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Short communication

Serum concentrations and pharmacokinetics of moxifloxacin in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass☆

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ABSTRACT

Although cephalosporins are recommended as primary agents, moxifloxacin may be a suitable second-line antibiotic in cardiac surgery, especially if additional Gram-negative coverage is warranted. Cardiopulmonary bypass (CPB) may alter the pharmacokinetics of drugs in numerous ways. Since no such data exist, the aim of this study was to assess the serum concentrations and pharmacokinetics of moxifloxacin in patients undergoing cardiac surgery with CPB. Fourteen coronary artery bypass graft surgery patients received an intravenous infusion of 400 mg moxifloxacin as peri-operative antibiotic prophylaxis. At 15 time points throughout a 24-h period, serum samples were obtained to measure moxifloxacin concentrations using high-performance liquid chromatography. In addition, a non-compartmental pharmacokinetic analysis, i.e. area under the concentration–time curve (AUC), volume of distribution at steady state (V_{SS}), drug clearance (CL), elimination half-life ($t_{1/2}$) and mean residence time (MRT), was performed in five patients. Apart from a slight transient decrease in moxifloxacin concentration at the onset, CPB did not affect the concentration–time curve. Mean ± standard deviation maximum drug concentration (C_{max}) (5.12 ± 1.58 μg/mL), AUC (36.5 ± 5.40 μg h/mL), V_{SS} (2.03 ± 0.30 L/kg), CL (11.2 ± 1.91 L/h), $t_{1/2}$ (9.47 ± 0.92 h) and MRT (12.9 ± 1.52 h) were comparable with historical data for healthy volunteers. We conclude that CPB does not alter the pharmacokinetics of moxifloxacin. No dose adjustments, especially with regard to the CPB circuit and its priming volume, are necessary in cardiac surgical patients.

1. Introduction

Moxifloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive, Gram-negative and atypical pathogens. It has a protein binding rate of ca. 40%, penetrates well into tissues, is eliminated via the hepatic route and has an elimination half-life between 11 h and 15 h, allowing once-daily dosing [1]. Although cephalosporins are recommended as primary antibiotics for prophylaxis in cardiac surgery [2,3], moxifloxacin might be a suitable agent in special clinical situations. For example, the Society of Thoracic Surgeons recommends levofloxacin, the precursor of moxifloxacin, if additional Gram-negative coverage is warranted and aminoglycosides are contraindicated [2]. In a recently published meta-analysis regarding antibiotic prophylaxis in cardiac surgery, quinolones were also taken into account for additional Gram-negative coverage [3]. Moreover, alternative antibiotic regimens to cephalosporins, addressing Gram-negative prophylaxis, potential toxic effects and the incidence of *Clostridium difficile* infections, are currently under debate [4]. Most cardiac surgical operations require the use of cardiopulmonary bypass (CPB). CPB has numerous impacts on the pharmacokinetics of drugs, e.g. haemodilution by the priming volume, hypothermia for organ protection, perfusion by non-pulsatile pumps, changes in the acid–base status, and sequestration of drugs by the bypass circuit [5]. Since no such data are yet available, the aim of this study was to assess the serum concentrations and pharmacokinetics of moxifloxacin in patients undergoing cardiac surgery with CPB.

2. Materials and methods

Following approval by the Ethics Committee of the Faculty of Medicine of the Technical University of Munich (Munich, Germany)

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and the regulatory authorities (EudraCT no. 2006-000369-12), 14 patients scheduled for elective coronary artery bypass graft (CABG) surgery with CPB aged 18–80 years gave their written informed consent. Exclusion criteria were: body mass index (BMI) >30 kg/m^2; left ventricular ejection fraction <50%; heart rate <40 beats/min; symptomatic arrhythmia; intake of drugs that are associated with torsades de pointes and/or QT prolongation, e.g. amiodarone and tricyclic antidepressants; serum potassium <3.8 mmol/L or >5.0 mmol/L; serum creatinine >1.3 mg/dL; serum glutamic pyruvic transaminase >50 U/L; hypersensitivity to fluoroquinolones; antibiotic therapy for infectious diseases within 2 weeks before inclusion; tendinopathy due to former fluoroquinolone therapy; and pregnancy and nursing mothers.

For peri-operative antibiotic prophylaxis, patients received a single intravenous infusion of 400 mg of moxifloxacin (Avelox®; Bayer Vital, Leverkusen, Germany) over 60 min following induction of anaesthesia. This is the regular dosing scheme recommended by the manufacturer. To avoid the risk of inadequate dosing, sequestration of moxifloxacin to the CPB circuit was excluded in a pilot experiment: 4.8 mg of moxifloxacin HCl was added to a CPB circuit filled with 924 mL of red blood cells, 900 mL of ringer lactate, 100 mL of 8.4% sodium bicarbonate and 5000 U of bovine heparin to give a concentration of ca. 2 μg/mL, which is usually observed in clinical practice [6]. The CPB circulated in a closed-loop manner and moxifloxacin concentrations were measured for 120 min. Starting with 1.86 μg/mL, a moxifloxacin concentration of 1.95 μg/mL was measured after 2 h. Thereby, sequestration of moxifloxacin to the CPB circuit could be ruled out.

Anaesthesia of the CABG patients was induced with midazolam 0.02 mg/kg, etomidate 0.2 mg/kg and sufentanil 1 μg/kg, tracheal intubation was facilitated with rocuronium 0.6 mg/kg, and anaesthesia was maintained with sufentanil 1 μg/kg/h, propofol 1 mg/kg/h and sevoflurane 0.8–1.2 vol.%. The depth of anaesthesia was assessed by the bispectral index. For extracorporeal circulation, a standardised CPB setting with a membrane oxygenator (Compactflo Evo®; Sorin, Mirandola, Italy) and non-heparinised tubing was used. Anticoagulation was established with an initial 375 U/kg intravenous bolus of bovine heparin; the target kaolin-based activated coagulation time was greater than 480 s and additional heparin was administered as required during CPB to maintain activated coagulation time above this level. The pump flow was 2.2 L/min/m^2 with a target arterial perfusion pressure between 50 mmHg and 70 mmHg. Blood gas management was performed by the α-stat method. After cross-clamping of the aorta, cold blood cardioplegia was used for cardiac arrest. CABG surgery was performed with mild hypothermia at 32 °C.

Patient characteristics and peri-operative data were taken from the anaesthesia records and the CPB protocols. Serum samples to determine the moxifloxacin concentrations were obtained before the antibiotic was given, at 5, 15, 30 and 60 min after end of infusion, before the start of CPB, at 5, 15, 30 and 60 min after the start of CPB, at the end of CPB, at 30, 60 and 120 min after the end of CPB, and 24 h after the infusion. In contrast to Patients 1–5, Patients 6–14 received a second infusion of 400 mg of moxifloxacin on the first post-operative day before the last blood sample (24 h after the infusion) had been obtained. This second dose was prescribed by the head of the intensive care unit who was not involved in the study, prolonging routine peri-operative antibiotic prophylaxis from 24 h to 48 h for all cardiac surgical patients. There were no serious adverse events.

An already published analytical moxifloxacin quantification method was adapted to an Agilent 1200 high-performance liquid chromatography (HPLC) system [7]. Serum preparation started by adding 1.7 μg (10 μL) of internal standard solution of ofloxacin (Sigma, Steinheim, Germany) to 100 μL of sample. The chromatographic setup was Solvent A [KH_2PO_4 (Roth, Karlsruhe, Germany) 10 μM, pH 4.5], Solvent B [gradient-grade CH_3CN (Baker, Deventer, The Netherlands)], injection volume 5 μL, a 2-mm Phenomenex precolumn (Phenomenex, Aschaffenburg, Germany) and a Phenomenex Synergy 4 μ Fusion-RP 80A column. The internal standard ofloxacin and moxifloxacin (Bayer, Leverkusen, Germany) were fluorescence detected at 296 nm extinction and 504 nm emission at 7.3 min and 8.1 min retention times, respectively. A linear gradient, starting with 5% solvent B and 0.4 mL/min flow and finally 90% solvent B at 10 min run time was used. Linearity of calibration was given over the whole concentration range. In quality control samples, a positive bias of 4.9% was detected with an accuracy of 9.4%. Overall, 76 quality control samples were measured at two concentration levels (1.7 μg/mL and 3.3 μg/mL). Correlation of the calibration curve was $r^2 = 0.9996$. The limit of detection was 141 ng/mL and the limit of quantification was 326 ng/mL. Non-compartmental pharmacokinetic (PK) analysis was performed with Kinetica 2000 v.3.0 (Thermo Scientific, Munich, Germany) and was limited to those five patients who did not receive a second dose on the first post-operative day.

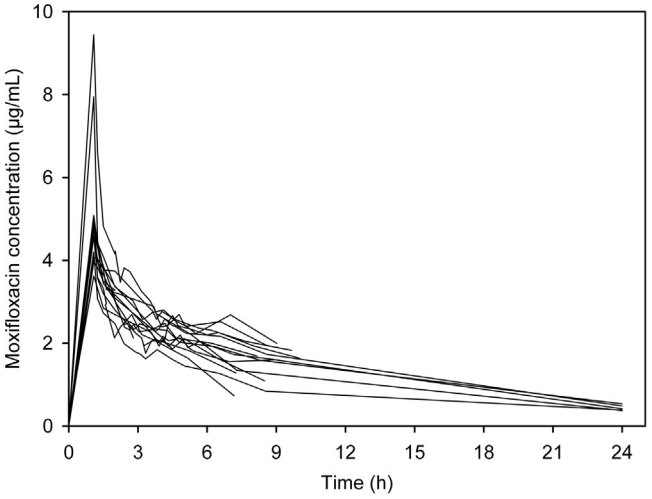

Fig. 1. Individual concentration–time curves of 14 coronary artery bypass graft patients. Only five patients received a single infusion of 400 mg moxifloxacin. The moxifloxacin concentrations at '24 h after the infusion' of the nine patients who received a second infusion on the first post-operative day before the last blood sample (at '24 h after the infusion') had been taken are not shown.

3. Results and discussion

The mean ± standard deviation (S.D.) age of the CABG patients was 65.6 ± 6.0 years, with a mean ± S.D. height of 173 ± 3.2 cm and weight of 78.4 ± 7.8 kg. Thirteen males and one female were investigated. The durations of CPB and aortic cross-clamping were 77.9 ± 19.7 min and 51.6 ± 16.5 min, respectively. The patients received 2200 ± 964 mL of ringer acetate and 821 ± 317 mL of 6% hydroxyethyl starch intravenously. The priming volume of the CPB circuit was 1637 ± 166 mL of ringer acetate, and blood loss within the first 24 h was 914 ± 306 mL. Red blood cells (1.5 ± 0.6 U) were given to four patients. One patient received two units of fresh frozen plasma and another patient received one unit of platelets. There was no re-thoracotomy for any reason. The individual concentration–time curves are shown in Fig. 1 and the mean concentration–time curve is shown in Fig. 2. The latter fits well within the mean curves of healthy volunteers taken from the studies of Stass and Kubitza [6] and Wise et al. [8].

Compared with the healthy volunteers studied by Stass and Kubitza [6], the maximum drug concentration (C_{max}) was higher in the CABG patients in the current study (Table 1). The reason for this higher C_{max} is not clear, but the other study in healthy