Pharmacokinetics of moxifloxacin in non-inflamed cerebrospinal fluid of humans: implication for a bactericidal effect

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Objectives: To evaluate the ability of moxifloxacin to penetrate healthy brain barriers.

Methods: Fifty patients received a single oral dose of 400 mg as an antimicrobial prophylaxis regimen for a short urological procedure under spinal anaesthesia. Serum and cerebrospinal fluid (CSF) were sampled at different time intervals post-drug intake and patients were divided into five groups, as follows: group I: 0.5–1 h; group II: 1–2 h; group III: 2–4 h; group IV: 4–6 h; and group V: 6–8 h. Concentrations of moxifloxacin were estimated after analysis by an HPLC system. Bactericidal activity of CSF samples of groups III and IV was assessed by a microdilution technique against two penicillin-resistant isolates of Streptococcus pneumoniae with MICs of moxifloxacin of 0.19 and 0.125 mg/L, respectively.

Results: Mean CSF concentrations of moxifloxacin of groups I, II, III, IV and V were 0.19, 0.87, 3.00, 4.07 and 1.82 mg/L, respectively. The mean bactericidal activity of CSF of group III was 8 and that of group IV was 4.

Conclusions: Single oral intake of 400 mg moxifloxacin is accompanied by good penetration through healthy meninges within 2–6 h post-dose and reached adequately high levels in human CSF exerting satisfactory bactericidal activity against penicillin-resistant S. pneumoniae. These results render novel perspectives for a role of moxifloxacin in CNS infections.

Keywords: penicillin resistance, brain barrier, Streptococcus pneumoniae

Introduction

The transport and diffusion of antimicrobials in the central nervous system (CNS) are strictly controlled by the blood–brain barrier and by the tight junctions between endothelial vasculature.1,2 The worldwide spread of isolates of Streptococcus pneumoniae with reduced susceptibility to penicillin and to third-generation cephalosporins has led to research efforts for agents able to achieve therapeutic concentrations in the CNS. Moxifloxacin is a new quinolone derivative with broad coverage against Gram-positive cocci, Gram-negative bacteria and atypical pathogens comprising even penicillin-resistant S. pneumoniae.3 Its high lipophilicity makes moxifloxacin a promising agent for penetration into the subarachnoid space and the CNS.

Although, several experimental studies have evaluated the role of moxifloxacin in the eradication of CNS infections in laboratory animals caused by penicillin-resistant S. pneumoniae and Escherichia coli,4–6 data in humans are lacking. The aim of this study was to evaluate the penetration of moxifloxacin through the blood–brain barrier in the non-inflamed cerebrospinal fluid (CSF). It was also investigated whether CSF could have any bactericidal activity against penicillin-resistant S. pneumoniae.

Patients and methods

Study design

This was a prospective study performed during the period December 2001–October 2003. Fifty patients (42 male, 8 female, mean ± SD age 66.5 ± 10.6 years) undergoing a scheduled urological operation...
Moxifloxacin in CSF

Estimation of drug levels

Concentrations of moxifloxacin were estimated by an HPLC analysis as previously described using ciprofloxacin as an internal standard. Briefly, 250 μL of sample was diluted with 250 μL of displacing reagent and centrifuged for 5 min at 2700 g. The displacing reagent consisted of 0.5% SDS (Merck, Darmstadt, Germany) and 20% acetonitrile (Merck) in 75 mM sodium phosphate buffer (pH 7.5). A 10 μL aliquot of the supernatant was injected into a HPLC system (Agilent 1100 Series; Agilent Technologies, Waldbronn, Germany) with the following elution characteristics: Nucleosil 100-5 C18 (4.6 mm × 250 mm, 5 μm) column at 37°C; mobile phase consisting of a pH 3.0 buffer composed of 25 mM Na_3PO_4 and 10 mM SDS, and acetonitrile 99% at a 35:65 ratio with a flow rate of 1 mL/min; and ultraviolet detection at 293 nm. The retention time of moxifloxacin was 2.8 min and its concentration was estimated (in mg/L) using a standard curve created with known concentrations of moxifloxacin. All determinations were performed in duplicate. The lower concentration of the standard curve was 0.09 mg/L and the upper concentration was 50 mg/L. The R² of the curve was 0.9997. The inter-day variation of the assay was 0.04%.

Bactericidal activity of CSF

Bactericidal activity of CSF was studied for all samples of groups III and IV, which were found to have the highest concentrations of moxifloxacin among the five groups (see below). Two penicillin-resistant isolates of _S. pneumoniae_ (1035 and 5731) were used. Both were isolated from blood of two HIV-positive individuals with lobar pneumonia. They were grown on Columbia agar (Becton–Dickinson, Sparks, MD, USA) enriched with 5% defibrinated sheep blood (E&O Laboratories Ltd). MICs of penicillin G, ceftriaxone, levofloxacin, moxifloxacin and vancomycin were determined by Etest according to the instructions of the manufacturer (AB Biodisk, Sole, Sweden). Bactericidal activity of CSF was estimated in a 96-well plate at a final volume of 100 μL per well in Todd Hewitt broth (Becton–Dickinson) with serial 2-fold dilutions of the CSF and 1 × 10⁴ cfu per well. Bactericidal activity was defined as the lowest CSF dilution killing 99.9% of colonies after 18 h of incubation at 37°C and 5% CO₂.

Statistical analysis

Since participants acted as healthy volunteers, the necessary number for each group was determined according to former publications. Concentrations are expressed as means and SDs. Comparisons between groups were performed by one-way analysis of variance (ANOVA) with post hoc Bonferroni correction. Correlations between serum and CSF concentrations were done by Spearman’s rank of order. Any value of P < 0.05 was considered significant.

Results

Concentrations of moxifloxacin in serum and CSF of the five groups of patients are shown in Table 1. No significant correlations were found between serum and CSF concentrations separately within each of the five groups. The mean CSF to serum ratio of the concentrations of moxifloxacin was 0.03 for group I, 0.26 for group II, 0.51 for group III, 0.81 for group IV and 0.53 for group V.

The drug was well tolerated by all patients. MICs of penicillin, ceftriaxone, levofloxacin, moxifloxacin and vancomycin for isolate 1035 were 1, 0.75, 1, 0.19 and 0.25 mg/L, respectively, and the MICs for isolate 5731 were 1, 1, 2, 0.125 and 0.25 mg/L, respectively. Mean bactericidal activity of CSF of group III against isolate 1035 was 8 (range 4–8) and that against isolate 5731 was 8 (range 4–8). Mean bactericidal activity of CSF of group IV against isolate 1035 was 4 (range 4–8) and that against isolate 5731 was 4 (range 4–8).

Discussion

Penetration of antimicrobials in the subarachnoid space is a limiting factor for the successful management of infections of the CNS. Moxifloxacin is a novel quinolone derivative with promising _in vitro_ activity against Gram-positive cocci. This is the first study in humans providing information on the concentrations of moxifloxacin in the CSF and on its penetration through the non-inflamed meninges after a single oral administration. Mean levels between 3 and 4 mg/L were detected in the CSF 2–6 h post-administration. No correlation was detected between serum

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum (mg/L, mean ± SD)</th>
<th>CSF (mg/L, mean ± SD)</th>
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</thead>
<tbody>
<tr>
<td>I (0.5–1 h)</td>
<td>2.08 ± 2.52</td>
<td>0.19 ± 0.61</td>
</tr>
<tr>
<td>II (1–2 h)</td>
<td>3.37 ± 1.61</td>
<td>0.87 ± 1.09</td>
</tr>
<tr>
<td>III (2–4 h)</td>
<td>6.55 ± 3.61</td>
<td>3.00 ± 1.84</td>
</tr>
<tr>
<td>IV (4–6 h)</td>
<td>5.49 ± 1.72</td>
<td>4.07 ± 1.15</td>
</tr>
<tr>
<td>V (6–8 h)</td>
<td>3.31 ± 1.71</td>
<td>1.82 ± 1.15</td>
</tr>
</tbody>
</table>

_P values of comparisons with group I in the same compartment: *not significant; *P = 0.002; *P = 0.039; *P < 0.0001; *P = 0.007._
and CSF levels, probably implying that penetration of moxifloxacin through the blood–brain barrier is performed by a mechanism other than simple diffusion.

Hypotheses about a probable role of moxifloxacin in the therapy of infections of the CNS are based on published data related to its in vitro activity against bacterial pathogens. Two large Greek surveys have been published on the in vitro susceptibility of \textit{S. pneumoniae}. The first involved 460 isolates in winter 2000 and 485 isolates in winter 2003 in Athens, all being colonizers of the nasopharynx. The second reported 780 isolates colonizing the nasopharynx of children <6 years old in day-care centres and 89 isolates from patients with lower respiratory tract infection. The MIC\textsubscript{90} of moxifloxacin for all isolates, comprising both penicillin-susceptible and penicillin-resistant isolates, was 0.25 mg/L. The MIC\textsubscript{90} for \textit{Neisseria meningitidis} is reported to be 0.008 mg/L.\textsuperscript{11} As a consequence, it may be hypothesized that the CSF concentration/MIC\textsubscript{90} ratio for \textit{S. pneumoniae} is almost 16 and for \textit{N. meningitidis} almost 500 when applying the greatest concentrations of moxifloxacin achieved in CSF in the present study. In the same context, the MIC\textsubscript{90} for methicillin-resistant \textit{Staphylococcus aureus} is reported to be 0.5 mg/L,\textsuperscript{12} yielding a respective ratio of 8. These calculations propose that moxifloxacin may be an adequate alternative either for the management of community-acquired CNS infections or even for chemoprophyaxis in neurosurgery.

Pharmacodynamics of fluoroquinolones is generally expressed by the AUC/MIC ratio.\textsuperscript{13} AUC in the CSF cannot be calculated in the present study because one single sample was drawn from each patient. Repeated CSF sampling can only be calculated above and renders the hypothesis for a role of moxifloxacin in CNS infections favourable.

Only one study has been published on the bactericidal activity of moxifloxacin against both penicillin-susceptible and penicillin-resistant \textit{S. pneumoniae}.\textsuperscript{16} Serum collected from 12 healthy volunteers after administration of a 3 day oral regimen of moxifloxacin was used. Mean serum bactericidal activity was 32. Taking into account that CSF levels in the present study were almost half those of serum, it may be postulated that these results on the serum bactericidal activity of moxifloxacin are in line with those reported here for CSF. Estimation of bactericidal activity presents, however, certain limitations that may be summarized as follows: (i) the time interval between drug administration and fluid sampling; (ii) the size of the applied inoculum; and (iii) the applied diluent.\textsuperscript{17}

Concentrations of moxifloxacin in CSF in humans were assessed in the present study in a setting of absence of meningeval inflammation. Previous experimental studies of meningitis in rabbits caused by \textit{S. pneumoniae} and \textit{E. coli} revealed that penetration of moxifloxacin was very satisfactory through the inflamed meninges,\textsuperscript{5,6} reaching concentrations equal to those reported here. As a consequence, it may be hypothesized that in the event of meningitis in humans, concentrations of moxifloxacin in CSF could be even higher.

The presented results revealed that oral intake of 400 mg of moxifloxacin is accompanied by good penetration through healthy meninges within 2–6 h post-dose and reached adequately high levels in human CSF exerting satisfactory bactericidal activity against penicillin-resistant \textit{S. pneumoniae}. Although studies with a larger number of patients may seem mandatory, these results render novel perspectives for a role of moxifloxacin in CNS infections.

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**Transparency declarations**

None to declare.

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