Pharmacokinetics of Piperacillin-Tazobactam in Patients with Severe Infections

Ana S. Rodríguez-Báez M.Sc.[1] , Arturo Ortiz-Álvarez MD.[2] , Melissa Romano-Aguilar, M.Sc.[1] , Fidel Martínez-Gutiérrez, Ph.D.[1] , Silvia Romano-Moreno, Ph.D.[1] , Rosa C. Milán-Segovia, Ph.D. [1] , Susanna Medellín-Garibay, Ph.D.[1]

[1] Universidad Autónoma de San Luis Potosí, San Luis Potosí, México.
[2] Hospital Central, "Dr. Ignacio Morones Prieto", San Luis Potosí, México.

coco_baezrdz@hotmail.com Tel: +49 157 37948921

Background

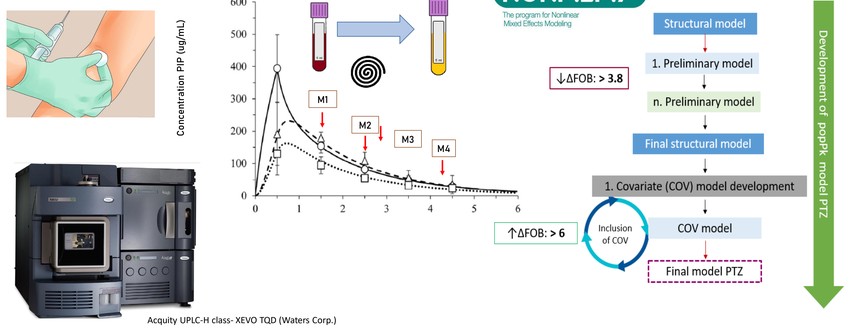
- β-lactams are the most prescribed group of antibiotics to treat severe infections [1].
- Among the penicillin class highlights Piperacillin-Tazobactam (PIP/TAZ) because of its broad spectrum and minimal adverse effect profile [1].
- Bactericidal effects are time-dependent and the PIP concentrations remain above the the minimum inhibitory concentration of targeted pathogen (%ft>MIC) [2].
- A maximum dose of 28g per day is recommended to achieve the therapeutic goal; however, a fixed regimen can produce clinical failures in special populations [2].

Objective

To develop and validate a population pharmacokinetic model of PIP/TAZ in patients with severe infections for the design of personalized dosage regimens based on the anthropometric and physiological characteristics of each patient.

Methods

Prospective, observational study in patients with severe infections receiving treatment with PTZ.
This study was approved by the Research and Ethics Committee (register 05-20).



Acquity UPLC-H class- XEVO TQD (Waters Corp.)

The analytical method was validated according to applicable US Food and Drug Administration (FDA) guidance for bioanalysis

Results

Primary results

Table 1. Patient demographics

Variable	*Value (n=52)*	*Reference value*
Age (years)[a]	45.54 ± 16.67	NA
Weight (Kg)[a]	67.52 ± 15.95	NA
Body mass index (Kg/m²)[a]	24.56 ± 4.70	NA
Albumin (g/dL)[a]	3.22 ± 0.69	3.5-5.4
Serum creatinine (g/dL)[b]	0.8 (0.33-5.46) 0.73 (0.3-4.29)	Men (0.7-1.3) Women (0.6-1.1)
**Creatinine clearance (mL/min/1.73 m²)*[b]	94.91 (12.59-280.7)	80-120
PCR (mg/dL)[b]	10.20 (0.1-39.50)	<1
Blood urea nitrogen (mg/dL)[a]	20.70 (3.70-76.80)	6-20
Glucose (mg/dL)[b]	124.5 (59-316)	<110

Data are shown as: [a]mean ± standard deviation; [b] median (interquartile range).
**Creatinine clearance: estimated by the Cockcroft-Gault formula*

Table 2. Pharmacokinetics parameters, inter-individual variability and residual error.

PK model	Parameter	PIP		TAZ	
		Mean	RSE (%)	Mean	RSE (%)
One-compartment open model					
CL (L/h)	Θ_1	8.79	12	12.6	14
V1 (L)	Θ_2	17.6	13	32.8	13
Interindividual variability associated to CL (%)	ω_{CL}	75.3%	12	88.7%	13
Interindividual variability associated to V1 (%)	ω_{V1}	67.2%	15	68.8%	18
Residual variability	σ	7.28 µg/mL	26%	0.22 µg/mL 17.32%	27 28

Residual variability as shown as: [a]standard deviation (g/mL); [b] coefficient of variation (%)
PIP and TAZ concentrations from 0.6 to 318.8 µg/mL
RSE: Relative standard error

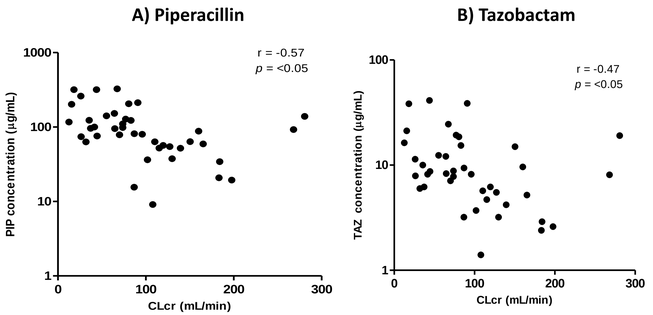


Figure 2. Correlation creatinine clearance with log plasma concentration of (a) PIP and (B) TAZ (n= 52).

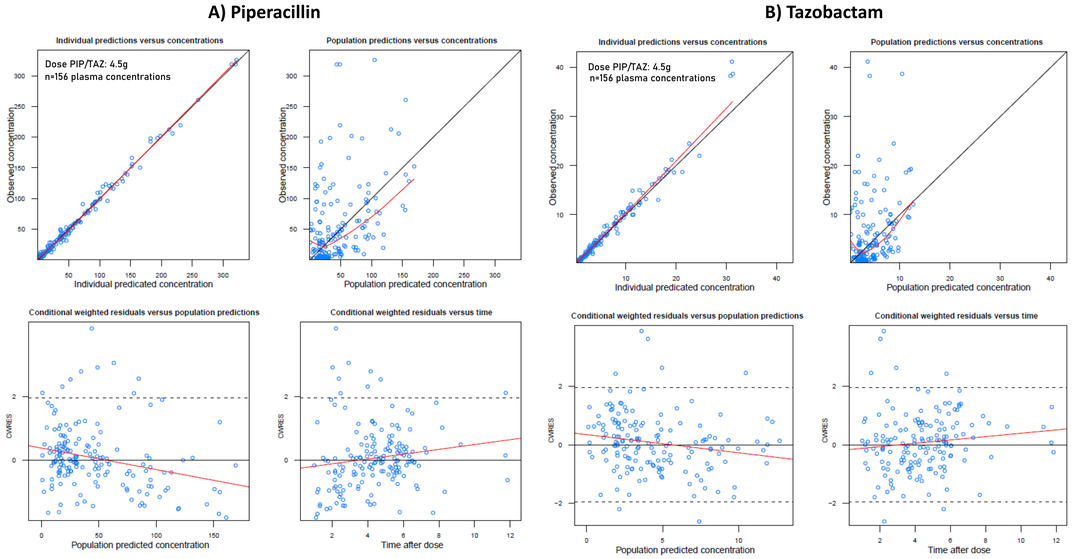


Figure 1. Goodness of fit scatter plots of DV versus PRED (a) PIP and (B) TAZ concentrations (including the identity line) for the one-compartment open model. Scatter plots of CWRES (including the identity line) for the one-compartment open model corresponding to the study group (n= 52).

Conclusions

Individualization and optimization of β-lactam dosing regimen are essential in drugs with wide IIV such as PIP/TAZ; therefore, the development of a population PK model will provide a valuable aid in explaining and quantifying some of this variability to allow a priori predictions to design initial regimens to reach the pharmacotherapeutic targets

References

1. Roberts, Jason A., Claire Roger, and Jan J. De Waele. "Personalized antibiotic dosing for the critically ill." (2019): 715-718.
2. Wong G, Briscoe S, McWhinney B, Ally M, Ungerer J, Lipman J, Roberts JA. Therapeutic drug monitoring of β-lactam antibiotics in the critically ill. Journal of Antimicrobial Chemotherapy. 2018 Nov 1;73(11):3087-94.

Future directions

1. This is preliminary study to determinate the PK characteristics of PTZ in patients with severe infections.
2. It is planned to enroll more patients to develop and validate individualized dosing of PIP/TAZ to attain a PK target

Funding and Disclosures

The authors would like to acknowledge the patients and clinical staff from the Hospital Central "Dr. Ignacio Morones Prieto". Funding for this study was provided by the Research Support Fund from Universidad Autónoma de San Luis Potosí (Project **C20-FAI-10-37.37**), and the Technological Research Council of Science (CONACYT) from México to Ana S. Rodríguez-Báez for a doctoral fellowship (**Grant 862428**).