A study to determine the pharmacokinetics and inflammatory fluid penetration of gatifloxacin following a single oral dose


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A single 400 mg oral dose of gatifloxacin was given to each of nine healthy male volunteers and the concentrations of the drug in plasma, cantharidine-induced inflammatory fluid and urine were measured over the following 24 h. The mean peak concentration in plasma of 4.1 mg/L was attained at a mean time of 1.8 h post dose. The mean peak concentration in inflammatory fluid was 3.6 mg/L and was attained at a mean time of 4.2 h post dose. The mean plasma elimination half-life of gatifloxacin was 6.8 h and that in inflammatory fluid was 7.2 h. The mean penetration into the inflammatory fluid was 117%. Recovery of drug from urine during the first 24 h post dose was 65% of that administered. Our data suggest that gatifloxacin dosed at 400 mg od should be adequate to treat systemic infections caused by most bacterial species.

Introduction

Gatifloxacin is an 8-methoxy-7-(3-methylpiperazinyl) fluoroquinolone which shows a broad spectrum of antibacterial activity, especially enhanced against Gram-positive bacterial pathogens (in particular Streptococcus pneumoniae including those strains resistant to penicillin). Preliminary information indicates that gatifloxacin has an elimination half-life of about 7–10 h suggesting that once daily dosing will be appropriate for the treatment of susceptible pathogens. In this study, the pharmacokinetics and penetration of gatifloxacin into an inflammatory exudate were examined following a single 400 mg dose given by the oral route.

Materials and methods

Nine healthy caucasian male volunteers between the ages of 19 and 39 years (mean age 29, mean height 178 cm, mean weight 81 kg) were enrolled. They had no history of serious illness, atopy (particularly allergy to fluoroquinolones), alcohol or drug abuse or an acute illness in the 14 days before the start of the study. They had not received any prescribed or over-the-counter medication (other than minor analgesics) in the 14 days before gatifloxacin administration.

Approval for this study was granted by the Hospital Ethics Committee and all volunteers gave written informed consent. All volunteers underwent a full history and examination, including ECG, and were shown to have normal haematological and biochemical profiles and normal urinalysis.

On the evening before the study, two 1 cm² 0.2% cantharidine-impregnated plasters were attached to the subjects' forearms to induce blister formation. Plasma samples were obtained from the contra-lateral arm following insertion of an iv catheter kept patent by flushing with 0.9% saline (Antigen Pharmaceuticals, Rosecrea, Ireland). The dose was given to the fasting subjects with 200 mL of water. The subjects then fasted for a further 3 h when a light breakfast was given. A further 2 h later fluid and food was allowed ad libitum.

About 10 mL of venous blood was collected before the dose, then 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 h post dose. Between 50 and 100 L of inflammatory fluid was aspirated with a fine needle before administration of the dose and then at 0.5, 1, 1.5, 2, 4, 6, 8, 12 and 24 h. The blister was re-sealed with a plastic spray dressing (Opsite, Smith & Nephew, Hull, UK). Urine was collected 0–4, 4–8, 8–12, 12–24 h post dose. At 30 h post dose the routine haematological and biochemical tests were repeated.

Drug analysis

All samples were analysed within 1 h of collection. Concentrations of gatifloxacin in plasma, inflammatory fluid and urine were measured using a microbiological assay. A ssay...
plates containing Iso-Sensitest agar (CM471, Oxoid, Basingstoke, U K) were flooded with a suspension of Escherichia coli 4004 (Bayer AG, Wuppertal, Germany) adjusted to an OD of 0.004 at 630 nm in sterile distilled water. The calibrator range was 0.125–2 mg/L. Internal controls and quality assurance samples were prepared in human plasma (Bradsure Biologicals, Market Harborough, U K) in 70% human plasma (to simulate the protein content of the blister fluid) and phosphate buffer (pH 7) for the assay of gatifloxacin in plasma, inflammatory exudate and urine, respectively.

The lower limit of detection was 0.06 mg/L. The between-assay coefficients of variation were 9.5% and 10.1% for concentrations of 0.2 mg/L and 1.5 mg/L, respectively and the correlation coefficient \( r^2 \) (calibration curves) over a concentration range of 0.13–2 mg/L was 0.9617.

Pharmacokinetic analysis

Standard non-compartmental analysis was used to determine the pharmacokinetic parameters. The maximum concentration of gatifloxacin in plasma (\( C_{\text{max}} \)) and time to \( C_{\text{max}} \) (\( T_{\text{max}} \)), the area under the plasma or skin blister fluid concentration curve up to the last measurable concentration (\( \text{AUC}_{\text{last}} \)), the area under the plasma or skin blister fluid concentration curve extrapolated to infinity (\( \text{AUC}_{\infty} \)), and the elimination half-life (\( t_{\frac{1}{2}} \)) in plasma or skin blister fluid were calculated by the non-compartmental model 200 of PCNONLIN version 4.2a (Scientific Consulting Inc., Apex, NC, USA).

Results

The mean concentration–time profiles found in plasma and inflammatory fluid following the administration of 400 mg gatifloxacin is shown in the Figure and the derived pharmacokinetic parameters are summarized in the Table.

![Figure. Gatifloxacin volunteer study: mean concentrations following a single 400 mg oral dose.](image)

<table>
<thead>
<tr>
<th></th>
<th>Blister</th>
<th>Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (mg/L) (b)</td>
<td>3.6</td>
<td>41</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>4.2</td>
<td>1.8</td>
</tr>
<tr>
<td>( t_{\frac{1}{2}} ) (h)</td>
<td>7.2</td>
<td>0.84</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{last}} ) (mg.h/L) (%)</td>
<td>28.7</td>
<td>8.8</td>
</tr>
<tr>
<td>( \text{AUC}_{\infty} ) (mg.h/L) (%)</td>
<td>36.9</td>
<td>9.4</td>
</tr>
<tr>
<td>Urine excretion (% of dose)</td>
<td>1170</td>
<td>0.25</td>
</tr>
<tr>
<td>Mean</td>
<td>5.4</td>
<td>9.3</td>
</tr>
<tr>
<td>S.D.</td>
<td>4</td>
<td>0.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>0.96</td>
<td>0.09</td>
</tr>
<tr>
<td>Maximum</td>
<td>0.29</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Table: Pharmacokinetic parameters of gatifloxacin in nine healthy volunteers following a single 400 mg dose
The mean $C_{\text{max}}$ of gatifloxacin in plasma was 4.1 mg/L. The $T_{\text{max}}$ was 1.8 h after oral administration. The mean terminal elimination half-life from plasma was 6.8 h, the range of individual values 6.3–8.4 h. The AUC$_{\text{last}}$ and AUC$_{0-\infty}$ were 27.9 and 31.4 mg.h/L.

Gatifloxacin penetrated into the inflammatory fluid moderately rapidly, the mean $T_{\text{max}}$ being 4.2 h. Individual variation was large, with a minimum of 1.5 h and a maximum of 8 h. The mean $C_{\text{max}}$ in the inflammatory fluid was 3.6 mg/L (range 2.2–7.6 mg/L). The mean elimination half-life of gatifloxacin from the inflammatory exudate was slightly greater than that from plasma (7.2 h). The individual variation was greater in the inflammatory fluid data than in the plasma data. The mean percentage penetration of gatifloxacin into inflammatory fluid, calculated by comparing the AUC$_{0-\infty}$ for measurements taken in the inflammatory exudate with that for measurements taken in plasma was 117.0%, range 138.5–103.7.

The mean urinary excretion of the drug in the 24 h following the oral dose was 65%; however, one volunteer excreted only 29.6% and collection may have been incomplete. If these data are removed the mean excretion is 69.4%. Physical examination revealed no abnormalities attributable to gatifloxacin administration. The biochemical haematological and ECG parameters studied revealed no abnormalities. One volunteer complained of a headache starting 8 h post dose which resolved 2 h later after administration of 1 g paracetamol.

**Discussion**

There is limited published information on the pharmacokinetics of gatifloxacin, including cases where it exists in plasma as two equi-active equi-proportional enantiomers. Our results are in good agreement with earlier findings in terms of the AUC data. We noted the $C_{\text{max}}$ to be slightly greater, at 4.1 mg/L while both the earlier reports found the value to be 3.8 mg/L. One of the earlier reports suggested a longer elimination half-life from plasma of 8.6 ± 1.4 h. Our data suggest a slightly lower value of 6.8 h in close agreement with Stahlberg et al.

Fluoroquinolones penetrate into inflammatory exudate to varying extents, ranging from 64% in the case of trovafloxacin to 133% for grepafloxacin, the greater protein binding of the former being a possible explanation for the difference. The protein binding of gatifloxacin is 20%. The extent of penetration of gatifloxacin, 117%, is very similar to that of ciprofloxacin and sparfloxacin (103% and 117%, respectively). As the mean 24 h concentration in the inflammatory fluid was c. 0.4 mg/L, and the MIC of 90% of S. pneumoniae, H. influenzae, M. catarrhalis, Chlamydia spp. and the majority of the Entero- bacteriaceae are ≤0.39 mg/L. This suggests that a wide range of organisms should be amenable to treatment.

There is work to suggest that certain pharmacodynamic parameters will be predictive of clinical response. The ratio of AUC to the MIC (AUIC) is said to reflect clinical efficacy. For S. pneumoniae this ratio is c. 80 for gatifloxacin; greater than that obtained with ciprofloxacin given as a 500 mg oral dose (AUIC = c. 60). The ratio of MIC to the $C_{\text{max}}$ is thought to be relevant in the prevention of the emergence of resistance. For gatifloxacin this ratio is c. 10, again approximately twice that of ciprofloxacin. These data suggest both that gatifloxacin will be successful in the treatment of respiratory tract infections caused by the pneumococcus, and that resistance will be less likely to emerge with the new compound in comparison with less active established agents.

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**References**


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