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BRIEF REPORT

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 in 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 bacterium) were assessed following ultrafiltration (Centrifree Ultrafiltration device; Millipore). Pharmacokinetic parameters were assessed with standard noncompartmental pharmacokinetic methods using the software package MWPharm, version 3.60 (Mediware). Ratios of the area under the concentration-time curves up to 24 h after administration of the dose (AUC_{0-24h}) 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

Table 1. Pharmacokinetic Parameters of Moxifloxacin Based on Total (bound plus unbound) Concentrations for 4 Patients

Parameter	Plasma sample, moxifloxacin daily dose		CSF sample, moxifloxacin daily dose	
	400 mg	800 mg	400 mg	800 mg
AUC_{0-24h}, mg× h/L	24.4 (20.5–24.5)	38.3 (32.2–42.4)	18.1 (14.8–19.8)	28.4 (24.9–28.9)
C_{max}, mg/L	2.57 (1.79–3.47)	3.65 (3.31–4.09)	1.29 (1.04–1.50)	2.22 (1.72–2.63)
T_{max}, h	1.0 (1.0–1.3)	2.0 (2.0–2.5)	4.0 (3.8–5.5)	4.0 (3.8–5.5)
C_{min}, mg/L	0.21 (0.17–0.26)	0.37 (0.24–0.48)	0.19 (0.14–0.24)	0.33 (0.25–0.38)
$T_{1/2}$, h	6.7 (6.0–7.5)	5.8 (5.0–10.0)	6.0 (5.7–7.3)	7.0 (6.4–7.4)
Cl/F, L/h	14.9 (12.6–30.6)	19.2 (15.3–24.62)	18.8 (17.5–34.6)	25.7 (24.2–31.2)
V_d, L	159 (143 161)	140 (139–142)	NA	NA
Geometric mean AUC/MIC ratio (range)	103 (60–196)	186 (132–322)	84 (56–154)	132 (95–226)
Unbound AUC/MIC ratio				
Patient 1	39	118	NA	NA
Patient 2	98	193	NA	NA

NOTE. Data are median values (interquartile range), unless otherwise indicated. AUC_{0-24h}, area under the concentration-time curve from 0 to 24 h; CL, total clearance; C_{min}, trough concentration of drug; C_{max}, maximum concentration of drug; NA, not applicable; T_{max}, time to maximum concentration of drug in serum; $t_{1/2}$, terminal elimination half-life; V_d, volume of distribution.

AUC_{0-24h} and the minimal inhibitory concentration (MIC) was calculated, because the AUC_{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_{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 21×10^6 cells/L (IQR, $15–25 \times 10^6$ cells/L; normal range, $0–3 \times 10^6$ 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_{CSF}/AUC_{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_{CSF}/AUC_{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_{CSF}/AUC_{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_{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

concentration-time curves, which is the gold standard to assess CSF/plasma ratios. This adds important information to the current knowledge and enables pharmacokinetic/pharmacodynamic parameter calculations. On the basis of unbound AUC_{CSF}/AUC_{plasma} ratios, an accumulation of moxifloxacin in CSF could be observed. Assuming that the AUC/MIC ratio, based on total drug concentration, is the best predictive model for efficacy for fluoroquinolones, the value of 100 has to be exceeded [13], but protein binding differs among the range of fluoroquinolones—and only the unbound drug fraction is antimicrobially active. In our 2 patients, in whom we measured unbound drug, we observed a considerable difference in the unbound concentration of moxifloxacin that could not be explained by moxifloxacin concentration–dependent protein binding [12]. To interpret the value of the AUC/MIC in patients to guide individual dosing is therefore difficult. Because all patients received rifampicin, which generally results in a nearly 30% reduction in the AUC [8] of moxifloxacin, it might be considered to increase the dosage of moxifloxacin to achieve moxifloxacin concentrations similar to those without rifampicin. Because the peak moxifloxacin level has good predictive value for the AUC, a CSF sample could be obtained 4 h after ingestion of the drug as a means to predict and verify the resulting CSF exposure. Although moxifloxacin-induced QTc prolongation should be assessed when a dosage is increased, significant prolongation was observed at higher AUCs of ∼86 mg × h/L, which is 2 times higher than in our study [14]. As a next step, we propose designing a prospective study to evaluate the efficacy and safety of dosing of moxifloxacin in patients with tuberculosis based on unbound AUC_{plasma}/MIC ratios.

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.

Acknowledgments

References

1. Rodriguez JC, Ruiz M, Lopez M, Royo G. In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against *Mycobacterium tuberculosis.* Int J Antimicrob Agents **2002**;20(6):464–7.
2. Codecasa LR, Ferrara G, Ferrarese M, et al. Long-term moxifloxacin in complicated tuberculosis patients with adverse reactions or resistance to first line drugs. Respir Med **2006**;100(9):1566–72.
3. Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in *Mycobacterium tuberculosis,* by use of an in vitro pharmacodynamic infection model and mathematical modeling. J Infect Dis **2004**;190(9):1642–51.
4. Alffenaar JW, de Vries PM, Luijckx GJ, van Soolingen D, van der Werf TS, van Altena R. Plasma and cerebrospinal fluid pharmacokinetics of moxifloxacin in a patient with tuberculous meningitis. Antimicrob Agents Chemother **2008**;52(6):2293–5.
5. Kanellakopoulou K, Pagoulatou A, Stroumpoulis K, et al. Pharmacokinetics of moxifloxacin in non-inflamed cerebrospinal fluid of humans: implication for a bactericidal effect. J Antimicrob Chemother **2008**;61(6):1328–31.
6. Ostergaard C, Sorensen TK, Knudsen JD, Frimodt-Moller N. Evaluation of moxifloxacin, a new 8-methoxyquinolone, for treatment of meningitis caused by a penicillin-resistant pneumococcus in rabbits. Antimicrob Agents Chemother **1998**;42(7):1706–12.
7. Rodriguez-Cerrato V, McCoig CC, Michelow IC, et al. Pharmacodynamics and bactericidal activity of moxifloxacin in experimental *Escherichia coli* meningitis. Antimicrob Agents Chemother **2001**;45(11):3092–7.
8. Nijland HM, Ruslami R, Suroto AJ, et al. Rifampicin reduces plasma concentrations of moxifloxacin in patients with tuberculosis. Clin Infect Dis **2007**;45(8):1001–7.
9. Stass H, Kubitza D, Schuhly U. Pharmacokinetics, safety and tolerability of moxifloxacin, a novel 8-methoxyfluoroquinolone, after repeated oral administration. Clin Pharmacokinet **2001**;40(Suppl 1):1–9.
10. van Klingeren B, Dessens-Kroon M, van der Laan T, Kremer K, van Soolingen D. Drug susceptibility testing of *Mycobacterium tuberculosis* complex by use of a high-throughput, reproducible, absolute concentration method. J Clin Microbiol **2007**;45(8):2662–8.
11. Wright DH, Brown GH, Peterson ML, Rotschafer JC. Application of fluoroquinolone pharmacodynamics. J Antimicrob Chemother **2000**;46(5):669–83.
12. Shandil RK, Jayaram R, Kaur P, et al. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against *Mycobacterium tuberculosis:* evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. Antimicrob Agents Chemother **2007**;51(2):576–82.
13. Nuermberger E, Grosset J. Pharmacokinetic and pharmacodynamic issues in the treatment of mycobacterial infections. Eur J Clin Microbiol Infect Dis **2004**;23(4):243–55.
14. Demolis JL, Kubitza D, Tenneze L, Funck-Brentano C. Effect of a single oral dose of moxifloxacin (400 mg and 800 mg) on ventricular repolarization in healthy subjects. Clin Pharmacol Ther **2000**;68(6):658–66.