Grepafloxacin: pharmacokinetics and tissue penetration

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Pharmacokinetic and tissue penetration studies of grepafloxacin, a new broad-spectrum fluoroquinolone, show that it has useful properties for the treatment of respiratory tract infections. Grepafloxacin has a volume of distribution that is larger than those of many of the other fluoroquinolones and is concentrated in alveolar macrophages, bronchial mucosa and epithelial lining fluid to a greater extent than are certain other fluoroquinolones. Grepafloxacin concentrations achieved in plasma after a 400-mg oral dose are well in excess of those required to inhibit the respiratory pathogens *Staphylococcus aureus, Haemophilus influenzae* and *Moraxella catarrhalis*. *Streptococcus pneumoniae* is also covered for most of the dosing interval, but at normal dose levels grepafloxacin might not inhibit *Enterococcus faecalis*. The maximum plasma concentrations and area under the concentration-time curve achieved with grepafloxacin suggest that it will be effective for the treatment of community-acquired pneumonia and acute exacerbations of chronic bronchitis. The pharmacokinetics of fluoroquinolones are among their most useful properties. The aim of this paper is to demonstrate whether the differences between grepafloxacin and the other fluoroquinolones are of therapeutic significance.

Key words: Pharmacokinetics, fluoroquinolone, grepafloxacin, respiratory tract infection, tissue penetration

STRUCTURE–ACTIVITY RELATIONSHIP

One of the main structural differences between grepafloxacin and other fluoroquinolones is the presence of the two amine groupings, a secondary and a tertiary amine, at position 7. Although difficult to prove, it is possible that the degree of amination of the molecule at this site may be related to some important pharmacokinetic properties. Although all fluoroquinolones have large volumes of distribution, fluoroquinolones with the structure described above tend to have larger volumes of distribution than the others [1].

A volume of distribution of 1 L/kg is equivalent to the body volume being penetrated by the drug. A drug with a volume of distribution of 2 L/kg or more is being concentrated somewhere in the body. In general, the fluoroquinolones concentrate at two important sites: within the phagocytic cells of the body—the white blood cells and macrophages—and in the various mucosae of the body, often the site of infection.

Thus, high volumes of distribution, leading to high tissue levels of drug, particularly in the phagocytes and mucosa, are important pharmacokinetic characteristics of the fluoroquinolones.

PHARMACOKINETICS

In an early study using grepafloxacin, six healthy male volunteers (mean age 28 years, mean weight 73 kg) were given a single oral dose of grepafloxacin, 400 mg [2]. The levels of the drug were measured in plasma, in urine and in a cantharidin-induced inflammatory fluid model. The data were analyzed by a two-compartment (plasma) or one-compartment (inflammatory fluid) model.

There is considerable biological variation in the inflammatory fluid data using this model. After oral administration, grepafloxacin was shown to penetrate rapidly into plasma and, somewhat later though still fairly rapidly, into the inflammatory fluid (Figure 1). Peak concentration was achieved at about 2 h in plasma
and about 80% for ofloxacin [6]. Grepafloxacin penetrates into the inflammatory fluid to a greater extent than any other fluoroquinolone we have studied.

Other multidose pharmacokinetic studies have shown similar results, with grepafloxacin half-lives of about 12–15 h (Table 2) [3]. Doubling the dose doubles the area under the concentration–time curve (AUC).

Minimum inhibitory concentrations

An oral dose of grepafloxacin, 400 mg, achieves plasma concentrations that are well in excess of those required to inhibit (in an in vitro model) the respiratory pathogens *Staphylococcus aureus*, *Haemophilus influenzae* and *Moraxella catarrhalis* [2,7]. *Streptococcus pneumoniae* was also covered for most of the dosing interval, but at normal dose levels grepafloxacin may not inhibit *Enterococcus faecalis* infections. *H. influenzae* and *M. catarrhalis* were covered for some 36 h after a single oral dose of grepafloxacin, 400 mg [2,7].

*Escherichia coli* and *Salmonella* spp. are extremely sensitive, and grepafloxacin would be expected to be active against them [8]. Grepafloxacin should not be used to treat infections with *Pseudomonas aeruginosa* or anaerobic organisms, such as *Bacteroides* spp.

Metabolism

In common with other fluoroquinolones, there is some metabolism of grepafloxacin with opening up of the ring structure at position 5, and some glucuronidation, the product of which has minimal microbiological activity compared to the parent compound. Grepafloxacin is eliminated by metabolism...
primarily through the liver. Metabolites account for less than 10% of the dose in plasma, urine and feces. Urinary excretion of unchanged drug ranges from 6% to 14% [9]. A total of 27% of drug is eliminated unchanged in the feces (data on file).

**TISSUE PENETRATION**

Respiratory tract penetration by fluoroquinolones can be assessed by measuring antibiotic concentration in the sputum by endotracheal suction, bronchial biopsy or bronchoalveolar lavage. Grepafloxacin is found to accumulate in the polymorphonuclear cells (Figure 2), where many pathogens can reside, and the concentrations achieved are greater than those for ofloxacin, levofloxacin and DR-3354 [10].

In epithelial lining fluid, there are very high concentrations that peak in excess of 10 mg/L (Table 3, Figure 3) [11,12]. Here, grepafloxacin is concentrated about 13-fold compared with ciprofloxacin, which concentrates 5–7-fold [4]. In bronchial mucosa, the mean levels exceed those in plasma by about three-fold [11]. Other fluoroquinolones tend to be concentrated 2–3-fold [13]. In alveolar macrophages, grepafloxacin is concentrated over 100-fold [11], compared with about 50-fold for ciprofloxacin [4].

In comparison, if other classes of antimicrobial agents are considered, β-lactam concentrations in

**Table 3** Respiratory tract pharmacokinetics of grepafloxacin; n = 24, mean time = 4.5 h (range 0.42–12.8 h)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Plasma mg/L</th>
<th>Bronchial mucosa mg/kg</th>
<th>Epithelial lining fluid mg/L</th>
<th>Alveolar macrophages mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.2</td>
<td>3.4</td>
<td>14</td>
<td>177</td>
</tr>
<tr>
<td>Range</td>
<td>0.18–2.3</td>
<td>0.8–8.4</td>
<td>1.7–48.6</td>
<td>13.5–417</td>
</tr>
<tr>
<td>Mean tissue/plasma ratio</td>
<td>3.1</td>
<td>12.3</td>
<td>12.3</td>
<td>181</td>
</tr>
<tr>
<td>Range</td>
<td>1.7–5.5</td>
<td>0.8–42</td>
<td>17–551</td>
<td></td>
</tr>
<tr>
<td>(±SD)</td>
<td>(±1.0)</td>
<td>(±8.9)</td>
<td>(±145)</td>
<td></td>
</tr>
</tbody>
</table>

Based on Cooke et al [11].
Table 4 Comparison of antimicrobial penetration of the respiratory tract with fluoroquinolones, β-lactams and macrolides

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Bronchial mucosa</th>
<th>Epithelial lining fluid</th>
<th>Alveolar macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolones</td>
<td>1.5–3:1</td>
<td>3–12:1</td>
<td>10–34:1</td>
</tr>
<tr>
<td>β-Lactams</td>
<td>0.4:1</td>
<td>0.25:1</td>
<td>0.1:1</td>
</tr>
<tr>
<td>Macrolides</td>
<td>2–10:1</td>
<td>10+:1</td>
<td>20+:1</td>
</tr>
</tbody>
</table>

*Deplends on time and the agent tested. Reproduced with kind permission from the BMJ Publishing Group, from Honeybourne [14].

bronchial mucosa only achieve about 40% of serum levels (Table 4) [14]. Some macrolides, e.g. azithromycin, penetrate the bronchial mucosa well, whereas others, such as erythromycin, do not. In epithelial lining fluid, β-lactams only reach concentrations 25% those of serum, whereas some macrolides penetrate well. Macrolides, but not β-lactams, penetrate alveolar macrophages [14].

CORRELATION OF PHARMACODYNAMICS AND OUTCOME

The ratio of peak concentration to MIC and of AUC to MIC are considered important for prediction of efficacy; which is used depends to some extent on the disease being treated. The Schentag data suggest that in nosocomial pneumonia the AUC/MIC ratio needed is about 125:1 [15]. This is achieved for grepafloxacin. In community-acquired pneumonia, in which it is not necessary to be quite so rigorous as in nosocomial pneumonia, either an AUC/MIC ratio of 50:1 or a peak/MIC ratio of 10 is considered reasonable [16]. Grepafloxacin would be expected to be effective in these two diseases, given that doses of 400 or 600 mg/day are used; with a peak AUC of 19.7 mg/L/h, a grepafloxacin peak serum level of about 1.4 mg/L and given an MIC of *Streptococcus pneumoniae* of about 0.12 mg/L, the AUC/MIC ratio is about 150 and the peak/MIC ratio is about 12.

CONCLUSIONS

The fluoroquinolones are interesting agents from a pharmacokinetic viewpoint. They penetrate rapidly into the blood, pass rapidly into extracellular fluid and inflammatory exudates, penetrate phagocytic cells (macrophages, white blood cells) and the mucosa and are concentrated in these sites and still maintain good serum levels relative to MICs. As might be expected, there is less penetration into some of the more

specialized sites of the body, such as cerebrospinal fluid and the anterior eye. For the important sites of common infections, such as lower respiratory tract infections, however, the high concentrations achieved with grepafloxacin are of considerable clinical importance.

References