Pharmacokinetics of Moxifloxacin in Cerebrospinal Fluid and Plasma in Patients with Tuberculous Meningitis

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Moxifloxacin cerebrospinal fluid (CSF) penetration was evaluated by obtaining full plasma and CSF time concentration curves for 4 patients with tuberculous meningitis. The geometric mean ratio of the areas under the curve for CSF to plasma were 0.82 (range, 0.70–0.94) at 400 mg once per day and 0.71 (0.58–0.84) at 800 mg once per day.

The outcome of tuberculous meningitis (TBM) is dominated by diagnostic delay and limited therapeutic options, because of adverse effects or resistance to first-line drugs, as well as poor cerebrospinal fluid (CSF) penetration of some of the first- and second-line drugs. The combination of isoniazid, rifampicin, pyrazinamide, and ethambutol or streptomycin is recommended for the treatment of TBM by the World Health Organization. However, this schedule is not based on strong scientific evidence; no randomized, controlled trials or extensive pharmacokinetic studies have supported these recommendations.

Moxifloxacin, which has the highest in vitro activity against Mycobacterium tuberculosis, compared with the other quinolones [1], has emerged as the most promising second-line agent for treatment of tuberculosis if adverse effects or drug resistance limit the use of first-line agents. Although moxifloxacin is not approved for tuberculosis treatment, it appeared to be well tolerated at a dose of 400 mg during long-term treatment of pulmonary tuberculosis [2]. This drug has shown the potential to shorten tuberculosis treatment in the murine model and is being evaluated in clinical trials as a first-line agent that may enable shortening of treatment. On the basis of vitro and in vivo studies, it has been suggested that a moxifloxacin dosage of 800 mg once per day can suppress resistance [3], but no safety data are available to support administration of this dosage. Moxifloxacin cannot be recommended yet for standard use in the treatment of TBM, because there is a paucity of data on the CSF penetration of moxifloxacin in humans [4, 5], and animal data have revealed variability in the CSF penetration of moxifloxacin [6, 7]. In addition, plasma drug concentrations of moxifloxacin are lowered by 30% by coadministration of rifampicin [8]. Therefore, additional studies involving humans are needed to measure plasma and CSF concentrations of moxifloxacin over time to establish the optimal dose for treatment of TBM.

Material and methods. Moxifloxacin was administered at an oral dosage of 400 mg once per day for at least 5 days, followed by 800 mg once per day. Plasma and CSF concentrations were evaluated twice (after each fifth dose; steady-state) [9]. The local ethics committee of the University Medical Centre Groningen approved the treatment protocol and informed consent of all included patients was obtained.

Blood and CSF samples were collected before moxifloxacin administration and at 1, 2, 4, 8, 12, and 24 h after administration of the dose. For plasma and CSF sampling, a peripheral intravenous catheter and an external lumbar drain were inserted. Patency of the peripheral catheter was maintained by a saline drip. Before a blood sample was taken, the drip was stopped, and the first 4 mL of blood were discarded. Total (protein-bound plus unbound) concentrations were assessed in plasma and CSF samples using a validated method on high-performance liquid chromatography with fluorescence detection [8] and unbound concentrations (which represent the drug that can cross biological barriers and interact with the bacteria) were assessed following ultrafiltration (Centrifree Ultrafiltration device; Millipore). Pharmacokinetic parameters were assessed with standard noncompartmental pharmacokinetic methods using the software package MWPPharm, version 3.60 (Medware). Ratios of the area under the concentration-time curves up to 24 h after administration of the dose (AUC0–24h) in CSF versus plasma were calculated to express the penetration of moxifloxacin in CSF. The patients’ M. tuberculosis isolates were subjected to drug susceptibility testing with use of the Middlebrook 7H10 agar dilution method [10]. The ratio of the
AUC\textsubscript{0–24h} and the minimal inhibitory concentration (MIC) was calculated, because the AUC\textsubscript{0–24h}/MIC ratio has been proposed to be the best pharmacokinetic/pharmacodynamic parameter to predict in vivo efficacy of fluoroquinolones against fast-growing gram-negative bacteria [11] and M. tuberculosis [12]. To assess the AUC\textsubscript{0–24h}/MIC more accurately, these values were also calculated for unbound drug concentrations [11]. To assess the safety of moxifloxacin at a higher dosage, the serum glucose level was determined, and liver and renal function tests were performed. Electrocardiography monitoring was performed to assess possible QTc prolongation.

All results are presented as median values with interquartile ranges (IQRs). Because data were not normally distributed, nonparametric tests (ie, the Wilcoxon signed-rank test and the Spearman correlation test) were used in the statistical analysis.

### Results

Four male patients were referred to our center for treatment of TBM during the period 2007–2008; the diagnosis was confirmed by leptomeningeal biopsy or CSF analysis; M. tuberculosis culture results were positive for all of the patients. Their median age was 47 years (IQR, 30–65 years), and the median body mass index (calculated as weight in kilograms divided by the square of height in meters) was 21.1 (IQR, 16.7–21.7). All patients had received rifampicin (600 mg once per day) and moxifloxacin (400 mg once per day). One patient received additional isoniazid.

During pharmacokinetic studies, the CSF was colorless and clear; the median total protein value was 0.6 g/L (IQR, 0.5–0.7 g/L; normal range, 0.3–0.7 g/L), the median glucose level was 2.5 mmol/L (IQR, 2.4–2.8 mmol/L; normal range, 2.2–4.4 mmol/L), and the median mononuclear cell count was $21 \times 10^6$ cells/L (IQR, 15–25 $\times 10^6$ cells/L; normal range, 0–3 $\times 10^5$ cells/L). MICs of moxifloxacin for M. tuberculosis ranged from 0.125 to 0.25 mg/L. Pharmacokinetic and pharmacodynamic parameters are shown in Table 1. The geometric mean AUC\textsubscript{CSF}/AUC\textsubscript{Plasma} ratio for total (bound plus unbound) concentrations was 0.82 (range, 0.70–0.94) at 400 mg once per day; this was not significantly different from the geometric mean AUC\textsubscript{CSF}/AUC\textsubscript{Plasma} ratio of 0.71 (range, 0.58–0.84) at 800 mg once per day ($P = .3$). Unbound concentrations could be measured in 2 patients. The unbound fractions of moxifloxacin were 40% and 60% in serum and 90% and 95% in CSF, both at doses of 400 mg and 800 mg. In these patients, the unbound AUC\textsubscript{CSF}/AUC\textsubscript{Plasma} ratios were 1.31 and 1.75 at a dose of 400 mg and 0.85 and 1.16 at a dose of 800 mg.

After administration of 400 mg and 800 mg of moxifloxacin, the AUC\textsubscript{CSF} was significantly related to the peak concentration in CSF ($R = 0.8; P < .001$). The time to reach the maximum concentration in CSF was significantly longer than the interval needed for plasma ($P = .002$).

Two patients continued therapy with moxifloxacin at 600 mg once daily for 2 months and 8 months, 1 patient continued therapy at 400 mg once daily for 9 months, and 1 patient continued treatment at 800 mg once daily for 4 months. During treatment with moxifloxacin, no adverse effects were reported that could be attributed to moxifloxacin, based on the evaluation of electrocardiograms, serum glucose levels, and blood sampling of renal and liver function.

### Discussion

We describe a combined CSF and plasma moxifloxacin concentration measurement over time in 4 patients treated for TBM during steady-state conditions. We show that moxifloxacin penetrates readily in CSF. This confirms earlier data on CSF penetration, which were based only on a single CSF sample, in patients undergoing a scheduled urological operation [5]. The data for our patients with TBM indicate complete CSF penetration.
Adequate moxifloxacin concentrations were achieved in CSF and in plasma using dosages of 400 mg to 800 mg once per day. Monitoring of moxifloxacin concentration levels may be warranted in patients who are concurrently taking an interacting medication or for whom there is a high in vitro MIC. These data suggest that moxifloxacin is an important addition in the treatment of TBM.

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References


