The influence of continuous venovenous haemodialysis on the pharmacokinetics of multiple oral moxifloxacin administration to patients with severe renal dysfunction

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What is already known about this subject

- Although renal excretion is one important route of excretion of moxifloxacin and its metabolites, moxifloxacin pharmacokinetics are similar in patients with varying degrees of renal impairment (but not on dialysis) and in healthy subjects.

What this study adds

- This study showed that moxifloxacin pharmacokinetics are comparable in patients with severe renal failure requiring haemodialysis and in healthy subjects and patients with impaired renal function not on dialysis.
- No dose adjustments are required for haemodialysis patients on oral moxifloxacin therapy.

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Aim

We investigated single dose and steady-state pharmacokinetics of moxifloxacin in eight venovenous haemodialysis patients.

Methods

Plasma, dialysate and urine pharmacokinetic parameters for moxifloxacin and its main metabolites were calculated after single and multiple (7 days) dosing with 400 mg day⁻¹.

Results

Moxifloxacin pharmacokinetics after a single dose and at steady state (multidose day 7) were comparable in patients with impaired renal function and healthy subjects (geometric mean/%CV AUC mg l⁻¹ h single dose 37.0/24.3 in haemodialysis patients vs. 29.8/22.6 in healthy subjects, 95% CI for ratio of haemodialysis patients to healthy subjects 99.34%, 154.60%; steady state 40.4/29.1 haemodialysis patients vs. 33.9/20.1 in healthy subjects, 95% CI for ratio of haemodialysis patients to healthy subjects 90/39%, 156.93%). In haemodialysis patients plasma concentrations of moxifloxacin at steady-state were elevated compared with those after a single 400 mg dose (AUC mg l⁻¹ h, geometric mean/%CV, 40.4/29.1) compared with 37.0/24.3; 95% CI for ratio of steady-state to single dose 87.29%, 136.52%, as were concentrations of metabolite M1 3.21/34.6 compared with 2.02/45.3, 95% CI for ratio of steady state to single dose 14.21%, 175.07%. Haemodialysis cleared about 9% of the dose as unchanged moxifloxacin.

Conclusions

No dose adjustments are required for venovenous haemodialysis patients on oral moxifloxacin therapy.

Introduction

Moxifloxacin is a broad-spectrum, third-generation quinolone antibiotic, with 20–50 times higher activity against Gram-positive pathogens, including *Streptococcus pneumoniae*, than ciprofloxacin and ofloxacin [1, 2]. The oral bioavailability of moxifloxacin is about 91%, and maximum concentrations are reached rapidly after administration in normal subjects [3, 4]. Moxifloxacin is cleared both nonrenally and renally, and up to 20% of the drug is excreted unchanged in the urine. Moxifloxacin is mainly metabolized to pharmacologically inactive metabolites M1 (an *N*-sulphate) and M2 (an acylglucuronide). About 38% of the dose is excreted as M1 in the faeces, and a further 14% as M2 by active renal tubular secretion [3].

The pharmacokinetics of moxifloxacin in healthy subjects are linear over a wide range of single oral and intravenous doses up to 1200 mg [3]. In a clinical study, the plasma concentrations of moxifloxacin following a single oral 400 mg dose in subjects with severe kidney failure (but not on dialysis) did not exceed those in healthy control subjects [5]. Renal impairment *per se* was not therefore expected to contribute significantly to changes in moxifloxacin pharmacokinetics. The aim of this study was to evaluate the pharmacokinetics of moxifloxacin and its main metabolites in haemodialysis patients after a single oral 400 mg dose and during steady-state dosing.

Methods

This two-period, nonrandomized, open, uncontrolled, single-centre study was approved by the local Ethics Committee and conducted in accordance with good clinical practice. Written informed consent was obtained from one female and seven male Caucasian patients (median age 36 years (range 22–44 years); median body weight 73.3 kg (range 53.3–83.5 kg)) receiving three 5-h, continuous venovenous, haemodialysis sessions per week. Blood flow rates varied from 0.2 to 0.3 l min⁻¹ and ultrafiltrate rates from 0.13 to 1.0 l h⁻¹. Dialysate flow rate was 0.5 l min⁻¹. Dialysis filters were Gambro Polyflux 210H, Fresenius F60 or F80 Highflux. All the subjects had a creatinine clearance < 20 ml min⁻¹ 1.73 m⁻².

In period 1, subjects received a single 400 mg dose of moxifloxacin on a nondialysis day followed by a washout phase of at least 1 week. Patients then entered period 2 (multidose period), in which 400 mg moxifloxacin was given once daily for 7 days, starting on a dialysis day. Dialysis was started 6 h after intake of the oral dose to allow complete absorption. Pharmacokinetic profiles were obtained following the single dose

and on days 1 (dialysis day) and 7 (nondialysis day) of period 2.

Venous blood samples were drawn predose and at intervals up to 72 h after the single dose and after dosing on multidose day 7 (plus a 96-h sample). On multidose day 1, samples were drawn predose and at intervals up to 24 h after dosing. Trough measurements for moxifloxacin were obtained on days 3 and 5 (dialysis days) of the multidose period. Dialysate was collected in 30-min fractions over the whole dialysis period to determine dialysate clearance. In patients with residual urine, urine was collected over 24 h on the single dose day and on multidose day 7 to determine renal clearance of moxifloxacin.

Moxifloxacin and metabolites M1 and M2 in heparinized plasma, urine and dialysate were determined using a validated HPLC method with fluorescence detection, with cinoxacin as internal standard [6]. Peak concentrations (C_{max}) and time to reach C_{max} (t_{max}) were directly determined from the individual plasma concentration–time profiles. Other pharmacokinetic parameters were calculated using noncompartmental methods [7]. The main pharmacokinetic parameters calculated were terminal half-life ($t_{1/2}$), area under the curve after single (first) dose extrapolated to infinity on the single dose day and multidose day 1 (AUC), AUC from 0 to 24 h at steady state on multidose day 7 (AUC(0,24 h)_{ss}), apparent oral clearance (CL/F), renal clearance (CL_{ren}), and dialysate clearance (CL_{dial}). Urinary and dialysate moxifloxacin excretion were calculated from urinary and dialysate drug concentrations and volumes. The validity of the concentration data was confirmed by co-analysing quality control samples, which were stored together with the study samples [6]. For moxifloxacin and metabolite M1 the lower limit of quantification (LLOQ) was 10 µg l⁻¹ and 57.6 µg l⁻¹, respectively. Coefficients of variation for AUC and C_{max} were between 13.53 and 20.94%.

A medical history and repeated physical examinations, electrocardiogram, blood pressure and heart rate measurements, haematology, clinical chemistry and urinalysis (where applicable) were obtained for each subject. Information on adverse events was collected by nonleading questioning and by spontaneous reporting.

Results

The mean plasma concentration–time courses for moxifloxacin and the trough plasma concentrations were similar after a single 400 mg dose and after dosing on multidose day 1 (dialysis) and day 7 (nondialysis). Dialysate concentrations were lower than those in plasma. Renal clearance did not contribute significantly to moxifloxacin excretion (Table 1), with only about 2%

Table 1

Comparison of the pharmacokinetic parameters of moxifloxacin following administration of single and multiple oral 400 mg doses to haemodialysis patients with historical data from normal subjects and subjects with various degrees of renal impairment but not receiving haemodialysis

	Pharmacokinetic parameters after a single dose				Pharmacokinetic parameters at steady-state		
	Haemodialysis patients (n = 8)		Severe renal impairment (n = 8) [5]	Historical data Moderate renal impairment† (n = 8) [5]	Healthy subjects (n = 12) [3]	Haemodialysis patients (n = 8) Multidose day 7	Historical data Healthy subjects at steady state (n = 7) [8]
AUC (mg l ⁻¹ h)*	37.0/24.3 (26.0–56.4)	34.0/32.3 (22.3–53.1)	44.0/29.1 (25.1–60.1)	35.8/30.7 (22.9–58.0)	29.8/22.6 (20.3–44.6)	40.4/29.1** (27.3–60.9)	33.9/20.1 (26.7–46.3)
C _{max} (mg l ⁻¹)*	2.47/19.2 (1.94–3.23)	2.6/21.8 (1.71–3.44)	3.16/14.0 (2.63–4.07)	3.45/43.0 (1.89–6.04)	2.50/25.9 (1.62–3.80)	3.16/23.4 (2.27–4.38)	3.24/17.5 (2.41–4.03)
t _{max} (h)†	1.2 (1.0–3.0)	2.0 (1.0–4.0)	1.0 (0.5–2.5)	0.8 (0.5–2.5)	2.0 (0.5–6.0)	3.0 (1.0–4.0)	1.5 (0.5–3.0)
t _{1/2} (h)*	14.1/20.9 (10.5–18.9)	11.6/47.5 (7.5–24.7)	14.5/19.2 (10.4–17.7)	16.2/14.9 (12.2–20.0)	15.6/14.0 (12.1–19.1)	18.7/25.1 (12.3–26.2)	15.1/4.9 (13.9–16.2)
CL/F (ml min ⁻¹)*	180/24.3 (118–256)	196/32.3 (126–299)	152/29.1 (111–267)	187/30.7 (115–292)	193/19.2 (134–242)	165/32.3 (110–245)	197/20.1 (144–250)
CL _{ren} (ml min ⁻¹)*	2.1/979 (0.9–10.7)	3.2/109 (0.8–9.8)	14.50/51.2 (9.5–27.8)	31.7/42.3 (17.8–48.2)	43/22.6 (24.2–57.3)	3.3/114 (0.7–11.8)	41.8/13.5 (36.5–50.5)
Ae _{ur} (0.24 h) (%)§	1.19 ± 1.07 (0.34–3.46)	1.73 ± 1.24 (0.22–3.43)	10.38 ± 4.18 (3.59–16.8)	18.1 ± 7.27 (6.62–26.1)	19.3 ± 2.77 (13.5–23.2)	2.45 ± 1.52 (0.35–4.84)	21.5 ± 3.73 (15.7–27.8)
CL _{dial} (ml min ⁻¹)*	n.a.	95.3/18.4 (71.2–131)	n.a.	n.a.	n.a.	n.a.	n.a.
Ae _{dial} (6–11 h) (%)§	n.a.	8.80/69.3 (6.99–12.8)	n.a.	n.a.	n.a.	n.a.	n.a.

*Geometric mean/% coefficient of variation (range); †Median (range); §Arithmetic mean ± SD (range); ¶Creatinine clearance < 30 ml min⁻¹ 1.73 m⁻²; ‡Creatinine clearance > 30 and ≤ 60 ml min⁻¹ 1.73 m⁻²; **AUC(0,24 h)_{ss}; n.a. = not applicable.

Table 2

Pharmacokinetic parameters of metabolite M1 following single and multiple oral administration of 400 mg of moxifloxacin in eight patients compared with historical data from eight healthy subjects

Parameter	Single-dose day	Multidose day 1	Multidose day 7	Healthy subjects [3]
AUC (0–24) (mg.h/L)*	2.02/45.3 (1.24–4.28)	2.03/43.7 (1.05–3.78)§	3.21/34.6 (2.11–5.30)	0.91/29.1 (0.748–1.19)
C _{max} (mg/L)*	0.27/49.7 (0.12–0.59)	0.27/62.8 (0.12–0.73)	0.34/46.7 (0.18–0.58)	0.15/33.1 (0.08–0.23)
t _{max} (h)†	1.10 (1.00–4.05)	1.05 (1.00–3.35)	1.05 (1.00–3.97)	1.75 (0.5–6.0)
t _{1/2} (h)*	8.51/47.5 (4.46–16.3)	5.86/29.9 (4.34–9.60)§	12.36/52.7 (4.49–22.9)	7.3/36.9 (3.3–10.7)

*Geometric mean/% coefficient of variation (range).

†Median (range).

§Six subjects.

of the dose excreted in urine over 24 h. About 9% of the dose was excreted during haemodialysis, though dialysate clearance was about 48% of total oral clearance (Table 1). Plasma concentrations of moxifloxacin were elevated during the multidose (steady-state) period (AUC mg l⁻¹ h, geometric mean/%CV, 40.4/29.1) compared with those after the single 400 mg dose (37.0/24.3, 95% CI for the ratio of steady-state to single dose (87.29%, 136.52%)) and the first multidose on day 1 (34.0/32.3, 95% CI for the ratio of steady-state to first multidose (95.03%, 148.64%)), but there was no evidence of excessive drug accumulation at steady-state. Comparison with data from previous studies in healthy subjects and patients with various degrees of impaired renal function [3, 5, 8] showed that exposure to moxifloxacin (AUC) is independent of the degree of renal impairment (Table 1).

Exposure (AUC) to metabolite M1 was comparable following the single dose and the first multidose (multidose day 1) (geometric mean/%CV, 2.02/45.3 (*n* = 8) vs. 2.03/43.8 (*n* = 6); 95% CI for ratio of first multidose to single dose 80.26%, 99.68%) (Table 2). Overall, the data on disposition excluded an accumulation of metabolite M1 at steady-state due to nonlinear pharmacokinetics. The pharmacokinetics of metabolite M2 were characterized by a very high intersubject variability. Metabolite M2 plasma concentrations were about five-fold higher than in healthy subjects. Renal and dialysate clearance did not contribute significantly to the elimination of either M1 or M2. Dialysis removed less than 1% of the drug dose as M1 and 4% as M2.

No moxifloxacin-related adverse events were noted. Electrolyte disturbances were the most common adverse events and are well described in haemodialysis patients.

Discussion

Many fluoroquinolones, e.g. levofloxacin and ciprofloxacin, are predominantly excreted via renal pathways [9], and dose adjustments are thus required in patients with renal impairment in order to avoid increases in drug exposure. Unlike these fluoroquinolones, moxifloxacin is excreted by multiple pathways [3, 9] and renal impairment *per se* does not significantly influence its pharmacokinetics [5]. While a critical accumulation of moxifloxacin in renal impairment is thus unlikely, conversely haemodialysis may theoretically remove substantial amounts of moxifloxacin from the systemic circulation, generating subtherapeutic drug concentrations.

A comparison of our findings with earlier data from single dose and steady-state studies demonstrates that the plasma pharmacokinetics of moxifloxacin are largely unaffected by renal failure requiring chronic haemodialysis. At steady state, concentrations of moxifloxacin were increased, as anticipated from the half-life and the dosing interval, but no excessive accumulation occurred. This finding is as expected on the basis of data from nondialysis-dependent subjects with severely impaired kidney function [5]. Chronic haemodialysis was effective in clearing moxifloxacin from the systemic circulation after oral intake, accounting for about 48% of apparent oral clearance. Although this suggests that haemodialysis should contribute significantly to drug clearance, it did not remove substantial amounts from the systemic circulation. These findings are in accord with data from patients in the intensive care unit undergoing either continuous venovenous haemodiafiltration [10] or extended daily dialysis [11], in whom moxifloxacin pharmacokinetics were similar to those in healthy subjects.

Exposure to metabolite M1 was only slightly increased in haemodialysis patients in keeping with its major elimination pathway via the faeces. In contrast, exposure to metabolite M2 was significantly greater in haemodialysis patients than in healthy subjects and subjects with impaired renal function [5], as expected from its mainly renal elimination. As M2 is pharmacologically inactive, however, the clinical relevance of this finding was considered to be minor.

These pharmacokinetic data confirm that no adjustments are necessary for dose or timing relative to haemodialysis for haemodialysis patients receiving 400 mg oral moxifloxacin once daily for 7 days.

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References

- 1 Aldridge KE, Ashcraft DS. Comparison of the *in vitro* activities of BAY 12–8039, a new quinolone, and other antimicrobials against clinically important anaerobes. *Antimicrob Agents Chemother* 1997; 41 (3): 709–11.
- 2 Dalhoff A, Krasemann C, Wegener S, Tillotson G. Penicillin resistant *Streptococcus pneumoniae*: review of moxifloxacin activity. *Clin Infect Dis* 2001; 32(Suppl 1): S22–9.
- 3 Stass H, Kubitz D. Pharmacokinetics and elimination of moxifloxacin after oral and intravenous administration in man. *J Antimicrob Chemother* 1999; 43(Suppl B): 83–90.
- 4 Ballow C, Lettieri J, Agarwal V, Liu P, Stass H, Sullivan JT. Absolute bioavailability of moxifloxacin. *Clin Ther* 1999; 21: 513–22.
- 5 Stass H, Kubitz D, Halabi A, Delesen H. Pharmacokinetics of moxifloxacin, a novel 8-methoxy-quinolone, in patients with renal dysfunction. *Br J Clin Pharmacol* 2002; 53: 232–7.
- 6 Stass H, Dalhoff A. Determination of BAY 12–8039, a new 8-methoxyquinolone, in human body fluids by high-performance liquid chromatography with fluorescence detection using on-column focusing. *J Chromatogr B Biomed Sci Appl* 1997; 702: 163–74.
- 7 Gibaldi M, Perrier D. *Pharmacokinetics*. New York: Marcel Dekker Inc, 1982.
- 8 Stass H, Kubitz D, Schöly U. Pharmacokinetics, safety and tolerability of moxifloxacin, a novel 8-methoxyfluoroquinolone, after repeated oral administration. *Clin Pharmacokin* 2001; 40(Suppl 1): 1–9.
- 9 Anderson MI, MacGowan AP. Development of the fluoroquinolones. *J Antimicrob Chemother* 2003; 51(Suppl 1): 1–11.
- 10 Fuhrmann V, Schenk P, Jaeger W, Salwa A, Thalhammer F. Pharmacokinetics of moxifloxacin in patients undergoing continuous venovenous haemodiafiltration. *J Antimicrob Chemother* 2004; 54: 780–4.
- 11 Czock D, Hüsige-Linde C, Langhoff A, Schöpke T, Hafer C, de Groot K, Swoboda S, Kuse E, Haller H, Fliser D, Keller F, Kielstein JT. Pharmacokinetics of moxifloxacin and levofloxacin in intensive care patients who have acute renal failure and undergo extended daily dialysis. *Clin J Am Soc Nephrol* 2006; 1: 1263–8.