A review of the penetration of sparfloxacin into the lower respiratory tract and sinuses

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There are a number of potential sites of infection in the lower respiratory tract. This review summarises the nature of these sites and the ways in which antibiotic penetration can be studied. The results of a single-dose and a multiple-dose study of the penetration of sparfloxacin into the respiratory tract are also provided. After a single oral dose of sparfloxacin 400 mg or a 400 mg loading dose on day 1 followed by 200 mg daily for 2 days, sparfloxacin concentrations in the bronchial mucosa, epithelial lining fluid and alveolar macrophages were higher than the corresponding concentrations in serum. Compared with other fluoroquinolones, sparfloxacin achieves higher concentrations at these sites. Sparfloxacin diffusion into maxillary sinus mucosa has been studied in patients with chronic maxillary sinusitis undergoing surgery. High concentrations of sparfloxacin were detected in sinus mucosa 2 to 5 h after administration of a single dose of sparfloxacin 200 or 400 mg.

Introduction

The concentration of an antimicrobial agent at the site of infection is generally considered to be an important factor for adequate bacterial killing in order to achieve clinical cure. From the viewpoint of pharmacodynamic processes, the respiratory tract is difficult to study because infection can occur in a number of distinct sites: the bronchi, in acute bronchitis and acute exacerbations of chronic bronchitis; the fluid lining the terminal bronchioles and alveoli (epithelial lining fluid or ELF), in pneumonia; and the alveolar macrophages and other intracellular loci for the 'atypical' pneumonias. The treatment of infected sinus mucosa is challenging because it is difficult for an antimicrobial agent to penetrate this compartmentalised and inflamed site. In this review, the nature of the relevant sites of infection are summarised and the penetration of sparfloxacin into the lower respiratory tract as well as into sinus mucosa are described.

Sparfloxacin is a newer fluoroquinolone agent with enhanced activity against respiratory tract pathogens (Cooper et al., 1990) and much of its clinical use will be in the treatment of lower respiratory tract infections and sinusitis. Thus, accurate knowledge of its penetration into the various sites is important.
Sites of potential infection

**Bronchial mucosa**

The mucosa of the mid and lower airways is bathed in sputum and many pharmacokinetic studies have measured drug concentrations in samples of expectorated sputum. Because sputum pools in the airways, it is an unsuitable fluid for pharmacokinetic studies, although antibacterial agent concentrations in sputum may have an influence upon the final clearance of pathogens from the airways. Bronchial mucosa, as obtained by fibreoptic bronchoscopy, consists of submucosa (53.4%), ciliated epithelium (22.3%), muscle (17.6%) and glandular tissue (7.0%) (Baldwin et al., 1992a). The total water content is about 70%. Most antimicrobial agents pass readily from capillaries into extracellular fluid and hence into interstitial fluid. Therefore, the concentrations in extracellular fluid can be assumed to be equivalent to those in serum. β-Lactams and aminoglycosides penetrate poorly into cells and achieve concentrations in the interstitial fluid similar to those found in serum. In a homogenised sample these agents would therefore only achieve concentrations as predicted by the extracellular water content, that is, no greater than 35–45% of that in serum. This is indeed what we have observed in the case of the β-lactams (Wise & Honeybourne, 1995).

**Epithelial lining fluid (ELF) and alveolar macrophages**

The non-fenestrated endothelium is the main barrier to the passage of drugs from capillaries to the pulmonary interstitial tissue (Weibel, 1969). Hence the ELF which bathes the alveoli has a significant barrier between it and the systemic circulation. It is possible to obtain accurate measurements of the concentrations of antimicrobial agents in the ELF by using urea (which readily crosses membranes) as a marker molecule, performing bronchoalveolar lavage (BAL) and using a highly sensitive assay system to analyse samples. This method has been reviewed by Baldwin, Honeybourne & Wise (1992a).

Alveolar macrophages also reside at this site and are important because the 'atypical' pathogens (*Legionella pneumophila* and *Chlamydia pneumoniae*) multiply within these cells. Aminoglycosides and β-lactams do not accumulate within alveolar macrophages, although Tulkens (1991) has shown that these antimicrobial agents are slowly taken up through endocytosis and localised in the lysosomes, where their activity is diminished by low pH. Tulkens has also demonstrated that fluoroquinolones accumulate throughout alveolar macrophages and that macrolides accumulate in the lysosomes. Alveolar macrophages are accessible to BAL (Baldwin et al., 1992a) and our group has undertaken studies on the penetration of different antimicrobial agents into alveolar macrophages (Wise & Honeybourne, 1995).

**Sinus mucosa**

The sinus mucosa is relatively thin and pressure induced by infection reduces the ability of blood to circulate in this tissue. Consequently, it is difficult for some antibacterial agents administered systemically to penetrate into this region in adequate concentrations. Tissue penetration of a given agent can be measured by administering the antibacterial agent pre-operatively and obtaining a tissue sample during surgery.
Other sites

Various workers have studied the penetration of antimicrobials into 'lung tissue' which usually implies the assay of drug concentrations in an open biopsy sample of pulmonary tissue. It is difficult to interpret the relevance of results obtained by these means; however, concentrations in excess of those in serum implies that the agent must be concentrated to some degree in these respiratory tissues. The penetration of drugs into pleural fluid is also frequently studied.

Penetration of sparfloxacin into pulmonary tissues and fluids

Bronchial mucosa, ELF and alveolar macrophages

The concentrations of sparfloxacin attained in bronchial mucosa, ELF and alveolar macrophages following single and multiple oral doses have been measured (Honeybourne et al., 1994).

Twenty-one patients of either sex aged ≥ 18 y undergoing investigation for suspected lung cancer were enrolled for a single-dose study. Each patient received sparfloxacin 400 mg orally before bronchoscopy. Sampling times following administration of sparfloxacin were 1–3 h (n = 5), 12 h (n = 5), 24 h (n = 6) and 48 h (n = 5). A bronchial mucosa biopsy was taken from one or the other subcarina and ELF and alveolar macrophages were obtained by BAL.

Eleven patients fulfilling the same inclusion criteria as described above were enrolled in the multiple-dose study. Each patient received an oral loading dose of sparfloxacin 400 mg on day 1 followed by sparfloxacin 200 mg daily on days 2 and 3. Bronchoscopy was performed and bronchial and serum samples were taken 2.5 and 5 h after the last dose was administered.

The results of the single-dose study are presented in Table I. Concentrations in bronchial mucosa, ELF and alveolar macrophages exceeded serum concentrations for each time period.

In the multiple-dose study one patient failed to attend for bronchoscopy and was withdrawn from the analysis. The results for the remaining ten patients are presented in Table II. Sparfloxacin concentrations at all sites were higher than those observed after single dose administration and the tissue/fluid:serum concentration ratios were enhanced.

Table I. Mean concentrations (± S.D.) of sparfloxacin in serum and pulmonary tissues and fluids after a single oral dose of 400 mg (adapted from Honeybourne et al., 1994)

<table>
<thead>
<tr>
<th>Mean time (h) (± S.D.)</th>
<th>No. of subjects</th>
<th>Serum (mg/L)</th>
<th>Bronchial mucosa (mg/kg)</th>
<th>ELF (mg/L)</th>
<th>Alveolar macrophages (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2 ± 0.6</td>
<td>6</td>
<td>0.8 ± 1.0</td>
<td>2.4 ± 2.7</td>
<td>10.3 ± 15.2</td>
<td>34.1 ± 39.1</td>
</tr>
<tr>
<td>13.1 ± 1.2</td>
<td>5</td>
<td>1.2 ± 0.4</td>
<td>2.6 ± 0.7</td>
<td>9.8 ± 5.7</td>
<td>61.3 ± 31.2</td>
</tr>
<tr>
<td>24.6 ± 0.8</td>
<td>5</td>
<td>0.6 ± 0.2</td>
<td>1.6 ± 0.5</td>
<td>10.2 ± 4.5</td>
<td>36.3 ± 10.9</td>
</tr>
<tr>
<td>49.4 ± 0.8</td>
<td>5</td>
<td>0.3 ± 0.2</td>
<td>1.1 ± 0.5</td>
<td>4.6 ± 3.8</td>
<td>37.9 ± 45.1</td>
</tr>
</tbody>
</table>
Table II. Mean concentrations (±s.d.) of sparfloxacin in serum and pulmonary tissues and fluids of 10 patients 2.5 to 5 h after repeated-dose administration (400 mg loading dose day 1 followed by 200 mg daily on days 2 and 3)

<table>
<thead>
<tr>
<th>Site</th>
<th>Sparfloxacin concentration (mg/L or mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>Bronchial mucosa</td>
<td>4.4 ± 3.0</td>
</tr>
<tr>
<td>ELF</td>
<td>15.0 ± 8.3</td>
</tr>
<tr>
<td>Alveolar macrophage</td>
<td>53.7 ± 38.4</td>
</tr>
</tbody>
</table>

Other respiratory tissues

In a multicentre study, a single oral dose of sparfloxacin 400 mg was administered to 24 patients who had a pleural effusion (data on file, Rhône-DPC, Europe; Veyssier, Levy & Touron, 1994). Pleural sampling was carried out in all patients at 4 h or 20 h. The mean ratio of site:serum concentration was 0.34 and 0.91, respectively. Hence, sparfloxacin is not concentrated in pleural fluid but it can be assumed that the concentration in this exudate/transudate would equilibrate with that in serum after repeated-dose administration.

In a separate study, 15 patients requiring surgery for bronchial or pulmonary cancer received a single oral dose of sparfloxacin 400 mg (data on file, Rhône-DPC, Europe). Blood and tissue sampling was performed 2 to 6 h post-dose (Group A) or 12 to 24 h post-dose (Group B). Intrabronchial mucus, healthy parenchyma, tumour tissue, bronchial wall and pulmonary artery wall samples were collected during surgery. In Group A, sparfloxacin concentrations in mucus, pulmonary parenchyma, tumour tissue, bronchial wall and pulmonary artery wall were 2-2.7, 5.9, 4.0, 2.8 and 2.7 times greater, respectively, than the corresponding serum concentrations. In Group B, sparfloxacin concentrations in mucus, pulmonary parenchyma, tumour tissue, bronchial wall and pulmonary artery wall were 2.4-2.7, 15.8, 5.0, 5.8 and 4.7 times greater, respectively, than the corresponding concentrations in serum.

Penetration of sparfloxacin into sinus tissues and fluids

Sparfloxacin concentrations in sinus tissues and fluids were determined in 35 patients undergoing surgery, 11 of whom had chronic maxillary sinusitis (data on file, Rhône-DPC, Europe; Massias et al., 1993). Thirty-one patients received a single dose of sparfloxacin 400 mg and the remaining four patients received sparfloxacin 200 mg. Between 2 and 5 h after administration of sparfloxacin 400 mg, the mean sparfloxacin concentration in maxillary sinus mucosa was 5.81 mg/kg. The mean tissue:plasma concentration ratios exceeded 2.86 for all the tissues analysed except adipose tissue. The highest mean ratio was found for sinus mucosa (9.0).

It is difficult to determine the relevance of these results because of the highly haemorrhagic nature of the samples collected. Additionally some of the patients were suffering from chronic sinusitis with a significant polypous component and therefore the secretions were mucous rather than purulent. Nevertheless, it has been shown that sparfloxacin does penetrate well into nasal secretions, reaching a mean peak concentration of 6.84 mg/L following a single oral dose of sparfloxacin 400 mg (data on file, Rhône-DPC, Europe). The maximum nasal secretion:serum concentration ratio was 15.4 and the average was 4.5.
Table III. Penetration of five fluoroquinolones into the respiratory tract (results expressed as site:serum ratio) (cf. Wise & Honeybourne, 1995)

<table>
<thead>
<tr>
<th>Fluoroquinolone</th>
<th>Dosage</th>
<th>Bronchial mucosa</th>
<th>ELF</th>
<th>Alveolar macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>250 mg bd × 4</td>
<td>1.7</td>
<td>1.9</td>
<td>14.3</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>400 mg daily × 4</td>
<td>1.9</td>
<td>2.8</td>
<td>15.8</td>
</tr>
<tr>
<td>Temafloxacin</td>
<td>600 mg bd × 3</td>
<td>1.6</td>
<td>3.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Rufloxacin</td>
<td>400 mg × 1</td>
<td>1.6</td>
<td>7.7</td>
<td>9.4</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>400 mg × 1</td>
<td>3.3</td>
<td>11.9</td>
<td>41.3</td>
</tr>
</tbody>
</table>

A comparison of sparflloxacin with other fluoroquinolones

Results of the respiratory tract penetration of sparflloxacin and four other fluoroquinolones are compared in Table III. The five agents all penetrated into bronchial mucosa to a similar extent, although the relative penetration of sparflloxacin was approximately twice that of ciprofloxacin, temafloxacin and the long acting agent, rufloxacin. Sparfloxacin also displayed superior penetration into ELF and alveolar macrophages. In-vitro studies have shown the intracellular penetration of sparflloxacin to be greater than that of other fluoroquinolones (Carlier, Faraji & Tulkens, 1990). Therefore, the greater penetration of sparflloxacin into pulmonary tissues and fluids probably reflects the physicochemical properties of sparflloxacin rather than its pharmacokinetic properties per se.

The sinus mucosa:plasma concentration ratio for ciprofloxacin in patients suffering from sinusitis has been found to range from 1.5 to 3 (Gehanno et al., 1992). Following a single dose of 400 mg of sparflloxacin, the mean plasma C_max was found to be 0.81 mg/L and the mean concentration in the sinus mucosa 9-fold greater (Massias et al., 1993).

Discussion

The results of Honeybourne et al., (1994) indicate that following administration of recommended dosages, sparflloxacin achieves concentrations in the bronchial mucosa several-fold higher than those necessary to inhibit common respiratory pathogens such as *Streptococcus pneumoniae* (sparfloxacin MIC_90 0.25 mg/L), *Haemophilus influenzae* (MIC_90 0.015 mg/L) and *Moraxella catarrhalis* (MIC_90 0.03 mg/L) (Cooper et al., 1990). ELF may equate to the fluid in which a bacterial pneumonia may develop and the concentration of sparflloxacin in ELF exceeds the MIC_90 of *S. pneumoniae* for as long as 48 h after a 400 mg dose (Cooper et al., 1990). The influence of inflammation upon the penetration of sparflloxacin into ELF is not known; however, sparflloxacin is concentrated in human PMNs (Carlier et al., 1990) and within these cells the quinolone is associated with the lysosomes as well as the cytosol. Release from the neutrophils is rapid.

In-vitro studies have been conducted to evaluate the penetration of sparflloxacin into murine macrophage-like cell lines (Carlier et al., 1990). Sparfloxacin is concentrated up to 11.9-fold in these cells whereas the corresponding values for ciprofloxacin and pefloxacin were 5.1- and 7.7-fold, respectively. In the study of Honeybourne et al. (1994), sparflloxacin concentrations in macrophages greatly exceeded those necessary to inhibit 'atypical' pathogens (Cooper et al., 1990). Hence, both in-vitro and in-vivo
studies suggest that sparfloxacin attains higher intracellular concentrations than certain other quinolones.

Concentrations of sparfloxacin achieved in the tissues and fluids of sinus tissue were higher than the reported MIC\textsubscript{90} values of the commonest aerobic organisms implicated in acute or chronic sinusitis.

There is sparse information on the relationship between tissue penetration of antimicrobial agents into the respiratory tract and clinical outcome. In bronchial infections, evidence from Anthonisen et al. (1987) and Orr et al. (1993) suggests that there is often a poor correlation between antibacterial treatment and clinical outcome and that only the most seriously ill patients benefit from therapy. Maesen et al. (1976) demonstrated that clinical improvement was more rapid when sputum concentrations of ampicillin (following bacampicillin therapy) exceeded the MIC of the pathogen for >3 h. In clinical trials, quinolones such as ofloxacin have proved effective for the treatment of acute exacerbations of chronic bronchitis (Ball, 1990) and there appears to be a better correlation between bronchial mucosal concentrations and clinical outcome than between serum concentrations and clinical outcome.

Similarly in bacterial pneumonia, the evidence that tissue concentrations of antimicrobial are relevant is circumstantial. Noone et al. (1974) showed that outcome was correlated with peak gentamicin concentrations. Nix et al. (1987) found a correlation between the ciprofloxacin MIC and the outcome of Gram-negative pneumonia. There is no direct evidence that concentrations of an antimicrobial agent in ELF or alveolar macrophages are relevant to clinical outcome. Indirect evidence from macrolide therapy (especially azithromycin) suggests that concentrations at these two sites certainly correlate better with cure than, for instance, serum concentrations.

In conclusion, although there is little firm evidence that tissue penetration is important, intuitively, an antimicrobial agent that achieves high concentrations at the site of infection would appear to be a reasonable choice over an agent that did not have this property. The fluoroquinolones all penetrate well into the various sites of the lower respiratory tract, although sparfloxacin achieves higher concentrations at these sites than other currently marketed fluoroquinolones. This, in conjunction with the superior activity of sparfloxacin against \textit{S. pneumoniae}, suggests that sparfloxacin would be a suitable choice amongst the fluoroquinolones to treat a wide variety of infections of the lower respiratory tract. Sparfloxacin also achieves good concentrations in sinus mucosa and has been shown to be effective clinically in the treatment of acute sinusitis (Gehanno et al., 1996).

References


