Pharmacokinetics of enoxacin and its oxometabolite after multiple oral dosing and penetration into prostatic tissue

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The objective of this study was to determine the concentrations of enoxacin and its oxometabolite in human prostatic tissue after multiple oral doses (400 mg bd) in 13 patients. On the first day of treatment, elimination half-lives were 6.8 h for enoxacin and 7.1 h for its metabolite; they were increased on day 4 (10.3 and 13.2 h, respectively). The ratios of drug concentration in prostatic tissue and plasma averaged 2.2 for enoxacin and 1.4 for its metabolite. In conclusion, concentrations of enoxacin achieved within the prostatic tissue were higher than plasma concentrations suggesting that there was an active transport mechanism.

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Introduction

Enoxacin is a synthetic antibacterial drug of the fluoroquinolone class, and is rapidly bactericidal against Gram-positive and -negative organisms including \textit{Pseudomonas aeruginosa} and Enterobacteriaceae.\textsuperscript{1} This drug has a bioavailability of c. 77–90\%, a large volume of distribution (c. 200 L), an elimination half-life of 3.3–5 h and a total clearance averaging 480 mL/min.\textsuperscript{2,3} However, enoxacin kinetics were dose-dependent at doses between 200 and 800 mg.\textsuperscript{2,3} The main metabolite, oxoenoxacin, had anti-bacterial activity about one-tenth that of the parent drug.\textsuperscript{1}

The distribution of enoxacin into prostatic tissue has been widely studied but no data are available on the distribution of the oxometabolite.

The aim of this study was to assess the pharmacokinetic profile of enoxacin and oxoenoxacin after multiple oral dosing, and to investigate their penetration into the prostatic tissue.

Materials and methods

Patients

This study was carried out in 13 male patients, ranging from 48 to 75 years old (mean ± s.d., 62.8 ± 7.33 years), and from 62 to 93 kg in weight (mean ± s.d., 74.7 ± 8.65 kg). These patients were hospitalized for benign prostatic adenoma (suprapubic or transurethral prostatectomy). They had no history of allergy to antimicrobial agents, and the results of physical examination, routine haematology, blood chemistry and urinalysis studies performed on each patient before the study were normal. The patients presented no evidence of acute progressive disease or renal (creatinine clearance, calculated according to Cockcroft and Gault formula, ranging from 56.2 to 88.7 mL/min) or hepatocellular failure. The patients were enrolled in the study after giving written informed consent. The study protocol was reviewed and approved by the institutional review board.

Study design

Before surgery, each patient was premedicated with enoxacin 400 mg bd orally for 3 days. A final (seventh) dose was given the day of surgery (day 4), c. 6 h before surgical incision, with a 12 h interval between the sixth and the seventh doses. Blood samples (6 mL) were collected in heparinized glass tubes: (i) immediately pre-dose; (ii) 0.5, 1, 2, 3, 4, 8 and 12 h post-dose on days 1 and 4; (iii) just before the first doses on days 2 and 3; (iv) at 16, 24 and 36 h post-dose on day 4; and (v) the day of surgery at the time of tissue sample. Plasma was separated from blood by centrifugation (3000 g for 10 min), then immediately put in to two polypropylene tubes.
To prevent urinary contamination of prostatic chips, the bladder was emptied of all urine before their removal. Prostatic tissue samples (c. 300 mg) were washed for 30 s in physiological saline to remove traces of blood or urine, dried on gauze and then put in a polypropylene tube. Plasma and tissue samples were immediately frozen and stored at –80°C until assayed. Concentrations of enoxacin and oxoenoxacin were determined by high-performance liquid chromatography.

Pharmacokinetic analysis

$C_{\text{min}}$ and $C_{\text{max}}$ are trough and peak observed concentrations, respectively. The time of the $C_{\text{max}}$ was designated $t_{\text{max}}$. Elimination half-life was determined from the slope of the log-linear part curves.

In order to take into account the residual plasma concentration before the seventh dose, the plasma concentrations ($C_{\text{corrected}}$) at each sampling time were corrected as follows: $C_{\text{corrected}} = C_{\text{observed}} - C_{\text{residual}}$ and $C_{\text{residual}} = C_{0} e^{-\lambda_{c} t}$, where $C_{0}$ is the plasma concentration before the seventh dose, and $\lambda_{c}$ is the elimination rate constant and $t$ is the time post-dose.

The areas under the curve (AUCs) were obtained by log-linear trapezoidal approximation: (i) on days 1 and 4 from zero (pre-dose) to 12 h ($\text{AUC}_{0-12}$); (ii) on day 1, from 0 to infinity by dividing the last observed data point by the elimination rate constant ($\text{AUC}_{0-\infty}$); and (iii) on day 4, using corrected concentrations, from 0 to 12 h, and from 0 to infinity.

The total body clearance of the parent drug was calculated from the relationship: $CL/F = \text{dose}/\text{AUC}$.

The accumulation ratios for the parent drug and its metabolite were calculated from: (i) $1/[1 - e^{-\lambda_{c} \tau}]$, where $\tau$ is the dosing interval; (ii) AUC (0–12 h)$_{\text{day 4}}$/AUC (0–12 h)$_{\text{day 1}}$; and (iii) from $C_{\text{max}}$ day 4/$C_{\text{max}}$ day 1.

Statistical analysis

Pharmacokinetic parameters ($t_{\text{max}}, C_{\text{max}}, \text{AUC}_{0-12}, \text{AUC}_{0-\infty}, CL/F$ and elimination half-life) evaluated after the first oral administration and after the last dose (computed using corrected concentrations) were compared using the Friedman test. In order to avoid a possible bias caused by different sampling schedules (12 versus 36 h, respectively), the elimination half-life and AUC were computed, on day 4, from drug concentrations versus time curve between 0 and 12 h.

A two-way ANOVA was performed to compare measured trough values. In case of a significant result, a simple contrast test was used to compare 2-by-2 each group. Before analyses, AUCs, $C_{\text{max}}$ and $C_{\text{min}}$ were previously transformed into their logarithms.

Unweighted least-squares regression analyses of AUC versus age, AUC versus creatinine clearance and plasma concentrations versus tissue concentrations were carried out. The significance of the regression was confirmed by the $F$-test. A $P$ value <0.05 was taken as the threshold of probability.

Results

Table I summarizes mean observed and calculated pharmacokinetic parameters; trough plasma concentrations are reported in Table II.

For both the parent drug and its metabolite, significant differences occurred between the following parameters: AUC$_{0-12}$, AUC$_{0-\infty}$, CL/F and elimination half-life, determined on day 4 and those determined on the first day of treatment. The accumulation ratios are presented in Table I. Methods B and C gave nearly identical results, but they were significantly different from those computed from the equation $1/[1 - e^{-\lambda_{c} \tau}]$.

Mean tissue/plasma ratios averaged 2.2 for enoxacin and 1.4 for oxoenoxacin. When tissue concentrations of enoxacin were plotted against corresponding plasma concentrations, a statistically significant straight line could be fitted to the data ($r = 0.57, P = 0.0386$). For the metabolite there was no significant relationship with corresponding plasma concentrations.

Strong correlations were found between creatinine clearance and AUC$_{0-12}$ ($r = -0.815, P < 0.0008$ on day 1, and $r = -0.707, P < 0.007$ on day 4 for enoxacin; $r = -0.741, P < 0.004$ on day 1 for oxoenoxacin). No significant relationship was found between AUC and age.

Discussion

Enoxacin showed a 37% reduction in CL/F and a 51.4% increase in elimination half-life after 4 days of treatment compared with day 1. Similar dose-dependent changes were reported after single$^{2}$ and repeated$^{3}$ doses and could be due to a saturable metabolism. The elimination half-life of the oxometabolite is similar to that of enoxacin and increased from day 1 to day 4.

Enoxacin is minimally bound to serum proteins (c. 35%); thus, when enoxacin concentrations are compared with the in vitro activity of the drug, it might be expected that repeated administration of enoxacin (400 mg bd) would lead to plasma enoxacin concentrations exceeding the MIC$_{90}$ of many Gram-negative bacteria (Enterobacteriaceae MIC$_{90}$ < 1 mg/L, *Haemophilus influenzae* MIC$_{90}$ = 0.12 mg/L) and methicillin-susceptible *Staphylococcus* (MIC$_{90}$ = 1 mg/L).$^{5}$ The MIC$_{90}$ of *Pseudomonas* spp. (2 mg/L) is also covered.$^{5}$

The prostatic tissue concentrations of enoxacin, 35–320% higher than plasma concentrations, suggested an active transport mechanism. The low protein binding and the pK$_{a}$ values (6 and 8) of enoxacin may favour entrapment in the

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Table I. Mean (± s.d.) pharmacokinetic parameters of enoxacin and oxoenoxacin

<table>
<thead>
<tr>
<th></th>
<th>Day 1 enoxacin</th>
<th></th>
<th>Day 1 oxoenoxacin</th>
<th></th>
<th>Day 4 enoxacin</th>
<th></th>
<th>Day 4 oxoenoxacin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>mean ± s.d.</td>
<td>min–max</td>
<td>mean ± s.d.</td>
<td>min–max</td>
<td>mean ± s.d.</td>
<td>min–max</td>
<td>mean ± s.d.</td>
</tr>
<tr>
<td>Peak (C\text{max}) (µg/L)</td>
<td></td>
<td>2741 ± 969</td>
<td>765–4891</td>
<td>336 ± 93.7</td>
<td>209–452</td>
<td>5080 ± 1131</td>
<td>3286–7706</td>
<td>363 ± 83.5</td>
</tr>
<tr>
<td>C\text{time of tissue sample} (µg/L)</td>
<td></td>
<td>1233–5429a</td>
<td>3559 ± 1164a</td>
<td>198 ± 88.1**</td>
<td>1131–363</td>
<td>1355–5429a</td>
<td>2440.5 ± 960.9</td>
<td>222.0 ± 102.2</td>
</tr>
<tr>
<td>Tissue concentration (ng/g)</td>
<td></td>
<td>–</td>
<td>–</td>
<td>3286–7706</td>
<td>262–529</td>
<td>3559 ± 1164a</td>
<td>198 ± 88.1**</td>
<td>1131–363</td>
</tr>
<tr>
<td>Cmax</td>
<td></td>
<td>7.60</td>
<td>12.00</td>
<td>1.25</td>
<td>1.00</td>
<td>2.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>AUC0–12 (µg L/h)</td>
<td></td>
<td>14 875 ± 4512</td>
<td>2148 ± 530</td>
<td>33084 ± 9558</td>
<td>2896 ± 770</td>
<td>19 195 ± 5824**</td>
<td>1307 ± 543**</td>
<td>21 862 ± 7309</td>
</tr>
<tr>
<td>min–max</td>
<td></td>
<td>0.5–2.0</td>
<td>1.0–3.0</td>
<td>0.5–2.0</td>
<td>1.0–3.0</td>
<td>0.5–2.0</td>
<td>1.0–3.0</td>
<td>0.5–2.0</td>
</tr>
<tr>
<td>t1/2 elim (last sampling time 12 h) (h)</td>
<td></td>
<td>6.80 ± 2.11</td>
<td>7.05 ± 3.21</td>
<td>12.4 ± 9.22**</td>
<td>14.7 ± 12.8**</td>
<td>10.3 ± 2.45***</td>
<td>13.2 ± 3.91****</td>
<td>21.4 ± 11.4</td>
</tr>
<tr>
<td>min–max</td>
<td></td>
<td>–</td>
<td>–</td>
<td>12.4 ± 9.22**</td>
<td>14.7 ± 12.8**</td>
<td>10.3 ± 2.45***</td>
<td>13.2 ± 3.91****</td>
<td>–</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td></td>
<td>21.4 ± 11.4</td>
<td>–</td>
<td>13.4 ± 4.15*</td>
<td>–</td>
<td>1.42 ± 0.23</td>
<td>1.45 ± 0.26</td>
<td>2.31 ± 0.57</td>
</tr>
<tr>
<td>Accumulation ratios</td>
<td></td>
<td>A</td>
<td>–</td>
<td>1.42 ± 0.23</td>
<td>1.45 ± 0.26</td>
<td>2.31 ± 0.57</td>
<td>1.38 ± 0.33</td>
<td>2.05 ± 0.79</td>
</tr>
</tbody>
</table>

Pharmacokinetic parameters computed from corrected plasma concentrations.

s.d., standard deviation; C\text{time of tissue sample}, plasma concentration at the time of tissue sample; AUC, area under curve; t1/2 elim, elimination half-life; CL, total clearance; min, minimum value; max, maximum value; A, from the equation 1/[1 – e–\text{t/12}] (theoretical ratios), where \text{t} is the dosing interval (i.e. 12 h); B, from AUC0–12, day 4/AUC0–12, day 1; C, from C\text{max} day 4/C\text{max} day 1. *P < 0.05; **P < 0.01; ***P < 0.001.

Table II. Mean (± s.d.) trough concentration values

<table>
<thead>
<tr>
<th></th>
<th>Day 2</th>
<th>Day 3</th>
<th>before drug intake</th>
<th>12 h after drug intake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxacin (µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± s.d.</td>
<td>1033 ± 400</td>
<td>1447 ± 706</td>
<td>1615 ± 834</td>
<td>1675 ± 695</td>
</tr>
<tr>
<td>Oxoenoxxacin (µg/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± s.d.</td>
<td>156 ± 39</td>
<td>183 ± 53</td>
<td>183 ± 62</td>
<td>167 ± 60</td>
</tr>
<tr>
<td>min–max</td>
<td>96–216</td>
<td>83.6–267</td>
<td>69.9–322</td>
<td>81.5–317</td>
</tr>
</tbody>
</table>

Min, minimum value; max, maximum value; s.d., standard deviation.

Enoxacin: day 2 statistically different from days 3 and 4; day 2 statistically different from day 4 (12 h); day 3 statistically different from day 4 (12 h).

Oxometabolite: day 2 statistically different from days 3 and 4; day 3 statistically different from day 4 (12 h).
human prostatic environment which has a lower pH than plasma (pH 7.28 in normal individual). The tissue concentrations reported in this study were all above the MIC of enoxacin for usual pathogens causing infections at this site (Enterobacteriaceae, methicillin-susceptible Staphylococcus aureus, Neisseria gonorrhoeae MIC$_{90} = 0.08–0.16$ mg/L) and enoxacin can be considered as a useful drug in the treatment of prostatitis and in prophylaxis of prostatic surgery.

As previously reported, enoxacin is tolerated well by patients, many of them elderly, with few side effects.7

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References


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