

Population Pharmacokinetics of Cefuroxime in Patients Undergoing Colorectal Surgery

eman ta zabal zazu

Universidad del País Vasco Euskal Herriko Unibertsitatea



E. Asín¹, I.F. Trocóniz², E. Campos³, J. Errasti³, J. Sáenz de Ugarte³, A.R. Gascón¹, A. Isla¹

¹ Pharmacokinetics, Nanotechnology and Gene Therapy Group, Faculty of Pharmacy, University of the Basque Country, Vitoria-Gasteiz, Spain

² Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Navarra.

³ Service of General Surgery, University Hospital of Alava (seat of Txagorritxu), Vitoria-Gasteiz, Spain

OBJECTIVES

To develop a population pharmacokinetic model for cefuroxime (CXM) used as a prophylactic in combination with metronidazole (MTZ) in patients undergoing colorectal surgery in order to quantify the degree of inter-patient variability (IPV) and identify the patient and surgery characteristics responsible for such variability.

EXPERIMENTAL PROCESS

Experimental Design. A prospective, open-label study was conducted with patients electively undergoing rectal or colon surgery. The study was conducted at University Hospital of Alava, seat of Txagorritxu (Vitoria, Spain). Sixty-two patients older than 18 years were included in the study. According to the surgical protocol of the hospital, all patients received 1.5 g of CXM and 1.5 g of MTZ administered as intravenous infusion previously to the surgery (within one hour). A predose blood sample was withdrawn from all patients and three to five samples were collected from each patient during the next 24 h. Determination of CXM concentrations in plasma samples was carried out by HPLC validated technique.

Structural model. A population pharmacokinetic model was developed using NONMEM 7.2 and the FOCE estimation method with interaction. Compartmental models were used to fit the data. Selection between models was based on the decrease of the objective function value (OFV), the parameters estimation errors and the goodness of fit (GOF) plots.

Covariates inclusion. Once a base model was selected, a total of 17 patient characteristics (table 1) were evaluated to be included in order to minimize the IPV and support a better fit. The identification of covariate candidates was carried out by stepwise covariate model building ("scm" tool by PsN-3.5.3). The following levels of significance were used during the forward inclusion and backward deletion ($p < 0.05$ and $p < 0.01$, respectively).

Model evaluation. GOF plots, precision of parameter estimates by bootstrap (Bootstrap tool by PsN-3.5.3) and visual predictive check (VPC) ("vpc" tool by PsN-3.5.3) were performed to study the suitability of the final model.

NOTE: Pirana software (version 2.7.1) was used to organize and handle all the population model development process.¹

RESULTS

Cefuroxime concentrations were best described by a two-compartment model. Based on the distribution of the random effects, a log-transformed dataset was used. IPV were included in the total body clearance (CL) and the apparent volume of distribution of the central compartment (V1). Correlation between these parameters was observed.

Table 2 depicts the parameter estimates and bootstrap ($n=2000$) results for CXM final model. CXM is eliminated renally by a one-order process (glomerular filtration) dependent directly on the creatinine clearance and a saturable process (tubular secretion) which is dependent on the CXM concentration. The CL was coded as it has been described previously for other betalactams.² Figure 1 shows the dependence of the total and partial clearance as a function of CXM concentration. The ASA score was a significant covariate for the V1, being V1 higher in those patients with higher ASA scores. The inclusion of covariates allowed to reduce the unexplained IPV from 37% to 22% for the CL, and from 56% to 54% for the V1.

Figure 2 shows the GOF plots where a good correlation between the observations and the population predictions is shown. Besides, a quite good distribution of the conditioned weighted residuals (CWRES) is shown over the population predictions. However, the VPC (figure 3) reveals that the CXM model based simulations capture well the raw data.

Table 2. Population pharmacokinetic parameters, including the shrinkage value^a, and bootstrap results for the CXM final model after intravenous infusion administration in patients undergoing colorectal surgery.

PARAMETER	Estimate [RSE(%)]	Bootstrap [Median (5th-95th percentile)]
$CL (L/h) = CL_{GF} + V_{max} \cdot X / (K_m + C_p)$ $CL_{GF} = \theta_{CL} \cdot (CL_{cr} / 74.38)^{\theta_{CL\alpha}}$	$\theta_{CL} = 1.1 (30)$ $\theta_{CL\alpha} = 1.62 (13)$	1.1 (0.46 - 2.03) 1.64 (1.36 - 2.18)
V_{max}	141 (15)	139 (10.4 - 180)
K_m	6.69 (36)	6.65 (2.79 - 11.71)
$V_1 (L) = \theta_{V1} \cdot (1 + (ASA - 2) \cdot \theta_{ASA})$	$\theta_{V1} = 11.9 (7)$ $\theta_{ASA} = 0.223 (28)$	11.8 (10.4 - 13.4) 0.219 (0.104 - 0.335)
$Q (L/h)$	8.53 (13)	8.65 (7.09 - 11.12)
$V_2 (L)$	17.5 (14)	17.5 (13.9 - 22.8)
$II_{V_{CL}} (\%)$	22 (18)	22 (15 - 28)
$II_{V_{V1}} (\%)$	54 (10)	54 (44 - 62)
Correlation $II_{V_{CL}} - II_{V_{V1}} (\%)$	85 (13)	84 (-)
Residual error $\sigma_{additive} (log-scale)$	0.19 (9)	0.19 (0.16 - 0.21)

CL = apparent total body clearance of the drug from plasma; CL_{GF} = clearance due to glomerular filtration; V_{max} = maximum rate of elimination for saturable renal elimination (tubular secretion); K_m = Michaelis-Menten constant for saturable renal elimination; CL_{cr} = creatinine clearance; V_1 = apparent volume of the central compartment; Q = inter-compartment clearance; V_2 = apparent volume of distribution of the peripheral compartment; ASA = American Society of Anaesthetists score; RSE = relative standard error; θ_{ijk} = shrinkage value for a parameter; ϵ_{ijk} = shrinkage value for the residual error.

^a $CL_{ijk} = 11\%$; $V_{1ijk} = 9\%$; $\epsilon_{ijk} = 18\%$

CONCLUSION

A two-compartment pharmacokinetic model for CXM in patients submitted to colorectal surgery was developed. Creatinine clearance was a covariate of CXM clearance and the ASA score, a covariate of V1. The inclusion of covariates reduced significantly the unexplained IPV of the pharmacokinetic parameters. This model could help to decide the most appropriate CXM dose regimen to diminish the incidence of infection in patients undergoing colorectal surgery.

Table 1. Summary of patient demographic data

Patients Characteristics	Mean (SD)	Range
Continuous covariates		
Age (years)	69.5 (12.2)	33-91
Weight (kg)	68.8 (10.5)	43-88
Haemoglobin (g/dL)	12.96 (2.22)	7.6-17.4
Leukocytes (/mm ³)	7005.2 (1943.0)	2700-14300
Serum creatinine (mg/dL)	0.91 (0.30)	0.52-1.85
Glucose (mg/dL)	111.4 (25.5)	55-194
Albumin (g/dL)	4.14 (0.88)	1.5-8
Total proteins (g/dL)	6.73 (0.93)	3.3-8.2
Creatinine clearance (C-G) (mL/min)	74.1 (26.2)	22.1-138.2
Categorical covariates		
Sex (%)	60 H/40 M	
Blood Transfusion (yes/no)	7/55	
ASA index* (1/2/3/4/5)	16/26/17/3/0	
Basal disease (NF/UF/RF)	49/12/1	
Diabetes mellitus (yes/no)	14/48	
Immunosuppression (yes/no)	2/60	
Immunosuppressive treatment (yes/no)	2/60	
Renal impairment (yes/no)	4/58	

*Health score set by the American Society of Anesthesiologists (ASA): 1 - A normal healthy patient, 2 - A patient with mild systemic disease, 3 - A patient with severe systemic disease, 4 - A patient with severe systemic disease that is a constant threat to life, 5 - A moribund patient who is not expected to survive without the operation and 6 - A declared brain-dead patient whose organs are being removed for donor purposes.

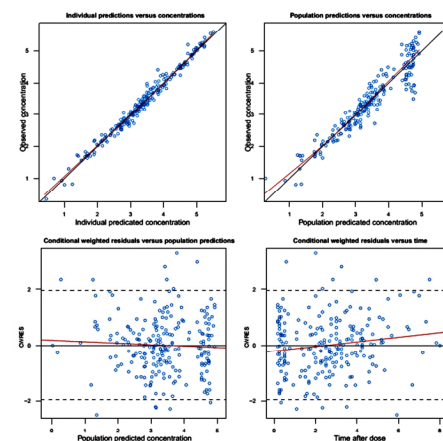


Figure 2. GOF plots corresponding to the CXM final model: scatterplot of observations (log-transformed) versus individual predictions (upper left panel) and population predictions (upper right panel). Conditioned weighted residuals (CWRES) versus population predictions (lower left panel) and time after dose in hours (lower right panel).

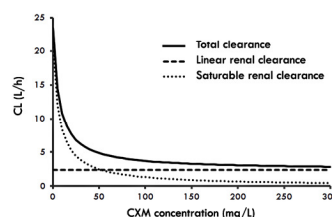


Figure 1. Representation of the total clearance, linear and saturable renal processes depending on the CXM concentration for a patient with a high glomerular filtration rate ($CL_{cr} = 120$ mL/min). A 50% of influence of each clearance is shown when the concentration is around 50 mg/L, which is in line with previous studies.³

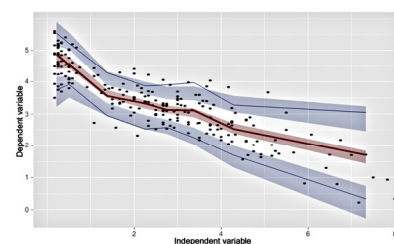


Figure 3. Results of the VPC ($n=1000$) performed with CXM final model. Dependent variable represents the log-transformed concentrations and the independent variable correspond to the time in hours. Solid lines represent the 50th percentile (red line) and the 5th-95th percentile (blue lines) of the observations. Red shaded area corresponds to the simulation-based 95% confidence interval for the median and blue shaded areas correspond to the simulation-based 95% percentile for the 5th and 95th percentile. The raw data are represented as black dots.

References:

- [1]. Keizer, R.J. *et al.* Comput Methods Programs Biomed 2011; 101(1): 72-9.
- [2]. Landersdorfer, C.B. *et al.* Antimicrob Agents Chemother 2012; 56(11): 5715-23.
- [3]. Gower, P.E. *et al.* Europ J clin Pharmacol 1977; 12: 221-7.

Acknowledgements

This work was supported by the Departamento de Educación, Universidades e Investigación (IT341-10), Gobierno Vasco, Spain. We would like to thank the Basque Government for research grant awarded to Eduardo Asín. We also would like to thank the Caja Vital Kutxa for the financial support.