Pharmacokinetics and Pharmacodynamics of Newer Fluoroquinolones

Gary E. Stein

Newer fluoroquinolones currently under development have excellent pharmacokinetic profiles, and several parameters have been improved compared with those of their predecessors. These compounds are well absorbed, have large volumes of distribution, and distribute into most tissues at concentrations equal to or greater than those observed in serum. Moreover, these newer agents have long serum elimination half-lives that allow for once-daily dosing. With the exception of complexes with multivalent cations that retard absorption, there is a relative lack of clinically significant drug-drug interactions with these antimicrobials. Increased microbiological potency against several important pathogens, along with an enhanced pharmacokinetic profile, will make these newer fluoroquinolones preferable over older compounds for the treatment of a variety of infections.

A new series of quinolone antimicrobials (table 1) are currently being developed, and several will be marketed over the next few years [1]. These compounds have several advantages over first-generation agents (nalidixic acid, cinoxacin, and oxolinic acid) and second-generation agents (norfloxacin, enoxacin, pefloxacin, ciprofloxacin, ofloxacin, lomefloxacin, and fleroxacin) [2]. Third-generation quinolones (levofloxacin, clinafloxacin, sparfloxacin, grepafloxacin, DU-6859a, and trovafloxacin) have increased in vitro activity against several important pathogenic organisms as well as augmented pharmacokinetic parameters [3].

These properties result in enhanced pharmacodynamic characteristics and should improve therapeutic outcomes against selected pathogens. In this article the pharmacokinetics, significant drug interactions, and pharmacodynamic potential of these newer fluoroquinolones are reviewed.

Pharmacokinetics

Absorption. Fluoroquinolone antimicrobials normally exhibit rapid dissolution in the gastrointestinal tract and are absorbed in the duodenum and jejunum. Peak serum concentrations are usually attained 1–2 hours after dosing in healthy persons [2]. The third-generation quinolones also exhibit maximal serum concentration (C_max) in ~1–2 hours, with the exception of sparfloxacin (table 2). Sparfloxacin is more slowly absorbed, and its C_max is observed in 4–5 hours [4]. This finding is most likely the result of the lower solubility of sparfloxacin in aqueous solution. Coingestion with food usually increases the time to peak serum concentration by ~1 hour for newer fluoroquinolones, but other pharmacokinetic values are unaltered [5, 9, 10].

The C_max varies significantly among these newer compounds. Following a 200-mg dose, peak levels in the range of 0.7 µg/mL (sparfloxacin) to 2.9 µg/mL (trovafloxacin) are attained (table 2). In dose-ranging studies it has been observed that an increase in dose will result in a linear increase in the C_max for these newer fluoroquinolones [4, 5, 8, 9, 11]. The area under the serum concentration–time curve (AUC) for these agents also increases linearly in proportion to dose. In contrast to its low C_max, sparfloxacin has a large AUC due to its long elimination half-life (table 2).

Distribution. The distribution volumes of the newer fluoroquinolones are large and may exceed those of second-generation compounds. For instance, the distribution volume of grepafloxacin and sparfloxacin have been estimated to be 3.5 L/kg and 4.5 L/kg, respectively [12]. The third-generation quinolones, like their predecessors, exhibit low protein binding. In general, <50% of these compounds binds to serum proteins, although trovafloxacin was found to average 70% protein binding, as determined by equilibrium dialysis [11]. Displacement of highly protein-bound drugs is unlikely with the newer fluoroquinolones, including trovafloxacin.

The penetration of third-generation quinolones into several different tissues and body fluids in humans has been demonstrated. Levofloxacin has been most extensively studied and has characteristics similar to those of ofloxacin [5]. Levofloxacin concentrations in most tissues or fluids are generally higher or similar to those observed in plasma. Considerably lower penetration ratios (16%–26%) occur in the aqueous humor and CSF [13, 14]. Inflammatory fluid penetration of several of the newer fluoroquinolones has been studied [7, 12, 15, 16]. In healthy volunteers, peak concentrations in chemically induced blisters ranged from 41%–81% of those found in serum (table 3).

Distribution into respiratory tract tissues and fluids is of particular interest with regard to these newer compounds because of their improved in vitro activity against common respiratory pathogens [17–19]. Concentrations of grepafloxacin, sparfloxacin, and trovafloxacin in lung tissues have been observed to be higher than those in serum. Trovafloxacin has
Table 1. A summary of third-generation quinolones that are currently being developed.

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Investigational number(s)</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinafloxacin</td>
<td>CI-960, PD 127391</td>
<td>...</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>OPC 17116</td>
<td>...</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>DR-3355</td>
<td>Lefuvaquin*</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>AT 4140, PD131501, RP64206</td>
<td>Zagam*</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>CP 99, 219</td>
<td>...</td>
</tr>
</tbody>
</table>

* Ortho-McNeil Pharmaceutical, Raritan, NJ.
† Rhône-Poulenc Rorer Pharmaceuticals, Collegeville, PA.

Table 2. Mean plasma pharmacokinetic parameters of third-generation quinolones. *

<table>
<thead>
<tr>
<th>Quinolone [reference]</th>
<th>Oral dose (mg)</th>
<th>( t_{\text{max}} ) (h)</th>
<th>( C_{\text{max}} ) (( \mu g/\text{mL} ))</th>
<th>( t_{1/2} \beta ) (h)</th>
<th>AUC (( \text{mg} \cdot \text{h}/\text{L} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sparfloxacin [4]</td>
<td>200</td>
<td>4.0</td>
<td>0.7</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td>Levofloxacin [5]</td>
<td>200</td>
<td>1.5</td>
<td>2.0</td>
<td>6.0</td>
<td>20</td>
</tr>
<tr>
<td>Grepafloxacin [6]</td>
<td>200</td>
<td>2.1</td>
<td>0.7</td>
<td>11</td>
<td>8.8</td>
</tr>
<tr>
<td>Trovafloxacin [7]</td>
<td>200</td>
<td>0.7</td>
<td>2.9</td>
<td>7.8</td>
<td>24</td>
</tr>
<tr>
<td>Clinafloxacin [8]</td>
<td>200</td>
<td>1.5</td>
<td>1.6</td>
<td>6.3</td>
<td>11</td>
</tr>
<tr>
<td>DU-6859a [9]</td>
<td>200</td>
<td>1.0</td>
<td>1.9</td>
<td>4.6</td>
<td>12</td>
</tr>
</tbody>
</table>

* Data are from single-dose studies of healthy volunteers.

NOTE. AUC = area under the serum concentration–time curve; \( C_{\text{max}} \) = maximal serum concentration of drug; \( t_{\text{max}} \) = time after dosing for maximal concentration to be reached; \( t_{1/2} \beta \) = elimination half-life.

Concentrations in serum, bronchial mucosa, and epithelial-lining fluid have been measured in patients following administration of grepafloxacin and sparfloxacin [21, 22]. Bronchoscopy performed 1–3 hours after a 400-mg dose of sparfloxacin enabled determination of median concentrations in the serum (0.5 \( \mu g/mL \)), bronchial mucosa (1.3 mg/kg), and epithelial-lining fluid (5.6 \( \mu g/mL \)). Grepafloxacin (400 mg) was given for 4 days to 6 patients who underwent bronchoscopy 2.2–2.9 hours after the final dose. Mean concentrations in serum, bronchial mucosa, and epithelial-lining fluid were 1.7 \( \mu g/mL \), 4.9 \( \mu g/kg \), and 17.3 \( \mu g/mL \), respectively.

The newer fluoroquinolones also have intraphagocytic bactericidal activity and achieve high intracellular levels. Concentrations of sparfloxacin and grepafloxacin in alveolar macrophages were found to be 5- to 9-fold higher than in serum [21, 22].

High concentrations of these antimicrobials have also been observed in kidney parenchyma, gallbladder tissue and bile, and genital tract tissues [5, 23, 24]. In a study of six surgical patients, mean grepafloxacin concentrations of 0.9 \( \mu g/mL \), 5.6 mg/kg, and 51 \( \mu g/mL \) were attained in serum, gallbladder tissue, and bile, respectively, at 2–5 hours after oral administration of 300 mg (once daily for 3 days) [23]. Grepafloxacin concentrations in gynecologic tissues, such as endometrium, myometrium, cervix, and ovary, were found to exceed maximum serum concentrations by 2–5 times [24].

Elimination. The fluoroquinolones are removed from the body by both renal and nonrenal routes of elimination [2]. High concentrations of unchanged drug can be found in the urine, bile, and feces.

When analyzing the urinary excretion of the third-generation quinolones, one finds these compounds fall into two distinct groups. Greater than 60% of unchanged drug can be recovered in urine following administration of levofloxacin, clinafloxacin, and DU-6859a [5, 8, 9]. In contrast, <10% of

Table 3. Inflammatory fluid penetration of third-generation quinolones.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grepafloxacin (400 mg)</th>
<th>Levofloxacin (500 mg)</th>
<th>Sparfloxacin (400 mg)</th>
<th>Trovafloxacin (200 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum ( t_{\text{max}} ) (h)</td>
<td>2.0</td>
<td>1.2</td>
<td>2.7</td>
<td>0.75</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (( \mu g/\text{mL} ))</td>
<td>1.5</td>
<td>6.6</td>
<td>1.6</td>
<td>2.9</td>
</tr>
<tr>
<td>( t_{1/2} \beta ) (h)</td>
<td>5.2</td>
<td>8.0</td>
<td>18</td>
<td>7.8</td>
</tr>
<tr>
<td>AUC (( \text{mg} \cdot \text{h}/\text{L} ))</td>
<td>12.0</td>
<td>53.2</td>
<td>32.0</td>
<td>24.0</td>
</tr>
<tr>
<td>Blist fluid ( t_{\text{max}} ) (h)</td>
<td>4.8</td>
<td>3.7</td>
<td>5.0</td>
<td>4.0</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (( \mu g/\text{mL} ))</td>
<td>1.1</td>
<td>4.3</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>( t_{1/2} \beta ) (h)</td>
<td>13.0</td>
<td>8.0</td>
<td>20.0</td>
<td>7.1</td>
</tr>
<tr>
<td>AUC (( \text{mg} \cdot \text{h}/\text{L} ))</td>
<td>22.0</td>
<td>54.0</td>
<td>37.0</td>
<td>15.0</td>
</tr>
</tbody>
</table>

Percentage penetration (blister fluid value/serum value)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Grepafloxacin (400 mg)</th>
<th>Levofloxacin (500 mg)</th>
<th>Sparfloxacin (400 mg)</th>
<th>Trovafloxacin (200 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} )</td>
<td>73.0</td>
<td>65.0</td>
<td>81.0</td>
<td>41.0</td>
</tr>
<tr>
<td>AUC</td>
<td>180.0</td>
<td>100.0</td>
<td>117.0</td>
<td>63.0</td>
</tr>
</tbody>
</table>

NOTE. See text for references and table 2 for definitions of abbreviations.
unchanged drug is found in the urine after doses of grepafloxacin, sparfloxacin, and trovafloxacin [4, 11, 12].

Changes in renal function can have a significant impact on the elimination of these drugs, including those that have low urinary recovery. For instance, the serum elimination half-life of sparfloxacin in patients with moderate or severe renal impairment (glomerular filtration rates of 22 mL/min and 7.7 mL/min, respectively) was found to be approximately two times higher than observed in healthy volunteers [25].

The effect of renal impairment on the pharmacokinetics of levofloxacin has also been studied [5]. The mean elimination half-lives in patients with creatinine clearances of 40–70 mL/min, 20–40 mL/min, and <20 mL/min were 6.4, 11, and 28 hours, respectively. Excretion into the bile of unchanged drug makes up only a small percentage of total elimination of these compounds, although concentrations in bile fluid can be several times higher than simultaneous levels in serum [5, 26]. High fecal concentrations have also been observed following the administration of newer fluoroquinolones such as grepafloxacin and sparfloxacin [6, 27].

Hepatic transformation of the third-generation quinolones is variable. Levofloxacin undergoes limited metabolism [5]. Conversely, grepafloxacin exhibits extensive metabolism to conjugated and unconjugated metabolites [28]. These metabolites represent minor components in the plasma, and active conjugates are much less potent than the parent compound.

Only one metabolite of sparfloxacin has been identified [27]. This conjugated metabolite is inactive and recovered in urine in a ratio of 2 to 1, metabolite to free sparfloxacin [4]. The major pathway for sparfloxacin elimination appears to be biliary excretion. The effect of liver impairment on the excretion of individual compounds will likely depend on their major route of elimination.

The serum elimination half-life of the third-generation quinolones ranges from 4.6 to 21 hours in healthy adults (table 2).

**Drug Interactions**

The absorption of quinolone antibiotics is significantly decreased by concomitant administration of compounds that contain multivalent metal cations such as aluminum, magnesium, zinc, iron, and calcium [29]. This effect appears to be due to the formation of insoluble drug-cationic chelate complexes in the gastrointestinal tract [30]. The bioavailability of third-generation quinolones has been shown to be decreased by ~50% when they are administered with aluminum-magnesium antacids [31]. It has been recommended that fluoroquinolones be given at least 2 hours prior to administration of these compounds [32]. A longer interval may be necessary with sparfloxacin because of its slower rate of absorption [4]. A significant interaction has also been observed when sparfloxacin and ferrous sulfate were administered together: the Cmax of sparfloxacin was diminished by 38% [33].

The clearance of other drugs can be altered by the coadministration of certain fluoroquinolones [29]. For instance, ciprofloxacin and enoxacin have been shown to inhibit theophylline and caffeine metabolism, resulting in adverse effects such as nausea, vomiting, and CNS excitement. Pharmacokinetic studies of sparfloxacin, levofloxacin, and trovafloxacin have found that these newer fluoroquinolones do not significantly alter theophylline metabolism in healthy volunteers [5, 34, 35].

A case involving a significant clinafloxacin-theophylline drug interaction has been reported [36]. In this case, the steady-state serum concentration of theophylline more than doubled following intravenous administration of clinafloxacin (200 mg every 12 hours). Clinafloxacin is known to inhibit the metabolism of theophylline in rats, but a controlled pharmacokinetic study of humans will be needed to substantiate this observation.

The quinolone antibiotics can cause competitive inhibition of γ-aminobutyric acid, and some nonsteroidal antiinflammatory drugs (NSAIDs) are known to enhance this inhibition [29]. In laboratory studies, inhibition of γ-aminobutyric acid by newer fluoroquinolones does not appear to be enhanced by NSAIDs. When compared with second-generation quino-
Antimicrob Chemother 1994;33:685-

Table 4. Correlation of pharmacokinetic and microbiological properties of third-generation quinolones against Streptococcus pneumoniae, Staphylococcus aureus, and Bacteroides fragilis.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg)</th>
<th>Serum C&lt;sub&gt;max&lt;/sub&gt; (µg/mL)</th>
<th>S. pneumoniae C&lt;sub&gt;max&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>S. aureus C&lt;sub&gt;max&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>B. fragilis C&lt;sub&gt;max&lt;/sub&gt;/MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinafloxacin</td>
<td>200</td>
<td>1.5</td>
<td>0.12</td>
<td>12.0</td>
<td>0.06</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>400</td>
<td>1.5</td>
<td>0.25</td>
<td>6.0</td>
<td>0.12</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>500</td>
<td>6.6</td>
<td>0.25</td>
<td>6.6</td>
<td>0.25</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>400</td>
<td>1.6</td>
<td>0.25</td>
<td>6.4</td>
<td>0.12</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>200</td>
<td>2.9</td>
<td>0.25</td>
<td>12.0</td>
<td>0.06</td>
</tr>
<tr>
<td>DU-6859a</td>
<td>200</td>
<td>1.9</td>
<td>0.12</td>
<td>16.0</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Finally, increasing activity against anaerobic organisms is another microbiological advantage of the newer fluoroquinolones [47, 50–53]. Moreover, these fluoroquinolones can be bactericidal under anaerobic conditions [54]. Even though the MICs for an organism such as Bacteroides fragilis are usually ≤2.0 µg/mL, several of the third-generation quinolones would normally attain serum levels above these inhibitory concentrations with standard dosing (table 4).

It appears that compounds such as clinafloxacin, trovafloxacin, and DU-6859a would have the greatest potential to successfully treat a variety of anaerobic infections. For example, trovafloxacin has been shown to significantly reduce colony counts of B. fragilis in a murine mixed-infection model [18]. These pharmacodynamic and animal model data suggest that clinical investigations of selected third-generation quinolones for the treatment of anaerobic infections are warranted.

Conclusions

The structural changes incorporated into these newer fluoroquinolones have made important contributions to their microbiological and pharmacokinetic profiles. These changes will be especially useful for the treatment of infections due to gram-positive bacteria. The third-generation quinolones may become preferable for the treatment of a variety of infections because of their broad spectrum of activity as well as their improved pharmacokinetics and the relative lack of serious drug-drug interactions.

References


