POPULATION PHARMACOKINETICS OF CEFOXITIN AS A PROPHYLACTIC ANTIMICROBIAL AGENT

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OBJECTIVES

The aim of this study was to develop a population pharmacokinetic (PPK) model of cefoxitin (FOX) as a prophylactic agent in patients undergoing elective rectal or colon surgery in order to quantify the degree of inter-patient variability and identify the patient characteristics responsible for such variability.

METHODS

Plasma concentration-time data were obtained from 56 patients who received 2 g FOX q2h during surgery. Table I lists the demographic data of the patients and details the sampling procedure.

The PPK model was developed using NONMEM VI and the FOCE estimation method with INTERACTION. Selection between models was based on the value of the objective function, the precision of parameter estimates and the goodness of fit plots. Once a base model was selected, patient characteristics including demographic, clinical, laboratory and surgical data were explored for influence on PK parameters. For model evaluation, parameter precision was evaluated computing the 2.5th, 50th, and 97.5th percentiles obtained from the analysis of 1000 bootstrap datasets [1]. Visual and numerical predictive checks were used to explore model performance of the selected model [2]. In both procedures 1000 datasets with the same study design characteristics as the original dataset were simulated.

Table I. Summary of patient demographic data and sampling procedure description

Patient characteristic		Mean (SD)	Range
Age (years)		68 (12)	36-86
Weight (kg)		71 (9)	53-92
Gender (%) Male / Female		61 / 39	
ASA score (%)	1 / 2 / 3 / 4	11 / 41 / 39 / 9	
Length of surgery (hours)		2.3 (0.8)	1-5
Laparoscopy (%)	Yes / No / NA	80 / 18 / 2	
Diabetes mellitus (%)	Yes / No	23 / 77	
Renal insufficiency (%)	Yes / No	4 / 96	
Malnutrition (%)	Yes / No	2 / 98	
Immunosuppression (%)	Yes / No	4 / 96	
Immunosuppressant treatment (%)	Yes / No	20 / 80	
Perioperative transfusion (%)	Yes / No	38 / 63	
Haemoglobin concentration in serum (g/dL)		12.8 (2.4)	7.4-19.7
Serum creatinine (mg/dL)		0.9 (0.2)	0.5-1.6
Glucose concentration in serum (mg/dL)		115.5 (32.4)	82-266
Leucocites (/mm^3)		7938 (3226)	2600-16700
Creatinine clearance (mL/min)		77.3 (21.5)	38.0-152.7
Number of doses received (n) 1 / 2 / 3 / 4		13 / 36 / 6 / 1	
Number of samples after each dose (n) 1st dose / 2nd dose / 3rd dose / 4th dose		67 / 74 / 8 / 1	
Dosing time (h) 1st dose / 2nd dose / 3rd dose / 4th dose		0 / 1.92-2.17 / 3.92-4.17 / 5.67	
Last sampling times after each dose 1st dose / 2nd dose / 3rd dose / 4th dose		2.17 / 3.67 / 4.75 / 6.17	

RESULTS

A one-compartment model best fitted the data. Creatinine clearance (CL_{CR}) was found to have a significant correlation with the total clearance of the drug. The population clearance was expressed as $11.5x(CL_{CR}/77)^{0.52}$ and the apparent volume of distribution was 12 L. The percentage of η-, and ε-shrinkage [3] was greater than 25%, and therefore the use of goodness-of-fit based on the normalized prediction distribution errors (npde) [4] was justified. The selected model was capable to capture the mean tendency and dispersion of the data during the first two administrations involving 90% of the observations available. The percentiles for C_{max} and AUC_{last} obtained from the simulated dataset during the performance of the numerical predictive check were in agreement with raw data, with median values of 159 mg/L, and 201 mg· h/L, respectively.

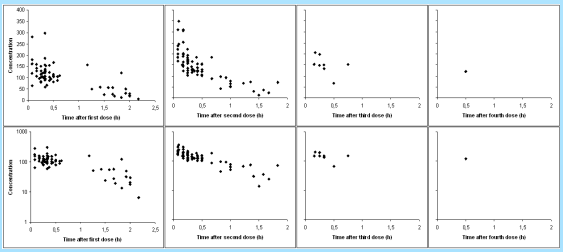

Figure 1. Normal plots (upper panels) and semi-log plots (lower panels) of cefoxitine plasma concentration vs time for the 56 patients. Data from each dose are represented in different panels.

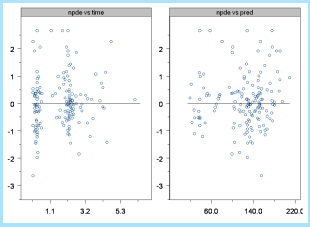

Figure 2. Left, scatterplot of normalized prediction errors (npde) versus time (lower left panel). Right, scatterplot of npde versus population predictions (pred).

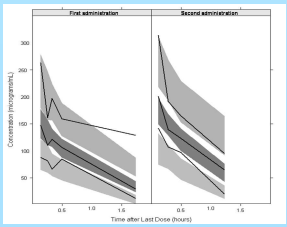

Figure 3. Results from the VPC. Solid lines, median, 5th and 95th percentiles of the observations. Gray areas cover the 90% confidence intervals of the 5th, median, and 95th percentiles of the simulated profiles.

Table II. Population pharmacokinetic parameters of cefoxitin in patients after intravenous infusion administration

Parameter	Estimate [CV(%)]	Median (2.5th-97.5th percentile)[a]
CL (L/h)= $\theta_{CL} \times \left(\frac{CL_{CR}}{77}\right)^{\theta_{CLCR}}$	θ_{CL}= 11.5 (5.4)	θ_{CL}= 11.4 (10.1 - 12.5)
	θ_{CLCR}=0.52 (33.2)	θ_{CLCR}=0.54 (0.22 - 0.99)
V (L)	12 (4.7)	11.9 (10.9 - 13.2)
IPV_{CL} (%)	27.1 (39.4)	26.4 (14 - 37)
IPV_{V}(%)	22 (63.2)	22.4 (7.5 - 33.4)
Residual $error_{additive}$ (mg/mL)	4.92 (42.3)	5.12 (1.29 - 16.3)
Residual $error_{proportional}$ (%)	24.1 (6.97)	23.5 (19 - 27)

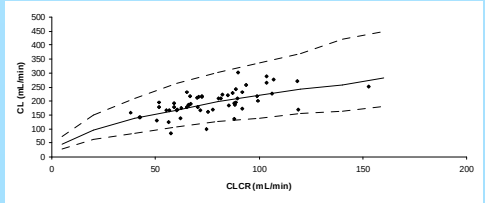

Figure 4. Plot of the individual predicted cefoxitin clearances versus creatinine clearance for the 56 patients (symbols). Lines represents the 5th, 50th, and 95th percentiles of 1000 simulations performed at CL_{CR} values of 5, 20, 40, 60, 80, 100, 120, 140, and 160 ml/min.

CONCLUSIONS

This study has quantified the influence of CL_{CR} on the PK of FOX in patients undergoing colorectal surgery. Considering that the main objective of antimicrobial prophylaxis is to maintain free-drug plasma levels above the MIC for common contaminating pathogens during the surgery, the developed PPK model will be helpful to redefine dose regimens of FOX for surgical prophylaxis in patients with high CL_{CR}.

References

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