Population pharmacokinetics of three alternative prophylactic antibiotics during cardiac surgery with extracorporeal circulation

Petr Santavy[1], Vendula Kubickova[2], Martin Sima[3], Karel Urbanek[2]

Aims. The aim of this pharmacokinetic study was to describe and quantify population pharmacokinetics of three antibiotics, cefazolin, ampicillin, and ciprofloxacin, used as antibacterial prophylaxis during cardiovascular surgery with the use of extracorporeal circulation (ECC).
Methods. Adult patients undergoing cardiac surgery with ECC were enrolled to this prospective, pharmacokinetic study. An intravenous bolus of 2 g of ampicillin, 2 g of cefazolin or 400 mg of ciprofloxacin was administered 60–30 min before surgery. Blood samples were collected at 15, 30, 45, 60, 120 and 180 min after the administration and at the end of the surgery. Plasma concentrations of the antibiotics were measured using HPLC methods. Serum concentration-time profiles were analyzed using nonlinear mixed-effects modeling approach.
Results. A total of 54 patients were enrolled into the study, 20 with ampicillin, 25 cefazolin and 9 ciprofloxacin. For all antibiotics, population pharmacokinetic models have been successfully developed.
Conclusion. We identified estimated glomerular filtration rate (eGFR) as the main factor determining the achievement of the pharmacokinetic/pharmacodynamic (PK/PD) target in ampicillin or cefazolin and body weight in ciprofloxacin prophylaxis during cardiac surgery with ECC support.

Key words: population pharmacokinetics, cardiac surgery, extracorporeal circulation, ampicillin, cefazolin, ciprofloxacin

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[1]Department of Cardiac Surgery, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic
[2]Department of Pharmacology, Faculty of Medicine and Dentistry, Palacky University Olomouc and University Hospital Olomouc, Czech Republic
[3]Department of Pharmacology, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czech Republic
Corresponding author: Karel Urbanek, e-mail: Karel.Urbanek@fnol.cz

INTRODUCTION

Surgical site infections represent a significant complication of cardiovascular surgery, increasing mortality and morbidity, leading to longer hospitalizations, and increasing cost of care[1]. Thus, use of prophylactic antibiotics is necessary condition of successful cardiac surgery. Beta-lactam antibiotics (aminopenicillins and first generation cephalosporins) are recommended as first choice for cardiac surgery with exception of patient contraindications or local prevalence of MRSA exceeding 20% (ref.[2]).

Compared to conventional surgical procedures, cardiac surgery is specific to the use of cardiopulmonary bypass (CPB) with extracorporeal circulation (ECC) in most patients. Among other things, this influences the pharmacokinetics of the prophylactically used antibiotics[3,4]. Recently, minimally invasive extracorporeal circulation (MiECC) has been developed to improve biocompatibility and minimize the systemic detrimental effects of the ECC (ref.[5]).

Only limited data is still available regarding the population pharmacokinetics of prophylactic antibiotics used in cardiac surgery with the use of cardiopulmonary bypass. The majority of published studies used individual pharmacokinetic approach or were limited by small number of blood samples, which precludes compartmental analysis[6,7]. Moreover, population models are not available for many antibiotics.

Probably the most used prophylactic antibiotic in cardiac surgery is cefazolin, which is a first-generation cephalosporin. It is preferred for prophylaxis in surgical procedures because of its optimal antibacterial spectrum and favorable pharmacokinetic properties. Perhaps equally effective and safe is ampicillin, a broad-spectrum aminopenicillin usually used in combination with the beta-lactamase inhibitor sulbactam[2]. Of the non-betalactam antibiotics, ciprofloxacin, a fluoroquinolone with good antibacterial effects, was very commonly used at the time of the design of this study. As will be mentioned later, during this study, its administration in cardiac surgery was discontinued because of suspected risk of serious cardiovascular adverse events[8].

The aim of this pharmacokinetic study was to describe and quantify the population pharmacokinetics of three different antibiotics used as antibacterial prophylaxis during cardiovascular surgery using extracorporeal circuits

(both ECC and MiECC) and build population models that will allow more targeted and precise dosing. We studied the pharmacokinetics of the three most frequently used antibiotics in cardiac prophylaxis: cefazolin, ampicillin, and ciprofloxacin. This trial was intentionally not designed for evaluation of clinical outcomes of antibiotic prophylaxis.

MATERIALS AND METHODS

This prospective, pharmacokinetic study was performed at the University Hospital in Olomouc, Czech Republic. Adult patients undergoing cardiac surgery with CPB were enrolled. Exclusion criteria were serum creatinine >200 μmol/L or chronic dialysis, body mass index <17 or >35 kg/m^2, hepatic injury with elevation of serum liver enzymes above 3xULN, previous administration of studied antibiotic in the 3 days preceding the prophylactic administration and use of extracorporeal elimination methods during the surgery.

The study was carried out in accordance with the principles of the Declaration of Helsinki. Approval was granted by the ethics committee of the University Hospital in Olomouc (approval No. 17-31540A). Written informed consent was obtained from each patient.

The study population was divided into 3 study arms according to used antibiotic (ampicillin, cefazolin, or ciprofloxacin). Each had to include patients both with and without extracorporeal circulation. Cardiopulmonary bypass was performed with a model S5 Stockert non-pulsatile roller pump system (Stockert S5, Sorin group) with oxygenator Terumo FX 25 (hardshell reservoir, integrated arterial filter) as standard (ECC) or minimally invasive (MiECC) extracorporeal circulation.

Enrolled patients received an intravenous bolus of 2 g of ampicillin (in the combination with 1g of sulbactam, Unasyn, Pfizer, spol. s r.o., Praha, Czech Republic), 2 g of cefazolin (Azepo 1g, Medochemie Bohemia, spol. s r.o., Praha, Czech Republic) or 400 mg of ciprofloxacin (Ciprofloxacin Kabi 400 mg, Fresenius Kabi s.r.o., Praha, Czech Republic). All antibiotics were administered 60–30 min before the start of surgery.

Blood samples were collected at 15, 30, 45, 60, 120 and 180 min after the antibiotic administration and at the end of the surgery. Three milliliters of whole blood were drawn into a vacuum tube with lithium heparin and placed on ice. Immediately after surgery, the samples were transferred to the laboratory, where plasma was obtained by whole blood centrifugation. The samples were stored at −80 °C until analysis. All plasma concentration measurements were performed with the Prominence LC–20A HPLC system, and an SPD-20A UV-Vis detector (Shimadzu, Kyoto, Japan).

Serum concentration-time profiles of all antibiotic agents (ampicillin, cefazolin, and ciprofloxacin) were analyzed using nonlinear mixed-effects modeling approach. The model parameters were assumed to be log-normally distributed and were estimated by maximum likelihood using the Stochastic Approximation Expectation Maximization (SAEM) algorithm within Monolix Suite software version 2021R1 (Lixoft SAS, Antony, France). Model development was performed in three steps: base model, covariate model and model evaluation.

RESULTS

In total, 54 (39 male and 15 female) patients undergoing cardiac surgery with the use of extracorporeal circulation were enrolled in the study. Demographic and laboratory characteristics of patients are given in Table 1.

There were 20 patients (12 males, 8 females) pretreated with amoxicillin and supported with standard ECC entered the first study group. The average duration of surgery in this group was 211 min, and extracorporeal circuit was used for an average of 115 min.

Twenty-five patients (19 males, 6 females) pretreated with cefazolin and received MiECC support were enrolled in the second study arm. Here, the operation lasted on average 191 min with 71-min mean duration of extracorporeal circulation support.

The third study group consisted of nine patients (8 males, 1 female) received standard ECC support and pretreated with ciprofloxacin. The average operation time in this group was 225 min with an average extracorporeal circulation time of 134 min.

Table 1. Demographic and laboratory characteristics of patients enrolled to the study.

	Ampicillin	Cefazolin	Ciprofloxacin
Age (years)	72 (62–74)	73 (63–75)	71 (62–77)
Body weight (kg)	81 (71–96)	89 (79–100)	85 (78–97)
Height (cm)	168 (164–175)	172 (168–174)	170 (164–181)
BSA (m^2)	1.91 (1.80–2.10)	1.99 (1.90–2.11)	1.97 (1.85–2.18)
Serum creatinine (μmol/L)	83 (79–104)	83 (75–93)	99 (82–110)
eGFR (mL/s/1.73 m^2)	1.08 (0.98–1.48)	1.52 (1.12–1.76)	1.23 (1.00–1.27)
Urea (mmol/L)	5.4 (4.1–6.6)	4.8 (4.3–6.3)	5.8 (5.7–8.5)
Total protein (g/L)	72.2 (69.3–73.9)	73.5 (67.5–77.4)	69.7 (63.0–70.5)
Albumin (g/L)	45.1 (42.9–47.0)	45.0 (42.9–48.4)	35.0 (31.4–37.0)
Bilirubin (μmol/L)	15.0 (11.0–21.0)	11.0 (8.0–18.0)	13.0 (11.0–20.0)

Data are expressed as median (interquartile range).

HPLC methods with UV detection for the determination of ampicillin, cefazolin and ciprofloxacin were introduced and validated[9,10]. A total of 418 samples were analyzed (152 ampicillin, 193 cefazolin and 73 ciprofloxacin) and 1156 analyses were performed (456 ampicillin, 478 cefazolin and 222 ciprofloxacin).

Two-compartmental model with linear elimination from the central compartment best fit concentration-time data of all antibiotics. A proportional error model was the most accurate for residual and interpatient variability in all models. All PK models were parametrized in terms of clearance (CL), volume of the central compartment (V1), volume of the peripheral compartment (V2), and inter-compartmental clearance (Q).

The population PK parameters for ampicillin, cefazolin and ciprofloxacin are given in Table 2. Among the investigated variables, the most appropriate covariates were eGFR for both ampicillin and cefazolin CL. On the other hand, the most appropriate covariate in ciprofloxacin model was body weight for V2. Ampicillin CL starting at 0.089 L/h and increased by 0.39 L/h with each 1 mL/s of eGFR. Ampicillin V1 and V2 are 10.09 and 12.04 L, respectively. Cefazolin clearance baseline is 0.021 L/h and increases by 0.66 L/h with each 1 mL/s of eGFR. V1 and V2 reach value of 15.18 L and 27.68 L, respectively. Ciprofloxacin CL is 0.65 L/h, while V1 is 58.31 L. Ciprofloxacin V2 started at 9.89 L and increases by 0.023 L of each kg of body weight.

DISCUSSION

This study describes the population pharmacokinetics of three antibiotics commonly used in cardiac surgery for prophylaxis. From the demographic data of all three study groups, the specificities of the study population are clearly visible. Patients undergoing cardiac surgery are significantly older than general population, with worsened renal functions and the predominance of men in this population is striking even in such a small sample. Overweight is also evident, although in this parameter the study population will not differ much from other groups of adult patients. In such a population, we can expect differences in pharmacokinetic parameters compared to healthy volunteers on whom the pharmacokinetic characteristics of drugs are routinely described.

Pharmacokinetic covariate observed in our study fully correspond with those described in previous studies using individual pharmacokinetic analysis. However, we used population approach enabling identification and quantification of predictive covariates, and ability to distinguish between inter- and intra-individual variability, or residual unexplained variability[11].

As beta-lactams belong to time-dependent antibiotics, the major PK parameter responsible for PK/PD target attainment is clearance. Therefore, eGFR as most appropriate covariate of both ampicillin and cefazolin clearance is key parameter determining its effective treatment. In contrast, for ciprofloxacin, as antibiotics with concentration-dependent effect, the most relevant PK parameter for achieving the PK/PD target is volume of distribution, and therefore body weigh as its main covariate allows optimization of ciprofloxacin prophylaxis.

The originally planned numbers of patients in ciprofloxacin study group could not be met since new risks of prophylactic administration in cardiac surgery were identified and it was no longer ethical to continue its use in the non-interventional study. However, complete sets of samples from nine patients were obtained, which is sufficient to construct a population model, but with some limitations on the validity of the obtained results.

A larger analysis in which to clearly identify the effect of ECC is planned with the use of an internal control group. Such validated results should be sufficient to trans-

Table 2. Estimates of the final ampicillin, cefazolin and ciprofloxacin population pharmacokinetic model.

Ampicillin			Cefazolin			Ciprofloxacin		
Parameter	Estimate	R.S.E. (%)	Parameter	Estimate	R.S.E. (%)	Parameter	Estimate	R.S.E. (%)
Fixed effects								
CL_pop (L/h)	0.089	23.4	CL_pop (L/h)	0.021	30.5	CL_pop (L/h)	0.65	7.62
β_CL_eGFR	0.39	38.3	β_CL_eGFR	0.66	20.1	V1_pop (L)	58.31	27.7
V1_pop (L)	10.09	10.9	V1_pop (L)	15.18	10.9	Q_pop (L/h)	2.67	19.7
Q_pop (L/h)	0.17	11.2	Q_pop (L/h)	0.11	24.4	V2_pop (L)	9.89	53.1
V2_pop (L)	12.04	24.3	V2_pop (L)	27.68	8.32	β_V2_BW	0.023	22.2
Standard deviation of the random effects								
Ω_CL	0.2	28.3	Ω_CL	0.2	33.6	Ω_CL	0.22	25.7
Ω_V1	0.25	41.9	Ω_V1	0.12	112	Ω_V1	0.36	67.0
Ω_Q	0.16	83.4	Ω_Q	0.92	35.6	Ω_Q	0.27	74.7
Ω_V2	0.37	87.9	Ω_V2	0.079	108	Ω_V2	0.038	119
Error model parameters								
Proportional	0.13	8.28	Proportional	0.16	6.7	Proportional	0.087	11.9

V1, volume of central compartment; V2, volume of peripheral compartment; CL, clearance; Q, inter-compartmental clearance; BW, body weight; BSA, body surface area calculated by DuBois formula; eGFR, estimated glomerular filtration rate calculated by CKD-EPI formula; R.S.E., relative standard error.

late the population pharmacokinetic data into specific dosing recommendations for cardiac surgery.

CONCLUSION

This study describes the population pharmacokinetic data for ampicillin, cefazolin, and ciprofloxacin in patients undergoing cardiac surgery with extracorporeal circulation support. As the main factor determining the achievement of the PK/PD target in prophylaxis during cardiac surgery with ECC support, eGFR was identified for ampicillin or cefazolin. On the other hand, body weight was found to be the most influencing factor for effective ciprofloxacin prophylaxis.

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