penetration of the intracellular environment and reach significant concentrations. Aminoglycosides and most β-lactams do not exhibit good intracellular penetration. The exception is clavulanic acid, which shows good penetration into alveolar macrophages, and may explain its bacteriological and clinical activity against Legionella spp.

Good intracellular penetration of an antimicrobial, however, does not necessarily correlate with its antibacterial activity. In a study of the effect of fluoroquinolones against macrophages infected with the intracellular pathogens Streptococcus aureus, Legionella pneumophila and Listeria monocytogenes, ciprofloxacin exhibited the lowest intracellular concentration (5.1 mg/L) but the greatest antibacterial effect, whereas sparfloxacin exhibited the highest intracellular concentration (14 mg/L), but the lowest antibacterial effect.26,27 Protein binding is important in the prediction of efficacy; only the unbound portion of the antimicrobial is available to exert an antimicrobial effect. Most fluoroquinolones, with the exception of trovafloxacin, are not highly bound: levofloxacin (25–40%), moxifloxacin (30–45%), ggrepafloxacin (44%), sparfloxacin (45%) and trovafloxacin (70–80%).28–32

Curve (AUBKC) and the intensity of antimicrobial effect (Iα).10,11 The most relevant predictor of clinical efficacy is the concentration of the antimicrobial at the site of infection. Because of the extreme difficulties in the measurement of this parameter, serum concentration and the derived parameters thereafter are surrogates of this.

Prediction of antimicrobial efficacy

β-Lactams and macrolides exhibit time-dependent antibiotic effects with minimal or moderate PAE. The β-lactams typically require serum concentrations to be maintained above the MIC for an organism (t > MIC), to demonstrate an effective clinical response.12 It is also an important parameter related to efficacy in oxazolidinones and macrolides, particularly erythromycin, and may also be important in glycopeptide antimicrobials (vancomycin and teicoplanin).13 Small frequent doses or continuous infusions will be the most effective regimens against a bacterial pathogen, if t > MIC is the main pharmacodynamic parameter of clinical outcome.

Aminoglycosides and fluoroquinolones exhibit concentration-dependent antibiotic effects with a moderate PAE.14 Clinical and animal studies have shown that Cmax/MIC correlates strongly with clinical response in this class.15–17 In vitro studies have shown that a Cmax/MIC ratio of >10 prevented the emergence of antibiotic-resistant microorganisms.18 Large infrequent doses producing high Cmax values will be the most effective regimen against a bacterial pathogen, if Cmax/MIC is the main pharmacodynamic parameter. A further parameter suggested as being important in determining clinical efficacy of fluoroquinolones is the AUIC,19,20 It has been shown that good efficacy is achieved in patient and animal infections if the AUIC exceeds 100.21–23 As long as the critical AUIC is reached, the size or frequency of dosing of the antimicrobial will not determine its efficacy.

Figure 1. Simple pharmacokinetic parameters.
Maximizing efficacy and reducing the emergence of resistance

Over a decade ago, a study of the effect of protein binding in β-lactams using a blister fluid model suggested that high protein binding was associated with low penetration into inflammatory fluids. More recently, in a similar model, inflammatory fluid penetration (AUC in blister fluid/AUC in serum) of the new fluoroquinolones was demonstrated as: sparfloxacin, 117%; ciprofloxacin, 117%; gatifloxacin, 113%; moxifloxacin, 104%; norfloxacin, 107%; and trovafloxacin, 63%. It was suggested that the higher protein binding of trovafloxacin may adversely affect tissue penetration of that drug.

Pharmacodynamics of fluoroquinolones

Historically, the antibacterial activity of fluoroquinolones in animal models has consistently correlated best with AUIC and it has been shown that good efficacy is achieved if the AUIC exceeds 100.

A clinical study of the treatment of nosocomial pneumonia in seriously ill patients with ciprofloxacin established that with an AUIC > 125, the probable clinical and bacteriological cure rates were 80% and 82%, respectively, whereas at an AUIC < 125 probable cure rates were 42% and 26%. A further study of the treatment of acute exacerbations of chronic bronchitis in seriously ill patients with grepafloxacin established that at an AUIC < 75, probable cure rates were 71%; at an AUIC of 75–175 they were 80% and at an AUIC > 175 they were 98%.

A study of the comparative pharmacodynamics of 10 fluoroquinolones against S. pneumoniae produced values of differing magnitude for the two pharmacodynamic parameters (AUIC and Cmax/MIC) but produced similar quinolone groupings. The lowest ratios were seen with lomefloxacin (<5, <1), known to have little activity against S. pneumoniae, and ciprofloxacin and ofloxacin (5–25, 1–5). Higher ratios were seen with the more active fluoroquinolones, levofloxacin, grepafloxacin and gatifloxacin (25–75, 5–10); trovafloxacin (75–250, 10–20) and the highest ratios with moxifloxacin, clinafloxacin and gemifloxacin (≥250, >20). The most recent study with levofloxacin suggests that a ratio of at least 12.2:1 correlates with favourable clinical and microbiological outcome.

Both the AUIC and the Cmax/MIC ratio can be affected by protein binding of the antimicrobial. Although trovafloxacin has in vitro activity similar to moxifloxacin against the most important pathogens and has good bioavailability, it is 85% bound to serum proteins, a high value for new fluoroquinolones. Moxifloxacin is less than 50% bound and thus has higher AUIC and Cmax/MIC ratios. A comparative study of the pharmacodynamic activity of five fluoroquinolones against S. pneumoniae, demonstrated that moxifloxacin (18–37.5) had a much greater Cmax/MIC ratio based on total antibiotic concentration than levofloxacin (3–6), sparflaxin (3) or grepafloxacin (5.6) and only slightly greater than trovafloxacin (12.4–26). When Cmax/MIC ratios based on unbound serum concentration were calculated, the value for moxifloxacin (18–37.5) was again greater than that for grepafloxacin (5.6), levofloxacin (3–6) or sparflaxin (3). (Table 1).

Similar results were achieved by calculating the AUIC. Moxifloxacin achieved the highest AUIC based on total serum antibiotic concentrations (192–400 mg h/L) followed by trovafloxacin (138–287 mg h/L), well above the recommended threshold of 125 mg h/L for seriously ill patients, compared with levofloxacin (24–48), grepafloxacin (65) and grepafloxacin (44). However, the AUIC based on unbound serum antibiotic concentration was high for moxifloxacin (106–280) and again lower for levofloxacin (29–36), sparflaxin (36), grepafloxacin (1.5–4.3) and trovafloxacin (17–86).

Overall, the antimicrobial activity of most fluoroquinolones in the presence of serum is decreased two-fold, with the exception of trovafloxacin where the decrease is four-fold.

Looking at ELF, as a surrogate for the concentration of the antimicrobial drug that may be present at the site of a pneumonic infection, in vitro studies have demonstrated that there was a considerable difference between the ratio of the AUIC (ELF/MIC) for S. pneumoniae against four fluoroquinolones. AUIC for moxifloxacin was 150, grepafloxacin was 120, trovafloxacin was 40 and levofloxacin was 20 (Figure 2).

Development of bacterial resistance

There appears to be a relationship between dosing, clinical failure and the subsequent development of bacterial resistance. It has been suggested that AUIC is important in the prevention of the emergence of resistance in fluoroquinolones.

A clinical study of the treatment of nosocomial pneumonia in seriously ill patients with ciprofloxacin demonstrated that the pathogen was eradicated from half of the patients with an AUIC of >250 on the first day of treatment. At an AUIC < 125, the pathogen was eradicated from only one-third of the patients. At a dose of 400 mg levofloxacin, the pathogen was eradicated from only 16% of patients.

### Table 1. Activity of fluoroquinolones against S. pneumoniae

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Dose (mg)</th>
<th>MIC90 (mg/L)</th>
<th>Cmax/MIC90</th>
<th>AUIC (mg h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>400</td>
<td>0.2</td>
<td>18–37.5</td>
<td>192–400</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>200</td>
<td>0.5</td>
<td>3</td>
<td>65</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500</td>
<td>2</td>
<td>3–6</td>
<td>24–48</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>400</td>
<td>50</td>
<td>5.6</td>
<td>44</td>
</tr>
</tbody>
</table>

*Based on total plasma concentrations. Data from Wise (1999).
The majority of the remainder of patients with an AUIC < 125 were clinical failures and showed stepwise increases in MIC, indicating that they were becoming resistant to treatment. AUIC values between 125 and 250 resulted in the same bacterial endpoint as those with values >250, but eradication was much slower; 6 days for 50% killing with an AUIC 125–250 compared with 1 day with AUIC > 250.

In acutely ill patients with nosocomial lower respiratory tract infections, of patients treated with an antimicrobial with an AUIC < 100, about 40% showed stepwise increases in MIC by day 4, and by day 20 about 80% showed reduced susceptibility, whereas with an AUIC > 100, only 8% of pathogens developed resistance by 20 days after initiation of therapy (Figure 3). There is less likelihood of resistance emerging if the concentration of antimicrobial adequately exceeds the MIC for a particular pathogen.

Discussion

The number of fluoroquinolones available from the pharmaceutical industry aimed mainly at respiratory tract infections, and particularly at S. pneumoniae, is likely to continue to increase over the coming years. Fluoroquinolone-resistant S. pneumoniae are already becoming a significant problem in the USA and Spain. Different resistance mechanisms exist in the fluoroquinolones, including the presence of the multidrug efflux pump gene, pmrA, associated with fluoroquinolone resistance in this species and this may govern the choice of a suitable antimicrobial. To minimize these problems we should utilize highly active antimicrobials with a high AUIC for S. pneumoniae. If the antimicrobial is present in a high enough concentration the appearance of a resistant mutant, which may be two- to four-fold less susceptible, will be prevented from growing and undergoing clonal expansion. The use of antimicrobials with a low AUIC and at low dosage as suggested by some pharmaceutical companies may exacerbate the problem.

The increasing knowledge of the pharmacokinetic and pharmacodynamic properties of the fluoroquinolones is important in helping us to choose the right antimicrobial for a clinical situation or for formulary inclusion, both from the perspective of outcome and also from the perspective of trying to prevent the emergence of resistance in certain groups of pathogens, particularly S. pneumoniae.

References

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