UNIVERSIDAD AUTÓNOMA DE SAN LUIS POTOSÍ

FACULTAD DE CIENCIAS QUÍMICAS

POSGRADO EN CIENCIAS FARMACOBIOLÓGICAS

“ESTUDIO FARMACOCINÉTICO POBLACIONAL PARA LA OPTIMIZACIÓN DE LA TERAPIA ANTIMICROBIANA CON PIPERACILINA-TAZOBACTAM EN PACIENTES CON INFECCIONES GRAVES”

TESIS PARA OBTENER EL GRADO DE DOCTORADO EN CIENCIAS FARMACOBIOLÓGICAS

PRESENTA

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San Luis Potosí, S.L.P., México Septiembre 2023

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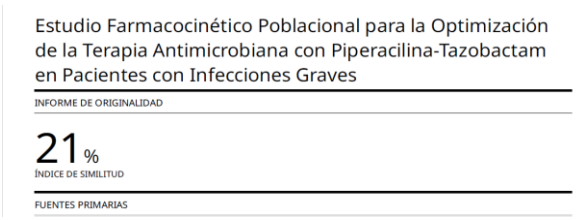
Estudio Farmacocinético Poblacional para la Optimización de la Terapia Antimicrobiana con Piperacilina-Tazobactam en Pacientes con Infecciones Graves

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DEDICATORIA

A mi madre, *por tu apoyo incondicional, gracias por estar cada primer y cada último día y ser el pilar más grande en mi vida.*

"It always seems impossible until it's done".

Nelson Mandela

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"People come into our lives for a reason, bringing something we must learn, and we are led to those who help us most to grow."

RESUMEN

Entre los antibióticos más utilizados para el tratamiento de infecciones moderadas a severas destaca la combinación piperacilina-tazobactam (PIP-TAZ) formulada por un antibiótico β-lactámico y un fármaco inhibidor de β-lactamasas, con actividad bactericida de amplio espectro. El objetivo farmacoterapéutico que correlaciona eficacia terapéutica con actividad bactericida depende del tiempo por el cual las concentraciones del fármaco permanezcan sobre la concentración mínima inhibitoria para el patógeno infectante (%fT >CMI). Actualmente, el ajuste de dosis de PIP-TAZ se basa en el aclaramiento de creatinina (CL_{CR}); sin embargo, en los pacientes críticos existen múltiples cambios fisiopatológicos que pueden alterar la farmacocinética de los fármacos, entre ellos PIP-TAZ. Lo anterior, puede ocasionar concentraciones supra- e infraterapéuticas incrementando el riesgo de falla terapéutica. Por lo cual, en el presente proyecto se evaluó el comportamiento farmacocinético de PIP-TAZ en pacientes con infecciones graves con la finalidad de desarrollar un modelo farmacocinético poblacional (popPK), que estableciera la variabilidad inter- e intraindividual y permitiera establecer regímenes de dosificación adaptados a las características de cada paciente. El estudio incluyó 67 pacientes con infecciones graves en tratamiento con PIP-TAZ. Las concentraciones plasmáticas de PIP-TAZ se determinaron mediante cromatografía de líquidos acoplada a espectrometría de masas. Se desarrolló un modelo farmacocinético poblacional para PIP-TAZ en pacientes con infecciones graves que permitió identificar la influencia de covariables significativas (CLCR y VIH) en la variabilidad interindividual. La validación interna de ambos modelos se realizó mediante la técnica de remuestreo con 1000 simulaciones y finalmente, se evaluó la capacidad predictiva mediante una validación externa de los modelos finales.

Palabras clave: Farmacocinética poblacional, Infecciones graves, Piperacilina-Tazobactam.

ABSTRACT

Due to its broad-spectrum effect, the piperacillin-tazobactam (PIP-TAZ) combination between a β-lactam antibiotic and a β-lactamase inhibitor drug is widely used to treat moderate to severe infections. The pharmacotherapeutic objective that correlates therapeutic efficacy with bactericidal activity depends on the percentage of time, in which the drug concentration should remain above the minimum inhibitory concentration during at least 50% of the dosing interval (%fT >MIC). Currently, PIP-TAZ dose adjustment is based on creatinine clearance (CLCR); however, in critically ill patients, multiple pathophysiological changes can alter the pharmacokinetics of drugs, including PIP-TAZ. The above can cause supra- and infra-therapeutic concentrations, increasing the risk of therapeutic failure. Therefore, in this study, the pharmacokinetic behavior of PIP-TAZ in patients with severe infections was evaluated to develop a population pharmacokinetic model, which would establish inter- and intra-individual variability and allow the establishment of dosing regimens based on patient characteristics. The study included 67 patients with severe infections receiving PIP-TAZ treatment. Plasma PIP-TAZ concentrations were determined by liquid chromatography coupled with mass spectrometry. A population pharmacokinetic model was developed for PIP-TAZ in patients with severe infections that allowed us to identify the influence of significant covariates on interindividual variability. The internal validation of both models was carried out using the resampling technique with 1000 simulations, and finally, the predictive capacity was evaluated through an external validation of the final models.

Keywords: Piperacillin-Tazobactam, Population pharmacokinetics, Severe infections,

ÍNDICE GENERAL

Estudio farmacocinético poblacional para la optimización de la terapia antimicrobiana con Piperacilina-Tazobactam en pacientes con infecciones graves.

1. Introducción

Piperacilina-tazobactam (PIP-TAZ) es una combinación de un antibiótico β-lactámico y un fármaco inhibidor de β-lactamasas ampliamente recomendado por las guías de práctica clínica debido a su actividad bactericida de amplio espectro contra bacterias Grampositivas y Gramnegativas. Por lo anterior, PIP-TAZ se prescribe para tratamiento de infecciones complicadas, tales como infección intraabdominal, neumonía, infecciones complicadas de piel y tejidos blandos, sepsis y choque séptico (1). Al ser un antibiótico β-lactámico, el objetivo farmacoterapéutico (PK/PD) que correlaciona la eficacia terapéutica con la actividad bactericida, depende del tiempo por el cual las concentraciones plasmáticas del fármaco permanecen sobre la concentración mínima inhibitoria para el agente causal durante al menos 50% del intervalo de dosificación ($\%fT_{50}$ >CMI) (2).

Actualmente, se recomienda una dosis máxima de 16 y 2 gramos al día con la finalidad de alcanzar el objetivo PK/PD; sin embargo, se ha reportado que 70% de los pacientes no logra el cumplimiento de este objetivo con la dosis estándar (3). De manera que se han propuesto estrategias para incrementar la tasa de cumplimiento, la principal es el ajuste de dosis basado en el aclaramiento de creatinina (CL_{CR}), reduciendo la dosis de acuerdo con el grado de daño renal en los pacientes.

A pesar de ello, en el caso de pacientes críticos con infecciones graves existen múltiples factores que condicionan su respuesta al tratamiento, alterando el comportamiento farmacocinético de los fármacos. Tales como, incremento del gasto cardiaco o síndrome de fuga capilar, que da lugar a un aumento del volumen de líquido intersticial, ocasionando edema e incremento del volumen de distribución (Vd) de P. Por otra parte, cambios en la función renal puede provocar una eliminación inadecuada de PIP-TAZ (4). Lo antes mencionado, puede resultar en concentraciones

subterapéuticas o tóxicas de PIP-TAZ y, por lo tanto, incrementa el riesgo de falla terapéutica del tratamiento antimicrobiano. En consecuencia, como resultado de la amplia variabilidad interindividual (VII) en la disposición y excreción de PIP-TAZ, la administración de dosis estándares del fármaco puede ser inapropiada para algunos pacientes. Con base a resultados previos, se estima que sólo el 64% de los pacientes con infecciones graves alcanza el objetivo PK/PD $\%fT_{50}$ >CMI en condiciones clínicas estándar (5).

Por lo anterior, la posibilidad de ajustar la dosis de PIP-TAZ mediante la cuantificación de sus concentraciones plasmáticas representa uno de los avances más relevantes generados en las últimas décadas para el tratamiento de infecciones graves. De manera que, a través de un enfoque farmacocinético poblacional es posible dilucidar el comportamiento farmacocinético e identificar las causas de la amplia VII en PIP-TAZ, con la finalidad de proponer regímenes de dosificación basados en las características clínicas y antropométricas de cada paciente.

2. Objetivos

2.1 Objetivo general

Caracterizar el comportamiento farmacocinético de PIP-TAZ en pacientes diagnosticados con infecciones graves para desarrollar un modelo farmacocinético poblacional no lineal de efectos mixtos, que establezca la variabilidad inter- e intraindividual y permita establecer regímenes de dosificación y estrategias de optimización adaptados a cada paciente.

2.2 Objetivos específicos

- Estandarizar y validar una técnica de cromatografía de líquidos de ultra alta resolución acoplada a un detector de masas en tándem (UPLC-MS/MS) para la cuantificación de PIP-TAZ en plasma sanguíneo.
- Cuantificar las concentraciones plasmáticas de PIP-TAZ tras la administración intravenosa en pacientes con infecciones graves.

- Desarrollar un popPK para PIP-TAZ que evalúe la influencia de variables antropométricas y clínicas en pacientes con infecciones graves.
- Realizar la validación interna mediante la técnica de remuestreo (“Bootstrap”) y validación externa del popPK obtenido.

3. Material y métodos

3.1 Diseño estudio y población.

Estudio realizado en el Hospital Central “Dr. Ignacio Morones Prieto” en San Luis Potosí, en colaboración con el Laboratorio de Farmacometría Aplicada y Laboratorio de Biofarmacia y Farmacocinética de la Facultad de Ciencias Químicas de la Universidad Autónoma de San Luis Potosí. El presente proyecto fue aprobado por el Comité de Investigación y el Comité de Ética en Investigación del Hospital (registro 05-20), así como el Comité de Ética en Investigación y Docencia de la Facultad de Ciencias Químicas (CEID) con clave CEID2020-013-S.

Se realizó un estudio analítico, prospectivo y observacional en el periodo mayo 2021 a julio 2023, en el que se incluyeron pacientes con diagnóstico o sospecha de infección grave (>18 años) provenientes del área de Cirugía, Medicina Interna y la Unidad de Cuidados Intensivos del HCIMP en tratamiento con PIP-TAZ. Pacientes bajo terapia de reemplazo renal, quemados, embarazadas o con alergias a penicilinas fueron excluidos del estudio.

Los pacientes o representantes legales designados firmaron un consentimiento informado previamente a su inclusión. Finalmente, datos clínicos y antropométricos de cada paciente se recopilaron a partir de su expediente clínico.

3.2 Desarrollo y validación de un método analítico por cromatografía de ultra alta resolución para la cuantificación de piperacilina-tazobactam en plasma.

La estandarización y validación de la técnica analítica fue realizada mediante un cromatógrafo de líquidos de ultra alta resolución Acquity UPLC System (ACQUITY UPLC Clase H, Waters), el cual cuenta con una bomba cuaternaria, automuestreador FTN acoplado detector de masas triple cuadrupolo XEVO-TQD con fuente de ionización por electrospray (ESI) (Waters Corporation®, Milford, Massachusetts, USA). La separación cromatográfica se realizó en una columna HSS T3 (2.1 X 100 mm, de 1.8 μm de tamaño de partícula) mediante una elución en gradiente de 7.5 min y flujo inicial de 0.2 mL/min, empleando una fase móvil compuesta ácido fórmico 0.1% en agua (A) y acetonitrilo grado masas (B) a una temperatura constante de 35°C y un volumen de inyección de 2 μL.

La detección y cuantificación por espectrometría de masas se realizó mediante el monitoreo de reacciones múltiples (MRM), operando la sonda de electrospray en modo de ionización positiva. Las condiciones de ionización y desolvatación fueron optimizadas para la cuantificación y detección de PIP-TAZ y dicloxacilina, como estándar interno: temperatura de desolvatación, 300°C; flujo de gas de desolvatación, 800 L/h y el voltaje del capilar, 2.8 kV. El voltaje de cono (V) para PIP, TAZ y dicloxacilina fue de 28, 24 y 28, respectivamente. Para la determinación de PIP, las transiciones (m/z) de cuantificación y detección fueron 518.12>142.99 y 518.12>160.03 con energías de colisión de 12 y 6 eV, respectivamente. Por otra parte, para TAZ las transiciones empleadas fueron 301.13>168.10 y 301.13>207.06, con energía de colisión de 14 y 10 eV, respectivamente. Finalmente, para dicloxacilina la transición empleada fue de 470.03>159.97 con una energía de colisión de 22 eV. El sistema fue operado mediante el Software MassLynx versión 4.1 (Waters Corporation®, Milford, Massachusetts, USA).

La validación del método analítico se realizó siguiendo los lineamientos de la Norma Oficial Mexicana NOM-177-SSA1-2013, en concordancia con la Guía para la Industria de Validación de Métodos Bioanalíticos de la Food and Drug Administration.

3.3 Determinación de las concentraciones plasmáticas de piperacilina-tazobactam en pacientes con infecciones graves.

PIP-TAZ se administró a criterio del médico tratante, en regímenes de dosificación estándar mediante infusión intermitente. En cada paciente, se tomaron de dos a cuatro muestras aleatorias de sangre venosa periférica (4 mL) en tubos BD Vacutainer™ con EDTA como anticoagulante. Una vez alcanzado el equilibrio dinámico, se recolectaron muestras cercanas a los siguientes tiempos: pre-dosis, 1, 4, 6, 8 y 12 h después del inicio de la infusión con PIP-TAZ.

Las muestras sanguíneas fueron centrifugadas durante 20 min a 1300 rpm, a 4°C para la separación del plasma sanguíneo. El sobrenadante fue transferido a tubos eppendorf y almacenado a -80°C hasta su análisis por UPLC-MS/MS.

Posteriormente, las muestras, controles y curva de calibración fueron extraídas empleando el siguiente proceso: inicialmente una proporción 1:2 utilizando una solución desproteinizante (dicloxacilina en acetonitrilo a una concentración de 10 μg/mL), posteriormente fueron centrifugadas durante 20 min a 14,000 rpm, 4°C; el sobrenadante fue centrifugado en las mismas condiciones por 10 min, el resultante fue diluido con agua grado HPLC (1:1) y colocado en viales de 2 mL para su almacenamiento en el automuestreador a 10°C una hora previo a su inyección.

3.4 Desarrollo y validación del modelo farmacocinético poblacional.

Para la elaboración del popPK se utilizó el programa farmacoestadístico NONMEM® v7.5.1 (ICON Development Solutions, Dublín, Irlanda). El procesamiento, manejo y visualización gráfica de los datos se realizó mediante la interfaz Pirana v. 2.9.8.

Los modelos farmacocinéticos se construyeron por separado para PIP y TAZ. Las estimaciones de los parámetros típicos, la VII asociada a los parámetros

farmacocinéticos y el error residual se determinaron usando el método de estimación de primer orden con interacción (FOCE-I). La VII fue modelada como exponencial, y la variabilidad residual fue evaluada como modelos de error homoscedástico (aditivo) y heteroscedástico (combinado y proporcional). El modelo estructural de PIP-TAZ de mejor ajuste se seleccionó en base a la evaluación de la función (OFV), el criterio de Akaike y los gráficos de bondad de ajuste.

Se evaluaron covariables clínicas y antropométricas, tales como: edad, creatinina sérica, peso, índice de masa corporal, peso corporal ideal, superficie corporal, aclaramiento de creatinina (CL_{CR}), comedicación y patologías concomitantes. El efecto de las covariables continuas fue evaluado mediante funciones lineales, exponenciales y en potencia, así como la influencia de covariables categóricas para construcción del modelo farmacocinético final. La selección de covariables se guió mediante pruebas de razón de verosimilitud a un nivel de significancia de $p<0.05$ ($\Delta OFV>3.84$) para inclusión; y $p<0.01$ para eliminación de la variable ($\Delta OFV>6.63$), gráficos de bondad de ajuste y la plausibilidad biológica.

La estabilidad y precisión de ambos modelos farmacocinéticos se determinó a través de una validación interna mediante la técnica de remuestreo o Bootstrap, y la evaluación visual predictiva (n=1000). Asimismo, se realizó la validación externa de los modelos farmacocinéticos poblacionales con un grupo de pacientes diferente a la población utilizada para realizar el modelo, pero con características antropométricas y clínicas similares. Las concentraciones plasmáticas observadas de PIP-TAZ de este grupo, se contrastaron con las concentraciones plasmáticas predichas por los modelos finales, evaluando la precisión y exactitud de los modelos finales a través del cálculo de errores de predicción medio, absoluto y la raíz del error cuadrático medio.

4. Resultados y Discusión

Los resultados de este proyecto están descritos en el artículo *"Evaluation of standard dosing regimens for Piperacillin-Tazobactam in Mexican patients with severe infections*

using a population pharmacokinetic approach". Enviado a la revista Clinical Pharmacokinetics para su publicación (Anexo II).

4.1 Características de la población de estudio.

Se incluyeron un total de 67 pacientes (45% mujeres). En el grupo de pacientes para la construcción del modelo (n=50) la edad promedio fue de 45 (± desviación estándar 15.8 años) y peso promedio de 68.1 ± 15.5 Kg. Mientras que, en el grupo de validación (n=13) fue de 49.5 ± 19 años, y 68.6 ± 10.3 Kg, respectivamente.

4.2 Método UPLC-MS/MS para la cuantificación de PIP-TAZ.

Se estandarizó y validó un método para la cuantificación de PIP-TAZ en muestras plasmáticas de pacientes adultos mediante UPLC-MS/MS. El método fue lineal en un rango de concentraciones de 0.6-100 µg/mL para PIP y 0.6-72 µg/mL para TAZ (R^2>0.99) con un límite de detección de 0.15 y 0.12 µg/mL, respectivamente. El porcentaje de recobro para PIP fue de 97% a 104% y 98% a 101% para TAZ. En términos de precisión y exactitud, se obtuvieron coeficientes de variación en un rango <15%, así como, el porcentaje de desviación promedio para muestras control y límite de cuantificación fue ≤15% y ≤20%, respectivamente.

Se cuantificaron un total de 166 concentraciones plasmáticas de PIP-TAZ en un rango de 0.6 a 261 µg/mL y 0.36 a 21.2 µg/mL, respectivamente, para el desarrollo de ambos modelos farmacocinéticos.

4.3 Análisis farmacocinético.

El modelo final seleccionado para describir y caracterizar el comportamiento farmacocinético de PIP y TAZ fue un modelo monocompartimental. A partir del cual se estimaron los parámetros farmacocinéticos típicos de aclaramiento y volumen de distribución, así como la incorporación de covariables significativas en el CL de PIP-TAZ, tales como CL_{CR} e infección por virus de inmunodeficiencia, a partir de las cuales se logró explicar un porcentaje de la VII en los parámetros farmacocinéticos de PIP-TAZ.

A través de la validación interna, mediante la técnica de remuestreo y la evaluación predictiva visual, se corroboró la precisión y estabilidad de los parámetros farmacocinéticos estimados mediante los modelos finales. Por otra parte, se demostró la capacidad predictiva de ambos, a través de la validación externa.

5. Conclusiones

Se desarrolló un popPK de PIP-TAZ en pacientes mexicanos con infecciones graves en el cual se demostró la influencia del CL_{CR} en el CL de ambos fármacos. Por otra parte, se demostró la importancia de monitorizar las concentraciones plasmáticas de PIP-TAZ en poblaciones susceptibles, tales como pacientes con VIH.

A partir de la elaboración del presente estudio fue posible dilucidar el comportamiento farmacocinético de PIP-TAZ y tras la evaluación externa del mismo se demostró la capacidad predictiva de ambos modelos; lo anterior servirá de referente para implementar estrategias de optimización del fármaco en pacientes con infecciones graves mexicanos.

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ANEXOS

A comparison of pharmacokinetics software for therapeutic drug monitoring of piperacillin in patients with severe infections

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ABSTRACT

Objective To evaluate the predictive performance of population pharmacokinetic models for piperacillin (PIP) available in the software MwPharm, TDMx and ID-ODs for initial dosing selection and therapeutic drug monitoring (TDM) purposes.

Methods This is a prospective observational study in adult patients with severe infections receiving PIP treatment. Plasma concentrations were quantified by ultra-high performance liquid chromatography coupled to tandem mass spectrometry. The differences between predicted and observed PIP concentrations were evaluated with Bland-Altman plots; additionally, the relative and absolute bias and precision of the models were determined.

Results A total of 145 PIP plasma concentrations from 42 patients were analysed. For population prediction, MwPharm showed the best predictive performance with a mean relative difference of 34.68% (95% CI −197% to 266%) and a root mean square error (RMSE) of 60.42 µg/mL; meanwhile TDMx and ID-ODs under-predicted PIP concentrations. For individual prediction, the TDMx model was found to be the most precise with a mean relative difference of 7.61% (95% CI −57.63 to 72.86%), and RMSE of 17.86 µg/mL.

Conclusion Current software for TDM is a valuable tool, but it may also include different population pharmacokinetic models in patients with severe infections, and should be evaluated before performing a model-based TDM in clinical practice. Considering the heterogeneous characteristics of patients with severe infections, this study demonstrates the need for therapy personalisation for PIP to improve pharmacokinetic/pharmacodynamic target attainment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Therapeutic drug monitoring (TDM) and model-precision dosing software have become crucial tools to optimise antimicrobial dosage regimens to maximize efficacy and reduce toxicity.

WHAT THIS STUDY ADDS

⇒ This study evaluated the predictive performance of population pharmacokinetic models for piperacillin implemented in three widely employed model-precision software in clinical care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study points out the need for personalised piperacillin dosing and the relevance of performing TDM for β-lactam drugs, considering heterogeneity among severe infection patients when using population models.

INTRODUCTION

Infectious diseases are a leading cause of morbidity and mortality worldwide, with rates between 26–80% mainly related to antimicrobial resistance.[1] Among acute care patients, there is a high prevalence of infections; approximately 50% of patients develop an infection that requires antimicrobial treatment.[2]

Patients with severe infections require early and appropriate antimicrobial therapy to control the causative microorganism and improve clinical outcomes[3 4]; however, evidence suggests that empirical treatment has been associated with increased resistance to the first-line antibacterial agents.[1]

In this setting, patients with severe infections show pathophysiological changes that alter drug pharmacokinetics (PK). Among the main alterations observed are changes in volume of distribution (Vd) caused by increased capillary permeability and hypoalbuminaemia, as well as changes in clearance (CL) by augmented renal clearance secondary to increased cardiac output and increased renal perfusion by vasopressor administration. Moreover, these patients could develop an organic dysfunction syndrome caused by the decline in health status, reflected in hepatic or renal dysfunction, occasioning a decrease in drug CL and higher serum concentrations with more risk of toxicity.[3 5]

Due to these alterations, the increasing resistance rates and the absence of new treatment options, current strategies are focused on personalised therapy-based therapeutic drug monitoring (TDM) to enhance antimicrobial exposure and minimise the risks of toxicity and resistance.[6 7]

TDM of antimicrobials has been focused on drugs with a narrow therapeutic range, those whose efficacy is concentration-dependent, and those whose efficacy is related to the area under the concentration-time curve, such as aminoglycosides and glycopeptides.[2 8] Meanwhile, TDM of β-lactams, the most prescribed antimicrobials, is not frequently performed due to time-dependent

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bactericidal effect, in which the free drug concentration should remain above the minimum inhibitory concentration (MIC) during >50% of the dosing interval (%fτ>MIC).[9–11]

Piperacillin (PIP) is a ureidopenicillin with a broad spectrum of activity against Gram-positive, Gram-negative, and β-lactamase producer strains by the coadministration with tazobactam (TAZ), a β-lactamase inhibitor; consequently, PIP/TAZ are usually prescribed to treat moderate to severe infections. Previous studies, such as the one developed by Wong *et al*[12] have demonstrated that standard doses of PIP/TAZ in critically ill patients may result in deficient PK/pharmacodynamic (PD) target attainment and suboptimal serum concentrations.[13 14] Other studies suggest that switching from intermittent infusion of PIP/TAZ to a prolonged infusion has been adequate but not enough to reach PK/PD targets in patients with augmented renal clearance.[13] The above emphasises the need to implement and improve TDM based on Bayesian approaches to achieve the PIP PK/PD targets in patients with severe infections.

Therefore, the aim of the study was to compare and evaluate the predictive performance of three different software for TDM of PIP in clinical practice.

METHODS

Study design

An observational analytical study was performed from May to November 2021 at the Hospital Central "Dr. Ignacio Morones Prieto" in San Luis Potosí, Mexico. The study was approved by the Research and Ethics Committee, with the register number 05–20. Before the sample and data collection, written consent was obtained from all patients or legally authorised representatives.

Patients and sample collection

Adult patients (aged >18 years) with severe infections receiving PIP/TAZ treatment were included. Patients with penicillin allergies, burn injuries, pregnant women, or those on renal replacement therapy were excluded.

Clinical and anthropometric data were collected for each patient on the sampling day, including age, weight, sex, complete blood count, blood urea nitrogen, glucose, aminotransferases, alkaline phosphatase, serum electrolyte test, C-reactive protein, albumin, and serum creatinine concentration.

PIP/TAZ was administered at standard dosage regimens of 4/0.5 g or 2/0.25 g every 6 or 8 hours, by intermittent infusion of 0.5–3 hours. Blood samples (4 mL) were collected at steady state before the next dose and at the following times after last dose: 1–2, 2–4, and 4–6 hours post-infusion. Samples were drawn in EDTA tubes and centrifuged at 305 x *g* for 20 min at 4°C; plasma was aliquoted and stored at −80°C until analysis.

Determination of PIP concentrations

PIP plasma concentrations were measured by a validated ultra-high performance liquid chromatography (UPLC) method on an Acquity UPLC H-class system coupled to a tandem triple quadrupole mass spectrometer XEVO TQD (Waters Corp) with an electrospray ionisation source (ESI).

Chromatographic separation was performed by injection of 5 µL of treated sample in a Waters Acquity HSS T3 column (2.1×100 mm, 1.8 m) at 35°C. The mobile phase consisted of 0.1% formic acid in water (A) and acetonitrile (B) at an initial flow rate of 0.2 mL/min. The elution gradient was as follows: from 0 to 2 min 28%B followed by a flux increase of 0.25 mL/min from 2 to 3.6 min and a linear gradient to reach 70%B; 3.6 to 4 min held at 70%; from 4 to 4.3, a linear increase to 85%B, 4.3–4.75 min held at 85%B, and 4.75 to 5 min a linear return to initial conditions followed by 1.5 min for column re-equilibration. The ESI was operated in positive mode, and quantification was performed in multiple reaction monitoring (MRM) mode with the following settings: capillary voltage, 2.8 kV; desolvation temperature, 300°C; desolvation gas flow, 800 L/h;cone voltage was set to 28 V for PIP and IS. The MRM transitions (m/z) for quantification were: PIP 518.12>142.99 and IS 470.03>159.97 with a collision energy (eV) of 12 and 22, respectively. Data analysis was performed by Waters MassLynx software.

Samples, calibration curve standards and quality controls were protein precipitated by adding 200 µL of internal standard working solution (dicloxacillin 10 µg/mL in acetonitrile) to 100 µL plasma and vortexed before centrifugation at 20 817 x *g* for 20 min; the supernatant was centrifuged for 10 min at 20 817 x *g*. A volume of 100 µL of the clear supernatant was transferred to a UPLC vial and dilution was undertaken with the same volume of water; vials were placed in the autosampler at 10°C.

The analytical method was validated according to applicable US Food and Drug Administration guidance for bioanalysis. Calibration curves were linear from 0.6 to 100 µg/mL for PIP (R^2 >0.99) with recovery between 97–104%. Inter-and intra-assay precisions depicted coefficients of variation (CV) of 4.59% and 6.49% for PIP, respectively. The method was accurate with deviations ranges of −6.5% to 6.03%; the limit of detection was 0.15 µg/mL and the limit of quantification was 0.6 µg/mL

Pharmacokinetics

Plasma concentration-time data for PIP were analysed for each patient. PK calculations were performed using Mediware software (MwPharm),[15] TDM by PharmacometrX (TDMx) software,[16] and individually designed optimum dosing strategies (ID-ODs)[17] which incorporate patient clinical and anthropometric data, and measured PIP concentrations through Bayesian feedback.

Based on population PK peer reviewed models included in MwPharm, TDMx, and ID-ODs, one- and two-compartment open models were employed for determination of the following individual PK parameters: CL, Vd, and elimination half-life ($t_{1/2}$). Predicted population PIP concentrations were obtained by simulation of the PIP scheme with the PK fixed parameters and incorporating patient physiological variables such as weight, serum creatinine concentration, age and gender. Predicted individual PIP concentrations were obtained after including observed PIP concentrations for each patient through Bayesian estimation incorporated on each TDM software.

Statistical analysis

Statistical analysis was performed using GraphPad Prism V.5 software (GraphPad Inc, California, USA). Grubb's test was performed to evaluate outliers; missing values were excluded from the analysis. The prediction performance was evaluated by precision and absolute and relative bias. The Bland-Altman method was calculated as a measure of absolute bias and precision (equation 1-2). Prediction error (PE) was calculated as the difference between predicted (Cp_{PRED})and observed (Cp_{OBS})PIP concentrations; the mean prediction error (MPE) was denoted as the arithmetic mean of PE (equation 3); the mean absolute error (MAE) was denoted as the arithmetic mean of absolute PE (equation 4); and the root mean square error (RMSE) was

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Table 1 Demographics and clinical characteristics of patients with severe infections treated with piperacillin

Variable	Value (n=42)
Age (years)*	45.52±17.1
Weight (kg)*	66±13
Body mass index (kg/m^2)*	24.5±4.6
Albumin (g/dL)*	3.10±0.65
Serum creatinine (g/dL)†	0.8 (0.33–5.46)
Creatinine clearance (mL/min/1.73 m^2)†‡	80.62 (12.59–280.7))
PCR (mg/dL)†	11.2 (0.1–39.50)
Blood urea nitrogen (mg/dL)*	28.64±20
Alkaline phosphatase (mg/dL)*	169±127.1
Glucose (mg/dL)†	129.2 (80.60–316)

Data are shown as: *mean±SD; †median (IQR).
‡Creatinine clearance: estimated by the Cockcroft-Gault formula.

Table 2 Pharmacokinetic parameters of piperacillin estimated through a priori and Bayesian approach in patients with severe infections

	Pharmacokinetic software		
Parameter	MwPharm	TDMx	ID-ODs
Population prediction			
$t_{1/2}$ (h)	0.89 (0.38–0.88)	0.77 (0.39–1.61)	0.75 (0.10–1.82)
CL (L/h)	7.30 (2.53–10.35)	15.10 (6.41–35.30)	8.89 (4.08–31.15)
Vd (L)	10.08 (6.98–14.40)	17.70 (10.90–24.80)	11.16 (1.16–15.60)
Individualised prediction			
$t_{1/2}$ (h)	1.44 (0.50–2.77)	1.77 (0.42–4.51)	0.80 (0.26–2.72)
CL (L/h)	7.23 (1.72–44.42)	9.15 (1.40–28.10)	9.83 (2.56–31.15)
Vd (L)	12.75 (6.57–48.93)	18.80 (5.95–40.10)	10.72 (3.73–20.22)

Data are shown as median (IQR).
CL, clearance; ID-ODs, individually designed optimum dosing strategies; $t_{1/2}$, elimination half-life; Vd, volume of distribution.

denoted as a measure of relative bias and precision (equation 5), as well as the corresponding 95% confidence interval (95% CI).

$$Abs\ BIAS = \frac{1}{n}\sum_{i=1}^{n}|Y_i - X_i| \quad (1)$$

$$\bar{d} \pm 1.96\, s = \sqrt{\frac{3s^2}{n}} \quad (2)$$

$$MPE = \frac{1}{n}\sum_{i=1}^{n}\left(Cp_{PRED} - Cp_{OBS}\right) \quad (3)$$

$$MAE = \frac{1}{n}\sum_{i=1}^{n}\left|Cp_{PRED} - Cp_{OBS}\right| \quad (4)$$

$$RMSE = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\left(Cp_{PRED} - Cp_{OBS}\right)^2} \quad (5)$$

RESULTS

Patient characteristics

Forty-two patients with severe infections (52% women) were included in the current study. The median age (IQR) was 48 (18–78) years with a total body weight of 65 (40–91) kg. The most frequent indication of PIP was for the treatment of necrotising fasciitis (17%) and other indications including abscess (12%) and pneumonia (9.5%); 94% of patients received non-steroidal anti-inflammatory drugs, 47% received enoxaparin sodium and 29% received vancomycin concomitantly. Additional clinical and anthropometric data are summarised in table 1.

Most of the patients received a PIP dosage regimen of 4 g every 6 hours as a 0.5 to 2 hour infusion (90.47%), and 2 g every 8 hours as a 1 to 3 hour infusion (9.52%), depending on renal function. At least two blood samples were collected per patient with a total of 145 PIP plasma concentrations included in the analysis.

Pharmacokinetic analysis

The median (IQR) PIP concentration at 1–2 hours, 2–4 hours, 4–6 hours, and 6–8 hours post-infusion was 88 (9.10–326), 45.30 (4–219.4), 28.20 (0.5–198.6), and 16.60 (13.10–105.6) µg/mL, respectively. For population and individual predictions, the PK parameters estimated are shown in table 2.

Comparative accuracy of observed PIP concentrations predicted with TDM software

Three population PK models were employed for the population and individualised prediction of PIP concentrations (table 3).

The absolute bias on population prediction was 34.68% (95% CI −197% to 266%), 90.64% (95% CI −135% to 316.31%), and 76.43% (95% CI −67.55% to 220%), for the MwPharm, TDMx, and ID-ODs models, respectively. Additionally, the absolute bias on individual prediction showed a mean relative difference of −2.82% (95% CI −60.70% to 55%) for the MwPharm model, 7.61% (95% CI −57.63% to 72.86%) for the TDMx model, and 72.38% (95% CI −91.36% to 236.12%) for the ID-ODs model.

According to the Bland-Altman analysis for population prediction, the model of MwPharm was the least biased, with a 95% CI from −197.10% to 266.47%; for the individual prediction, the TDMx model was found to be the most precise with a 95% CI from −57.64% to 72.87% in predicting the measured concentrations. The Bland-Altman percentage plots for population and individual predictions are shown in figure 1.

The relative predictive performance of the PK software in terms of MPE and RMSE concerning the prediction value are shown in figure 2. The negative MPE (range) values in population prediction of −41.21 (−260 to 28.71) µg/mL in TDMx and −31.42 −276 to 19.90) µg/mL in ID-ODs software demonstrate that both tend to underpredict PIP concentrations; meanwhile MwPharm predicted PIP concentrations show MPE (range) values equally distributed around zero −12.95, −252 to 128 µg/mL). The RMSE value for population prediction of MwPharm, TDMx and ID-ODs was 60.42, 66.62, and 68.83 µg/mL, respectively (table 4).

The comparison between the observed and individual predicted data show that the model by Li *et al* (2005) was found to be least biased with an MPE of −5.81 (5% CI −97.57 to 39.93) µg/mL, followed by the model of MwPharm with 4.61 (95% CI −51.01 to 155.08) µg/mL, and finally the model of Felton *et al* (2014) with −43.15 (95% CI −255.19 to 28.07) µg/mL. According to the RMSE, individual predictions by TDMx software were the most precise with the lowest value of 17.86 µg/mL.

DISCUSSION

Previous studies have evaluated the population pharmacokinetics of PIP in patients with severe infections[18 19]; however, the current study evaluates the predictive performance of PK models available in different TDM software packages.

The use of software centred on posteriori analysis has been considered as a strategy to improve TDM and establish dosing regimens based on population pharmacokinetics and individual

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Table 3 Equations of the evaluated population pharmacokinetic models for piperacillin

Software	Reference	Population	Model	IVV	RV
MwPharm	Roberts *et al* (2010)	Critically ill patients with sepsis (n=16) Age (years): 22–65 Female (%): 31	Two-compartment open model (NONMEM) $CL=17.1\left(\frac{WT}{70}\right)$ V1 (L)=7.2 V2 (L)=17.8 Q (L/h) = 52 ALAG (h^{-1}) = 0.07	Exponential CV_{CL}: 29.8% CV_{V1}: 26.4% CV_{V2}: 73.3% CV_{Q}: 50.2% CV_{ALAG}: 43.7%	Combined 25.3% 3.2 mg/L
TDMx	Li *et al* (2005)	Patients with complicated intra-abdominal infection (n=41) Age (years): 18–85 Female (%): 27	One-compartment open model (NONMEM) CL (L/h) = 5.05 + 9.60 CL_{CR} /89 Vd (L)=22.3 WT/81.8	Exponential CV_{CL}: 27.7% CV_{Vd}: 25.2%	Combined 18.5% 1.77 mg/L
ID-ODs	Felton *et al* (2014)[22]	Critically ill patients (n=146) Age (years): 20–58 Female (%): 36	Parallel first-order/Michaelis Menten (Pmetrics) $\frac{dX1}{dt} = R\,(1) - \left(\frac{CLi + (CLCR\ CLs)}{Vci + (Wt\ Vcs)} + kcp\right) X1 + kpc\ X2$ $\frac{dX2}{dt} = Kcp\ X1 - Kpc\ X2$ $V_{máx}$ (mg/h) = 898.91 (median: 808.31) Km (mg/L) = 90.13 (median: 77.43) V_c (L)=13.67 (median: 15.78) K_{cp} (h^{-1}) = 9.19 (median: 3.79) K_{pc} (h^{-1}) = 20.95 (median: 28.58) CL (L/h) = 6.62 (median: 6.89)	$SD_{Vmáx}$ (mg/h) = 402.61 SD_{Km} (mg/L) = 74.14 SD_{Vc} (L)=7.20 SD_{Kcp} (h^{-1}) = 10.25 SD_{Kpc}=16.91 SD_{CL} (L/h) = 3.81	

ALAG, time lag from dose infuser to patients; CL, clearance; CLCR, creatinine clearance; CLi, clearance due to non-renal means; CLs, fraction of piperacillin clearance due to creatinine clearance; ID-ODs, individually designed optimum dosing strategies; IVV, interindividual variability, expressed as CV (coefficient of variation) or SD (standard deviation); Kcp and Kpc, first-order intercompartmental rate constants; NCA, non-parametric model; Q, intercompartmental clearance; R1, infusion of piperacillin; RV, residual variability; V1, central volume of distribution; V2, peripheral volume of distribution; Vcs, volume of the central compartment proportional to body mass; Vd, distribution volume; Vi, volume of the central compartment not related to body mass; Vmáx, maximum rate of clearance by the Michaelis-Menten clearance mechanism; WT, total body weight; X1-X2, amount of piperacillin in central and peripheric compartment.

physiological and observed concentration data.[6 20] The TDM programs used differ in availability, cost and interface. MwPharm is one of the interactive clinical software most employed in European hospitals with a trial version available for 30 days; ID-ODs is a simulation tool powered by R software and is frequently used in Australia with an option to acquire an advanced account that improves simulation run; TDMx, a model-informed precision dosing software, is freely available online.[6 21]

According to the individual estimation, currents findings show considerable differences in precision and accuracy between the PK models. Through the Bland-Altman analysis, it was possible to observe a moderate negative trend of differences in the model implemented in MwPharm, proportional to the magnitude of PIP measured concentrations. The bias increased when higher PIP concentrations were observed. Furthermore, a difference >60 µg/mL would be significant for measuring PIP concentrations; the above may lead to PIP underprediction and erroneous initial dose, increasing the risk of overdose-induced toxicity, such as nephrotoxicity and neurological deterioration in some patients.[12]

The model of Felton *et al*,[22] implemented in ID-ODs software, showed the higher difference between the observed and

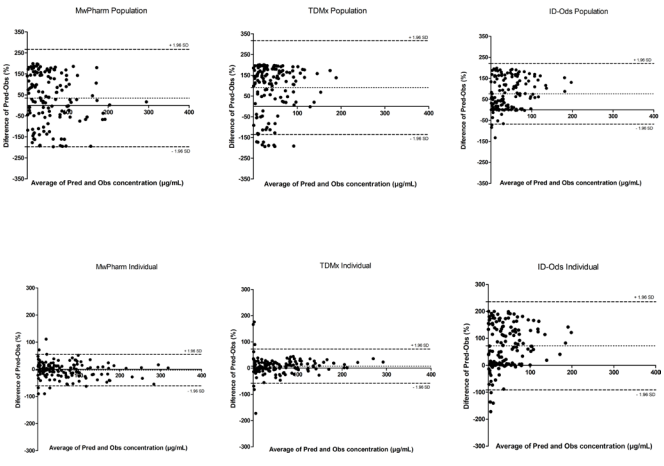

Figure 1 Bland-Altman analysis of the relative difference between predicted (Pre) and observed (Obs) piperacillin concentrations versus the mean of predicted and observed concentrations for the models evaluated. Dotted lines show the 95% limits of agreement and the bias of each model, respectively.

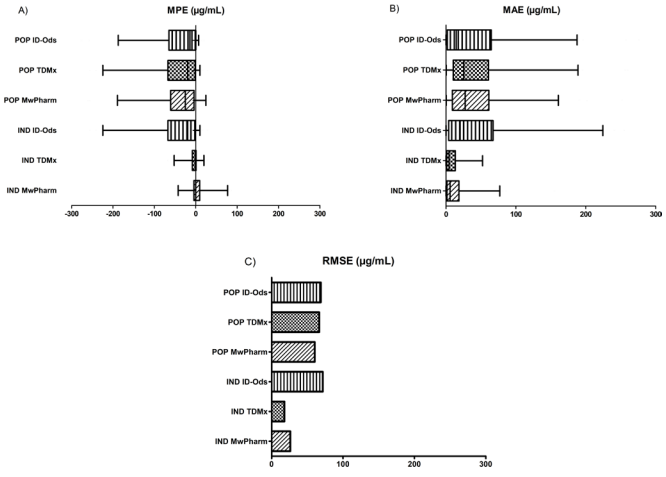

Figure 2 Evaluation of predictive performance of the population pharmacokinetic models for piperacillin. (A) Mean prediction error (MPE) (µg/mL). (B) Mean absolute error (MAE) (box represents IQR including the median, whiskers represent minimum and maximum). (C) Root mean square error (RMSE) (bar represents mean).IND, individualised data; POP, population data.

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Table 4 Evaluation of the predictive performance of the population pharmacokinetic models for piperacillin available in three software for model informed precision-dosing

Pharmacokinetic software	MPE (µg/mL)	95% CI	MAE (µg/mL)	95% CI	RMSE (µg/mL)
Population data					
MwPharm	−12.95	−49.90 to 32.53	41.52	34.24 to 48.80	60.42
TDMx	−41.21	−52.63 to 33.68	43.93	35.62 to 52.24	66.22
ID-ODs	−31.74	−50.18 to 31.80	32.37	32.73 to 50.90	68.83
Individualised data					
MwPharm	4.61	0.33 to 8.89	14.67	11.08 to 18.27	26.19
TDMx	−5.81	−8.60 to −3.0)	10.30	7.88 to 12.73	17.86
ID-ODs	−43.15	−52.63 to 33.68)	45.26	36.06 to 54.46	71.59

Data are shown as: mean (95% CI).
ID-ODs, individually designed optimum dosing strategies; MAE, arithmetic mean of absolute prediction error; MPE, mean prediction error; RMSE, root mean square error.

the predicted PIP concentrations; additionally, it was the least precise model with the broadest 95% limits of agreement. The higher bias observed could be attributed to the wide variability of the population studied by Felton *et al*, who included patients undergoing colorectal, abdominal, and thoracic surgery, and patients with ventilator-associated pneumonia.[22 23] Moreover, the model used a parallel linear Michaelis-Menten to describe the data; however, it has been reported that the PK of PIP in patients with severe infections show a better fit with a one-compartment model and first-order elimination.[19 24 25]

By contrast, the Li *et al* model implemented in TDMx software used a one-compartment model to fit the observed data in patients with complicated intra-abdominal infections, incorporating creatinine clearance in estimating CL and body weight to estimate the Vd[26]; this model showed the lowest bias when predicting observed PIP concentrations, as well as the narrowest agreement limits. The better fit of data available to the model from Li *et al* can be attributed to similarities to the group of the study, in which patients with hemodialysis, plasmapheresis, or organ failure were excluded,[26] similar to current non-inclusion criteria.

One unanticipated finding was that, in contrast to the individual prediction, based on current evaluation, the population estimates from Li *et al*[26] and Felton *et al*[22] showed the highest degrees of bias, respectively, whereas the model from MwPharm *et al* showed the closest line of equality within the confidence interval of the percentage of differences between the predicted and observed PIP concentrations; however, the three models have an extensive 95% limits of agreement. Most of the TDM software evaluates the interface; nonetheless, the population models implemented are selected from the literature and are considered a good fit for predictive performance for informed precision dosing purposes.[27] However, adapting the tools commonly used in pharmacometrics for population model diagnostics and standardised use is still necessary.[28]

Additionally, through the MPE and RMSE evaluation, it was possible to corroborate that for population prediction, the model of Li *et al* and Felton *et al*[22] tends to underpredict the PIP concentrations[22 26]; meantime, the model of Roberts *et al*[10] shows slightly a better fit to current data. Based on this analysis, for individual prediction the model from Li *et al*[26] was also found to be the most precise and least biased; this could be attributed to diverse factors, including the method applied in the PK modelling procedure, differences in the patient population,[29] as well as the unpredictable variability observed in patients with severe infections.[5 7]

The CL calculated through the Bayesian approach is consistent with the range from previous reports from 7 to 16.6 L/hour.[13 19 25] In contrast to previous findings, the Vd was higher, and thus can be associated with some of the physiological changes observed. On average, the current population showed hypoalbuminaemia; this decrease in serum albumin could be one of the reasons for the increased Vd, as well as the presence of edema due to the administration of intravenous drugs that can lead to fluid overload[3 5 9] or due to increased capillary permeability secondary to a systemic inflammatory response.[3 4] Therefore, some of the relevant covariates included in previous PK models may differ from those that could improve the characterisation of the typical PK parameters of PIP in the current population. The above emphasises the pathophysiological changes that could affect the appropriate antimicrobial exposure. Previous studies have reported wide variability in PK/PD target achievement in patients with severe infections; Osthoff *et al*[5] reported that 55% of patients did not achieve 100%fτ>MIC when selecting the MIC susceptibility breakpoint for meropenem and PIP[5]; moreover, Roberts *et al*[7] found that one-fifth of patients do not reach a minimum PK/PD target of 50% fτ>MIC.[7] Consequently, in patients with severe infections, improving the probability of target attachment depends on the site of infection, the MIC of the causative pathogen and the dosing regimen.[12]

Therefore, given the wide interindividual variability in patients with severe infections, it is crucial to consider their specific clinical condition, co-medication, and pathophysiological changes to optimise PIP therapy,[9 12] through strategies that allow dose adjustment based on PIP concentrations to maximise the achievement of PK/PD targets.

The usefulness of a TDM strategy and subsequent dose adjustment based on measured concentration is increasing the relevance of optimising treatment for critically ill patients with high and unpredictable variances in PK profiles, to stop the continuing emergence of antimicrobial resistance and to reduce healthcare costs.[6 12 21]

The present study has several limitations. First, the characteristics of the population may not match the targeted population included in the different PK models; these models may be more accurate in patient populations that are more like those from their studies. Second, only the predictive performance of the population pharmacokinetic models available in TDM software was evaluated. Third, a protein binding of 20% was assumed; therefore, this may lead to some inaccuracies, given that patients with severe infections may have lower protein binding. Depending on patient fraction unbound levels, a model could over- or under-predict the PIP concentrations.[30]

CONCLUSION

The predictive performance of different PK models for PIP available in TDM software packages were evaluated and applied to a

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heterogeneous population of patients with severe infection. The PK model available in TDMx demonstrated the best predictive performance on individual prediction, but MwPharm was better for population prediction; however, the three analysed software show extensive limits of agreement. Considering the wide inter-individual variability in the PK parameters and the heterogeneity of disease-related variables in patients with severe infections, these characteristics should be fully considered to personalise PIP therapy in routine clinical practice. This study enhances the need to perform routine TDM in patients undergoing PIP treatment for severe infections to ensure PK/PD target attainment.

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Data availability statement Data are available upon reasonable request. Derived data supporting the findings of this study are available from the corresponding author Medellin Garibay PhD on request.

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Clinical Pharmacokinetics

Evaluation of standard dosing regimens for Piperacillin-Tazobactam in Mexican patients with severe infections using a population pharmacokinetic approach

--Manuscript Draft--

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Abstract:	Piperacillin-tazobactam a combination of a β-lactam antibiotic with a β-lactamase inhibitor frequently used in critically ill patients to treat moderate to severe infections due to its broad-spectrum antibacterial activity. This population develop pathophysiological changes that increased the variability in treatment response, leading to a 30% of probability of target attainment. Therefore, the aim of this study was to characterize the pharmacokinetics parameters of piperacillin-tazobactam in Mexican patients with severe infections and describe the covariates with significant influence on drug disposition and excretion to propose individualized dosing regimens achieving therapeutic targets. An observational analytical study was performed on 67 patients (aged>18 years) with known or suspected severe infection receiving piperacillin-tazobactam treatment at Hospital Central “Dr. Ignacio Morones Prieto.” Sample were collected at the steady state, and plasma concentrations were quantified through Liquid Chromatography coupled to Mass Spectrometry. Population pharmacokinetic analysis was performed by nonlinear mixed-effects modeling. Internal validation was performed by bootstrap and visual predictive check (n=1000); moreover, external validation was carried out to evaluate the predictive capacity of final models by an a priori approach using a different group of patients. A total of 166 and 40 plasma concentrations were available for model development and external validation, respectively. Piperacillin-tazobactam pharmacokinetics was best described by a one-compartment open model with exponential interindividual variability associated with clearance and distribution volume; a homoscedastic model error was chosen. Creatinine clearance demonstrated a significant influence on piperacillin-tazobactam clearance. Additionally, piperacillin clearance decreased by 56% in patients with human immunodeficiency virus. Internal validation indicates the stability and accuracy of the final models, moreover the external validation showed a mean prediction error 2.35 µg/mL of (95% confidence interval,-0.37,5.08) for piperacillin and -1.92 µg/mL (95% confidence interval, -4.20,0.36) for tazobactam, respectively. In conclusion, population pharmacokinetic models have been developed and validated for piperacillin and tazobactam. The dosing recommendations in patients with severe infections should consider the renal function of the patient, and close monitoring is needed in patients with human immunodeficiency virus to avoid the risk of toxicity.
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Cover Letter

UNIVERSIDAD AUTÓNOMA
DE SAN LUIS POTOSÍ

September 21th, 2023

Amitabh Prakash, Ph.D.

Editor-in-Chief

Clinical Pharmacokinetics

Dear **Dr. Amitabh Prakash**,

I am submitting a research article for consideration of publication in the Clinical Pharmacokinetics. The manuscript is entitled ***"Evaluation of standard dosing regimens for Piperacillin-Tazobactam in Mexican patients with severe infections using a population pharmacokinetic approach".*** The manuscript comprises an abstract of 330 words and 4209 words of the main text that compiles the results of a population pharmacokinetic approach for Piperacillin-Tazobactam in Mexican patients with severe infections to assess the model utility of their clinical ability to estimate drug concentrations and thus improve the antimicrobial treatment in Mexican patients.

This work has not been published elsewhere and it has not been submitted simultaneously for publication in another journal. All authors have made substantial contributions to this manuscript and have read and approved for submission at Clinical Pharmacokinetics.

Thank you for your consideration.

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1. Introduction.

Appropriate antibiotic therapy is essential to decrease mortality, morbidity, and healthcare costs associated with severe bacterial infections. Thus, diverse programs have emerged to promote their correct use and reduce secondary antimicrobial resistance. Although medical advances, the proper infection control system remains challenging due to the delay in identifying causative agents and their antimicrobial susceptivity [1].

Acute and critical care patients with sepsis, post-cardiac arrest, catheters, mechanical ventilation, stroke, major surgery, and burns are prone to develop severe infections; thence, to management, physicians prescribe an empiric and targeted antibiotic therapy with broad-spectrum antibiotics to ensure optimal activity against the most common bacteria [2]. Consequently, it is estimated that approximately 54% of hospitalized patients in Latin America require treatment with antibiotics [3].

One of the most prescribed antibiotics for treating moderate to severe infections is Piperacillin-tazobactam, a combination between a β-lactam antibiotic and β-lactamase inhibitor, due to its extended-spectrum against the *Pseudomonas* and *Enterobacteriaceae* spp. [4,5]. As β-lactam, the piperacillin pharmacokinetic/pharmacodynamic (PK/PD) index is time-dependent, whereby the free drug concentration should remain above the minimum inhibitory concentration of the targeted pathogen (%*f*T >MIC). An optimal 50%*f*T >MIC was associated with clinical efficacy; however, recent studies showed that a higher threshold of up to 100%*f*T >MIC is needed to reach a maximal bactericidal effect in special populations, whereas, for tazobactam, the optimal PK/PD index is as well time-dependent, in which the free drug concentration should remain above a concentration threshold, based on the level of β-lactamase [6,7].

Piperacillin-tazobactam is primarily cleared by glomerular filtration and tubular secretion. Therefore, there is a high relationship between renal function and drugs concentrations; thus, the dose adjustment is suggested based on the patient's renal function [8]. Other strategies have focused on the drug administration as an extended infusion to reach the extension of the 100% %*f*T >MIC [6].

Despite this, in the case of acute and critical care patients, the conventional administration guideline may be inadequate due to the pathophysiological changes associated with their conditions. In the most common scenario, these patients receive constant intravenous fluid administration, leading to capillary leakage. Moreover, post-surgical drains or decreased protein binding can markedly influence the volume of distribution (V_d). On the other hand, hypoalbuminemia associated with systemic inflammatory response syndrome, increased renal perfusion, or augmented renal clearance (ARC) (creatinine clearance >130 mL/min) secondary to increased cardiac output may alter the drug excretion [9]. Because of these changes, acute and critical patients exhibit a vast and unpredictable variability in antibiotics PK, leading to subtherapeutic drug exposure, high rates of clinical failure, or increasing toxicity risk.

A strategy to optimize the piperacillin-tazobactam dose and prevent adverse clinical outcomes is based on the population pharmacokinetic analysis (popPK), which describes the typical PK of the drug, and explains the interindividual variability observed in special populations. In this context, piperacillin-tazobactam PK has been evaluated through diverse popPK conducted in critically ill patients, identifying the main covariates that alter piperacillin-tazobactam disposition and excretion [10]. The clearance (CL) of piperacillin and tazobactam has been related to creatinine clearance (CL_{CR}); meanwhile the total body

weight has influenced drug disposition. Other covariates significantly impacting piperacillin-tazobactam PK are mean arterial pressure, unbound fraction, effluent rate, type of patient, and sieving coefficient [10].

Using the popPK models for piperacillin-tazobactam, it has been possible to optimize dosing regimens through individualized therapeutic approaches; however, considering that most studies have been conducted in Europe, Asia, or Australia [10], there could be considerable differences in precision and accuracy between popPK models when predicting drug concentrations outside the original population used for model development[11].

Therefore, the aims of this study were to characterize the popPK parameters of piperacillin-tazobactam in Mexican patients with severe infections and describe the covariates with significant influence on drug disposition and excretion.

2. Methods.

2.1 Study design and Population.

The study was approved by the Research and Ethics Committee from the Hospital Central "Dr. Ignacio Morones Prieto" from San Luis Potosí, Mexico (Register 05-20). Written consent was obtained from all patients or legally acceptable representatives before enrollment.

A prospective, observational, and analytical study was performed in patients (aged > 18 years) hospitalized and receiving piperacillin-tazobactam treatment for proved or suspected severe infection, between May 2021 and July 2023. The non-inclusion criteria were (i) burn injuries, (ii) pregnancy, (iii) continuous renal replacement therapy, and (iv) known or suspected hypersensitivity to penicillin.

From each patient's medical record, the following clinical and anthropometric data were recorded: sex, age, height, weight, blood cells count, blood urea nitrogen, serum albumin, glucose, electrolytes, creatinine, aminotransferases, and C-reactive protein. Additionally, concomitant therapy (vancomycin, furosemide, corticosteroids, omeprazole, antipsychotics, anticoagulants, and non-steroidal anti-inflammatory drugs (NSAIDs)), as well as co-morbidities were registered.

The CL_{CR} was estimated using the Cockcroft-Gault equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), and the Modification of Diet in Renal Disease (MDRD-4) [12–14]. Furthermore, size descriptors such as body mass index (BMI), lean body weight (LBW), ideal body weight (IBW), and body surface area (BSA) were calculated for each patient [15].

2.2 Treatment and sampling collection.

Piperacillin-tazobactam was administered at the physician's discretion at standard dosage regimens of 4/0.5 g, 3/0.375 g, or 2/0.25 g every 6 or 8 hours by intermittent infusion of 0.5-3 hours.

Blood samples (4 mL) were drawn from an intravenous catheter in the arm opposite the infusion site, at least 24 h after the initial dosing and at the following sparse sampling time points: 0 (prior to the next dose), 1-2, 4-6, 6-10 and 12 h post-infusion. Samples were collected in EDTA tubes, centrifuged at 305 x *g* for 20 min at 4°C, separated, and stored at -80°C until analysis.

2.3 Bioassay Methodology.

Piperacillin and tazobactam plasma concentrations were simultaneously assayed by a validated ultra-high performance liquid chromatography method on an Acquity UPLC H-class system coupled to a tandem triple quadrupole mass spectrometer XEVO TQD with an electrospray ionization (ESI) source (Waters Corp.®, Milford, Massachusetts, USA).

The methodology reported by Cunha et al. [16] was adapted for drugs quantification. Samples, calibration curve standards, and quality control samples (100 µL) were extracted by adding 200 µL of internal standard (IS) working solution (dicloxacillin 10 µg/mL in acetonitrile). After centrifugation at 20 817 x *g* for 20 min at 4°C, the supernatant was centrifugated for 10 min at 20 817 x *g*. A volume of 100 µL of the clear supernatant was transferred to a glass vial and diluted (1:1) with LC-grade water; vials were placed in the autosampler at 10°C.

Chromatographic separation was performed by injection of 2µL of treated sample on a Waters Acquity HSS T3 column (2.1 x 100 mm, 1.8 µm) at 35°C. The mobile phase consisted of 0.1% formic acid in water (A) and acetonitrile (B) at initial flow rate of 0.2 mL/min. Piperacillin and tazobactam were eluted through gradient pump as follows: from 0 to 2 min 28% B followed by a flux increase of 0.25 mL/min from 2 to 3.6 min and a linear gradient to reach 70% B; 3.6 to 4 min held at 70%; from 4 to 4.3 a linear increase to 85%B, 4.3-4.75 min held at 85% B, and 4.75 to 5 min a linear return to initial conditions followed by 1.5 min for column re-equilibration. Mass spectrometry conditions consisted of multiple reaction monitoring (MRM) with a positive ESI mode, using the following optimized settings: capillary voltage, 2.8 kV; desolvation temperature, 300°C; desolvation gas flow, 800 L/h nitrogen. Cone voltage (V) for piperacillin, tazobactam and IS was: 28, 24 and 28,

respectively. The MRM transitions (m/z) for drugs quantification were: piperacillin 518.12>142.99, tazobactam 301.13>168.10, and IS 470.03>159.97 with a collision energy (eV) of 12, 14 and 22, respectively. Data were processed and analyzed by the software MassLynx v4.1.

Bioanalytical method was validated in accordance with the applicable US Food and Drug Administration (FDA) guidance for bioanalysis [17]. The detection limit was 0.15 μg/mL and 0.12 μg/mL for piperacillin and tazobactam, respectively; meanwhile, the limit of quantification was 0.6 μg/mL for both drugs. A linear relationship was obtained between response and drugs concentration (R^2>0.99) in the range 0.6-100 μg/mL for piperacillin and 0.6-72 μg/mL for tazobactam. The recovery for piperacillin ranged from 97% to 104% and for tazobactam from 98% to 101%. The method was accurate with deviation ranges of -6.5 to 6.03% and -4.03 to 4.30%, respectively. For piperacillin and tazobactam the intra- and inter-assay precisions depicted coefficient of variation (%CV) of 2.1 to 10% and 2.91 to 9.26%, and 4.59 to 6.49%, and 3.13 to 5.59%, respectively.

Concentration values outside the linear range of the calibration curve were diluted (1:2) with LC-grade water; meanwhile, concentrations below the limit of quantification were assessed by the M5 Beal Method [18].

2.4 Population Pharmacokinetic Analysis.

Pharmacokinetic analysis of piperacillin-tazobactam was performed through a non-linear mixed-effects modeling approach using NONMEM® software version 7.5.1 (ICON Development Solutions, Dublin, Ireland) in conjunction with Perl-Speaks-NONMEM. Data handling, processing, and graphic visualization were conducted with the Pirana workbench

version 2.9.8. Pharmacokinetic models were built separately for piperacillin and tazobactam. Subroutines ADVAN1 TRANS2 and ADVAN3 TRANS4 were used to evaluate the one- and two-compartment pharmacokinetic open models. Estimations of typical model parameters, interindividual variability (IIV) and residual variability (RV) were calculated using the first-order conditional estimation method with interactions (FOCE-I). Diagnostic scatter plots were used to evaluate the goodness of fit through the model-building procedure. Precision of the parameter estimates was evaluated by the covariance step. The IIV was assessed as exponential, and the RV was evaluated as homoscedastic (additive) and heteroscedastic (combined, proportional) model errors. The structural pharmacokinetic models were selected based on the visual inspection of the piperacillin and tazobactam concentration-time profiles, goodness of fit plots, and the Akaike (AIC) information criteria.

After establishing an adequate structural model, covariates identified as potentially influencing pharmacokinetic parameters based on minimum objective function value (OFV) and with physiological plausibility were evaluated by a stepwise forward inclusion followed by the backward elimination process. A total of 20 covariates were evaluated; continuous covariates (e.g., age, body size descriptors, serum creatinine, serum albumin, and CR_{CL} by Cockcroft-Gault, CKD-EPI, and MDRD-4 equations) were centered at their median values. The influence of each covariate on pharmacokinetic parameters was evaluated using linear, hockey-stick, exponential or power functions and dichotomous or polychotomous for categorical covariates (e.g., diagnosis, mechanical ventilation, edema, and concomitant drugs administration). Covariate selection was guided using likelihood ratio tests at a significance level of $p<0.05$ for forward inclusion (ΔOFV>3.84) and $p<0.01$ for backward exclusion (ΔOFV>6.63).

2.5 Model Validation.

The final population pharmacokinetic models were internally validated by bootstrap analysis based on 1000 resamples from the original database. The final models were considered stable and unbiased if the typical value of each parameter obtained was close to the median and within the non-parametric 95% confidence intervals built with the databases generated by resample technique. A visual predictive check (VPC) was performed by simulating 1000 datasets of the original dataset. The 5^{th}, 50^{th} and 95^{th} percentiles of simulated drug concentrations with 95% confidence intervals were overlapped with the observed concentrations at each time point to evaluate the predictive performance of both models.

In addition, both models were externally validated with another group of patients with similar characteristics to those included in the model development. Additionally, external validation was performed with previous popPK studies of piperacillin-tazobactam in critically ill patients. Model selection was based on patients' characteristics and covariates who had been recorded; exclusion criteria were models developed in patients undergoing continuous renal replacement therapy. *A priori* method was performed to evaluate the predictive performance of the population pharmacokinetic models. To evaluate the predictive performance of the final population models, piperacillin and tazobactam concentrations from the validation group were compared with the predicted values. Accuracy and bias were evaluated through the mean absolute error (MAE), the root mean square error (RMSE), and the mean prediction error (MPE), respectively [11].

3. Results.

3.1 Patients.

Sixty-seven patients with severe infections (45% women) were included in this pharmacokinetic study. Four patients were excluded from the analysis since (i) only one sample could be collected and (ii) were identified as potential outliers and excluded (n=3). Clinical and anthropometric data are summarized in Table 1.

Piperacillin-tazobactam was prescribed to treat complicated skin and soft tissue infections (32%), pneumonia (36%), intra-abdominal infections (25%), and sepsis (7%). Sixty-two percent of the patients were from surgery, 32% from internal medicine, and 6% from the intensive care unit. Only thirty-three percent of patients were undergoing mechanical ventilation; edema formation was present in 25% of patients. Diabetes mellitus was the most frequent concomitant disease (33%), followed by hypertension (19%), cancer (16%), and were positive for human immunodeficiency virus (HIV) (8%). The most common co-medication was acetaminophen, NSAIDs, vancomycin, and corticosteroids in 89%, 59%, 29%, and 22% of patients, respectively.

Concerning piperacillin-tazobactam administration, the standard dose of 4/0.5 g every 6 h was mainly prescribed (90%), followed by 2/0.25 g (8%) and 3/0.75 g every 8-12 h (2%). In infusion rates for piperacillin-tazobactam ranging from 666 mg/h (46%) to 8000 mg/h and 83 mg/h to 1000 mg/h.

3.2 Population pharmacokinetics model and internal validation.

A total of 166 piperacillin-tazobactam plasma concentrations were available for model development, ranging from 0.6 to 261 μg/mL and 0.36 to 21.2 μg/mL, respectively, with 2 up to 4 samples per patient and sampling times from 0.5 to 12 h after the last dose.

Based on the minimum AIC, and the distribution of residuals in diagnostics plots the observed plasma concentration-time profiles of piperacillin and tazobactam were best described by a one-compartment open model with exponential IIV associated to CL and V_d (expressed as coefficient of variation; %CV). A homoscedastic error model was chosen based on individual predicted (IPRED) vs. observed plasma concentration (DV) plots and considering that the final RV was estimated as 17.18% for a mean piperacillin plasma concentration of 44.42 μg/mL, and 18.75% for a mean tazobactam plasma concentration of 4.32 μg/mL [Supplementary Figs. S1-S2]. The typical pharmacokinetic parameters in the structural model for piperacillin were CL_{PIP} of 10.1 L/h and V_{dPIP} of 21.4 L; the IIV were 61.5% and 48.5% for CL and V_{dPIP}, respectively, and a RV of 7.4 μg/mL (OFV = 1113.638). For tazobactam, the initial estimates were CL_{TAZ} of 13.7 L/h (IIV of 63.9%) and V_{dTAZ} of 30.1 L (IIV of 45.5%), and a RV of 0.81 μg/mL (OFV = 356.741).

Continuous covariates that significantly influenced piperacillin-tazobactam PK were CLCR on both drugs with ΔOFV of -30.08 for piperacillin CL and ΔOFV of -23.77 for tazobactam CL. Considering the equations to estimate kidney function usually implemented in clinical practice, the Cockcroft-Gault formula resulted in a higher decrease in the OFV. It explained 17% of the IIV associated with the total CL of piperacillin, and 14% of tazobactam. Even though diverse size descriptors were evaluated, an influence on piperacillin and tazobactam

$V_{d.}$ was not observed. Categorical covariates such as HIV and pneumonia significantly influenced piperacillin CL (ΔOFV of -8.14 and -6.15, respectively). Nonetheless, on the backward elimination step, pneumonia was removed from the final model as significant covariate. For tazobactam, the concomitant medication with corticosteroids provided a significant decrease in the OFV when included on tazobactam V_d (ΔOFV, -7.259); however, despite the distributions obtained from bootstrapping to visualize the real influence of the concomitant medication, this covariate was insufficiently characterized and was excluded from the final model.

Therefore, the final model for piperacillin (OFV, 1075.41) was (Eq. 1):

$$Patient\ without\ HIV: CL(L/h) = 11.1 \times (CLCR/92.45)^{0.589} \quad (1)$$

$$Patient\ with\ HIV: CL(L/h) = 6.17 \times (CLCR/92.45)^{0.589} \quad (2)$$

$$Vd(L) = 21.5$$

The final model for tazobactam (OFV, 331.58) was (Eq. 3):

$$CL(L/h) = 14.2 \times (CLCR/92.45)^{0.572} \quad (3)$$

$$Vd\ (L) = 30.1$$

The population parameter values and IIV estimated by the final models are summarized in Table 2. Additionally, the goodness of fit plots of population predicted (PRED) vs observed (DV) piperacillin and tazobactam plasma concentrations, individual predicted (IPRED) vs DV, conditional weighted residuals (CWRES) vs PRED and CWRES vs time after dose of the final models are displayed in Fig. 1-2.

The internal validation of piperacillin and tazobactam models through bootstrap analysis (n=1000) indicates the stability and accuracy of PK parameters since no difference >5% was observed when compared between the final estimates and the median. Moreover, the median estimates are within non-parametric 95% CI, which reflects stability of the final models (Table 2). In addition, the VPC showed that most of the observed concentrations for piperacillin and tazobactam (>80%) were appropriately overlapped within the 5^{th} and 95^{th} percentile of the predicted data, as displayed in Fig. 3.

3.3 External validation.

External validation of both models was performed with 40 piperacillin and tazobactam plasma concentrations ranging between 2.3 to 108 μg/mL for piperacillin and 0.36 to 30.3 μg/mL for tazobactam from 13 patients with similar characteristics to the population study group (Table 1).

The prediction ability of the final model was compared with the structural models for both drugs and five additional popPK studies depicted in Table 3. The MPE decreased by 5.24 μg/mL from the structural piperacillin model and adequately distributed around zero. Meanwhile, for tazobactam, a lower value from the final model was obtained with the MPE well distributed around zero. The RMSE for both models demonstrated acceptable predictive performance of the final models for piperacillin-tazobactam concentrations in Mexican patients with severe infections compared to the selected models.

4. Discussion.

Previous studies have been focused on optimizing piperacillin-tazobactam treatment in special populations, such as critically ill patients [10]. Some popPK studies in adult patients

are summarized in table 3; however, the Mexican population has not been considered in any of the previous studies.

Asín-Prieto et al. [19], Udy et al. [20], Tamme et al. [21], and Sukarnjanaset et al. [22] have described the PK of piperacillin-tazobactam by two-compartment open models. Nevertheless, with the sparse sampling schedule during the distribution phase, current data was better fitted by a one-compartment open model. On the other hand, most studies have modeled RV as heteroscedastic model error ranging from (%CV) 1% to 44%, and SD from 0.19 μg/mL to 13.3 μg/mL [10]. Asín-Prieto et al. reported an additive approach to describe the RV in critically ill patients undergoing continuous renal replacement therapy [19]. The difference between current findings is remarkable: one of the main discrepancies can be attributed to limited number of samples per patient included and the physiological intra-individual variation [23,24].

The typical CL value of the current study lies within the range previously reported from 2.25 to 17.1 L/h [25,26]. In contrast to previous findings, the tazobactam CL was slightly higher [5,7,27]. As hydrophilic drugs, they are typically excreted unchanged by the kidney. Therefore, fluctuations in renal function may significantly alter their elimination rates. Considering that the most significant proportion of patients in this study was from surgery, one of the most common changes in these types of patients is ARC secondary to systemic inflammation, increased cardiac output or high quantities of intravenous fluids, which increment the renal perfusion and consequently increases the renal clearance leading to subtherapeutic drug exposure [9]. There is a dispute about linear or non-linear PK of piperacillin since it is renally eliminated by a linear process (glomerular filtration) and a saturable process (active tubular secretion) [28], nonetheless, in this study, this could not be

confirmed; considering that non-linear PK would be observed when plasma concentrations exceed the Michaelis-Menten constant (K_m= 245 ± 127.17 μg/mL) [29], only 9% of the piperacillin concentrations in this group of patients were greater than 118 μg/mL.

As anticipated, the CL_{CR}, the most frequent covariate in previous studies[10], significantly influenced piperacillin and tazobactam CL. Diverse equations have been extensively studied and compared in diverse populations for estimating renal function. A controversial aspect regarding using the Cockcroft-Gault equation is assigning patients to higher kidney function categories; subsequently, higher dosage recommendation with this equation would be expected compared with the MDRD-4 and CDK-EPI formulas [30]. Nyman et al. [31] suggest that MDRD-4 and the Cockcroft-Gault equation are highly correlated with measured glomerular filtration, however, MDRD-4 equation overestimates the CL_{CR} in comparison with the Cockcroft-Gault formula. In the present study, the Cockcroft-Gault equation showed better association with piperacillin-tazobactam CL, this finding agrees with the study conducted by Sukarnjanaset et al. [22], who reported that the Cockcroft-Gault equation show a better estimation of CL. On the other hand, an unexpectedly significant covariate was HIV status which remarkably decreased piperacillin CL. HIV infection is a chronic, life-long disease that may affect nephron structures. It has been described as a cytopathic effect of the virus within the renal parenchymal cell, disrupting regular activity [32]. Moreover, other causes of acute kidney injury (AKI) in HIV patients are decreased kidney perfusion and acute tubular necrosis secondary to ischemia and medication exposure [33,34]. Nevertheless, HIV patients from the present study were males with advanced HIV infection and were polymedicated. Hence, this could explain the increased piperacillin concentration in those patients. However, the influence of HIV on piperacillin CL should be taken with caution and

should be furthered investigated. Meanwhile, ventilator-associated pneumonia also showed an influence in reducing the piperacillin CL; nonetheless, it was not found to significantly impact in the final models, mainly due to the limited number of patients included with this condition.

Regarding the V_d, current findings are consistent with other published popPK studies for piperacillin-tazobactam, ranging from 9.61 to 35.8 L [22,26] ,and 17.5 to 51.93 L [19,21], respectively. It is relevant to show that higher V_d has been observed in polytraumatized, obese, or patients with intra-abdominal infections, considering hypoalbuminemia present in current population, augmented extravasation into the interstitial space could arise. Additionally, capillary leak syndrome might be raised when vasoactive and fluid agents are administered causing an increase in the V_d [9]. On the other hand, a greater sensitivity of tazobactam to expand towards the extracellular compartment than piperacillin has been described, which might explain the higher V_d observed [19].

In contrast to other studies, current popPK models were not able to statistically support TBW as a significant covariate on V_d for piperacillin or tazobactam; however, given the narrow range between TBW or any other size descriptors recorded, the likelihood of estimating a size descriptor covariate would be scarce. Meanwhile, concomitant administration of corticosteroids resulted in increased tazobactam V_d, that may be associated to the effect of corticosteroids on kidney receptors leading to water and sodium retention via mineralocorticoid receptors, as consequence contributes to the rise in blood pressure [35], nonetheless this covariate was insufficiently characterized and was excluded from the final model.

The covariate inclusion partially explained the high initial IIV estimated by the structural models. However, high variability remained in the final popPK models. Previous studies had described a final IIV ranging from 14.8% to 57.4% [26,27] and 25.2% to 75% [19,36] for piperacillin CL and V_d, respectively. Meanwhile, for tazobactam, the IIV reported goes from 25% to 43.2% for CL [19,27] and 31.4% to 78.3% for V_d [27,36]. Considering the pathophysiological changes and the heterogeneous characteristics in critically ill patients, a high IIV is expected.

In this matter, a priori model evaluation was performed to assess the predictive performance and applicability to the prediction errors from the final popPK models improved concerning the base models.

Based on current data set, the model by Klastrup et al. [26] showed the lowest difference between the observed and predicted data between the previously published popPK studies; additionally, it was the most precise model. The similarities among current piperacillin final model may explain this. By contrast, the higher bias observed in the study by Chen et al. [5] could be attributed to the differences between populations. The model by Li et al. showed a slight underprediction of piperacillin-tazobactam plasma concentrations; despite this, based on a cut-off value of RMSE<25%, the model may still be appropriated for piperacillin prediction. In general, it was observed a good predictive performance on tazobactam data. However, one unanticipated finding was that the only model developed for tazobactam tended to overpredict the drug concentrations. These discrepancies can be attributed to the fact that differences in populations can lead to changes in pharmacokinetics due to physiological, pathological, or environmental factors [37]. Finally, through the MPE and

RMSE evaluation, it was possible to corroborate the validity of the final models for their application in clinical prediction purposes in Mexican population.

One of the main limitations of the present study was the restricted number of patients included which may impede to identify other covariates to explain some of the remaining variability. Second, as mentioned before, with the sampling schedule, it was difficult to characterize both drugs' distribution phases. Third, the evaluation of the likelihood of target attainment should be evaluated for further application of the model. Most of the studies have focused on piperacillin's antibacterial activity; however, tazobactam evaluation should be considered to provide an adequate strategy to treat infections caused by β-lactamases producing bacteria (ESBL). It thus may maintain piperacillin-tazobactam as a viable non-carbapenem treatment option for treating ESBL infections.

5. Conclusions.

A population pharmacokinetic model of piperacillin-tazobactam has been developed in Mexican patients with severe infections. It has been demonstrated the influence of CL_{CR} and HIV infection on piperacillin CL. Meanwhile, tazobactam PK was significantly associated with CLCR. Considering the wide IIV and the heterogeneity of disease-related variables in patients with severe infections, the applicability of the final models in clinical practice was evaluated by the predictive performance in external validation, suggesting its reliable application for predicting *a priori* piperacillin-tazobactam plasma concentrations in the Mexican population.

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Figure legends.

Figure 1. Goodness-of-fit plots for the final population pharmacokinetic model of piperacillin in patients with severe infections. (A, B) including identity line. Conditional weighed residuals (CWRES) versus population observed concentrations (C) and time after last dose of the final model (D).

Figure 2. Goodness-of-fit plots for the final population pharmacokinetic model of tazobactam in patients with severe infections. (E, F) including identity line. Conditional weighed residuals (CWRES) versus population observed concentrations (G) and time after last dose of the final model (H).

Figure 3. Prediction-corrected visual predictive check for the final piperacillin (A) and tazobactam (B) models. Blue circles, the observed concentrations in the current study; Solid lines represent the median (red) and the 95^{th} and 5^{th} percentiles (blue) of the observations. The shaded area derived from simulations (n=1000) representing the 90% confidence intervals for the median (red area) and the 95^{th} and 5^{th} percentiles (blue areas of the simulated profile.

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Table 1. Demographic and clinical data from patients included in the population and validation data set.

Variable	Population group (n=50)	Validation group (n=13)
Gender (male/female)	**29/21**	**7/6**
Age (years)	45.3 ± 15.8	49.5 ± 18.8
Height (m)	1.66 ± 0.09	1.67 ± 0.06
Total body weight (kg)	68.1 ± 15.5	68.6 ± 10.3
Body mass index (kg/m^2)	24.6 ± 4.7	24.7 ± 3.7
Lean body weight (kg)	48.6 (43.8-57.9)	47 (46.6-59.6)
Body surface area (m^2)	1.70 ± 0.22	1.77 ± 0.14
Ideal body weight (kg)	59.8 ± 10.4	60.8 ± 7.6
Serum albumin (g/dL)	3.5 (3.1-3.8)	2.7 (2.5-3.5)
Blood urea nitrogen (mg/dL)	21.4 (14.4-38.2)	21 (18.3-23.8)
White blood cells (K/uL)	14.8 (43.8-57.9)	11 (9.1-15.4)
Glucose (mg/dL)	125 (106.7-155.3)	105.2 (93.5-159.5)
Serum creatinine (mg/dL)	0.785 (0.62-1.4)	0.8 (0.61-0.8)
Creatinine clearance (mL/min/1.73 m^2)	92.5 (63.3-147.65)	109.54 (79-149)
C-reactive protein (mg/dL)	14.8 (5.92-27.7)	8.2 (6.6-8.6)
Glasgow score	15 (9-15)	15 (8-15)

[a]Data are expressed as mean ± standard deviation or median (interquartile range)
[b]Creatinine clearance calculated with Cockroft-Gault formula.

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Table 2. Final population pharmacokinetic models and internal validation for Piperacillin and Tazobactam.

Model	Population PK model (n=50)				Bootstrap (n=1000)			
	Parameter	Mean	RSE (%)	Shrinkage (%)	Median	95% CI		Bias[a](%)
						2.5th	97.5th	
Piperacillin								
CL (L/h)	θ_1	11.1	6	----	11.03	9.64	12.46	0.61
V_d (L)	θ_2	21.5	10	----	21.35	17.68	25.89	0.70
Influence of CL_{CR} on CL	θ_3	0.589	14	----	0.59	0.42	0.78	-0.54
Influence of HIV on CL	θ_4	6.17	12	----	6.15	4.41	8.13	0.38
IIV CL (%)	ω^2_{CL}	40.9	14	7	40	26.45	50.99	3.45
IIV V_d (%)	ω^2_{Vd}	48	16	20	47	31.62	61.64	3.96
RV (µg/mL)	σ	7.46	39	25	7.29	4.64	10.18	3.79
Tazobactam								
CL (L/h)	θ_1	14.2	8	----	14.17	12.07	17	0.20
V_d (L)	θ_2	30.1	12	----	30.2	23.85	39.36	0.99
Influence of CL_{CR} on CL	θ_3	0.572	21	----	0.572	0.29	0.78	1.64
IIV CL (%)	ω^2_{CL}	49.8	9	6	48.69	38.72	56.56	3.99
IIV V (%)	ω^2_{Vd}	45.5	22	26	43.8	24.49	62.44	4.56
RV (µg/mL)	σ	0.81	39	24	0.81	0.55	1.14	4.01

CL: Clearance; CI: Confidence interval; CL_{CR}: Creatinine clearance; HIV: Human immunodeficiency virus; IIV: Interindividual variability; PK: Pharmacokinetic; RSE: Relative standard error; RV: Residual variability; V_d: Distribution volume.
[a]Bias calculated with percentage error equation.

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Table 3. External evaluation of Piperacillin and Tazobactam models with validation group and five other published population pharmacokinetic models in adults.

Reference	Population	Pharmacokinetic model and parameter estimate	IIV (%CV)	Residual variability	MPE (CI 95%) (µg/mL)	MAPE (CI 95%) (µg/mL)	RMSE (µg/mL)
Current study (Base model)	Mexican adult patients with severe infections	***Piperacillin*** $CL(L/h) = 10.1$ $Vd(L) = 21.4$	IIV_CL=61.5 IIV_V_d=48.5	SD=7.47 µg/mL	7.60 (0.59,14.61)	18.82 (14.68-22.96)	22.65
		Tazobactam $CL(L/h) = 13.7$ $Vd(L) = 30.1$	IIV_CL=63.9 IIV_V_d=46	SD=0.81 µg/mL	-1.35 (-4,1.29)	4.56 (2.32,6.80)	8.27
Current study (Final model)		***Piperacillin*** $Patient\ without\ HIV: CL(L/h) = 11.1 \times (CLCR/92.45)^{0.589}$ $Patient\ with\ HIV: CL(L/h) = 6.17 \times (CLCR/92.45)^{0.589}$ $Vd(L) = 21.5$	IIV_CL=40.9 IIV_V_d=48	SD=7.46 µg/mL	2.35 (-0.37,5.08)	6.99 (5.34,8.65)	8.63
		Tazobactam $CL(L/h) = 14.2 \times (CLCR/92.45)^{0.572}$ $Vd(L) = 30.1$	IIV_CL=45.6 IIV_V_d=40	SD=0.81 µg/mL	-1.92 (-4.20,0.36)	3.15 (1.01,5.28)	7.30

Chen et al.[5] 2016	Patients with Nosocomial Infections	***Piperacillin*** $CL(L/h) = 9.14 + 4.6^{(CLCR/68.7)}$ $Vd(L) = 12.2 + 9.49^{(TBW/61.1)}$	IIV_CL=31.1 IIV_V_d=38	CV=9.33%	-30.21 (-39.38, -21.04)	30.21 (21.04,39.38)	41.13
Chung et al.[27] 2015	Obese and non-obese patients with complicated intra-abdominal infections	***Piperacillin*** $CL(L/h) = 11.3 + [0.0646 \times (CLCR - 105)] + [0.0579 \times (BMI - 35)]$ $Vd(L) = 31.3 + [0.132 \times (TBW - 120)]$	IIV_CL=14.8 IIV_V_d=31.4	CV=15.5% SD=5.27 µg/mL	4.74 (-4.73,14.21)	23.18 (17.33,29.02)	29.22
		Tazobactam $CL(L/h) = 10.1 + [0.0272 \times (CLCR - 105)]$ $Vd(L) = 34.3$	IIV_CL=43.2 IIV_V_d=78.3	CV=27.3%	0.40 (-2.21,3.0)	5.46 (3.55,7.37)	8.05
Li et al. [35] 2005	Patients with complicated intra-abdominal infection	***Piperacillin*** $CL(L/h) = 5.05 + 9.6 \times CLCR/89$ $Vd(L) = 22.3 \times TBW/81.8$	IIV_CL=27.7 IIV_V_d=25.2	CV=18.5% SD=1.77 µg/ mL	-15.03 (-18.95, -11.12)	15.03 (11.12,18.95)	19.19
		Tazobactam $CL(L/h) = 4.92 + 5.44 \times CLCR/89$ $Vd(L) = 23 \times TBW/81.8$	IIV_CL=40.2 IIV_V_d=32.1	CV=13.5% SD=0.40 µg/ mL	-1.39 (-3.77,0.99)	3.81 (1.72,5.89)	7.49
Klastrup et al. [26] 2020	Critically ill patients	***Piperacillin*** $CL(L/h) = 2.25 + 0.119 \times CLCR$ $Vd(L) = 35.8$	IIV_CL=57.4 IIV_V_d=-NA	CV=22.6%	0.96 (-2.60,4.51)	8.45 (6.20,10.69)	10.87

Kalaria et al. [7] 2020	Critically ill patients	***Tazobactam*** $CL(L/h) = 5.27 \times (CLCR/120)^{0.33}$ $Vd(L) = 20$	IIV_CL=68 IIV_V_d=----	CV=44.1%	19.87 (11.44,28.31)	21.16 (13.06,29.26)	32.76
CL: Clearance; CLCR: Creatinine clearance; CV: Coefficient of variation; *CI: Confidence interval; V_d: Distribution volume; IIV: Interindividual variability; PK: Pharmacokinetic; RSE: Relative standard error.*							

Fig. 1

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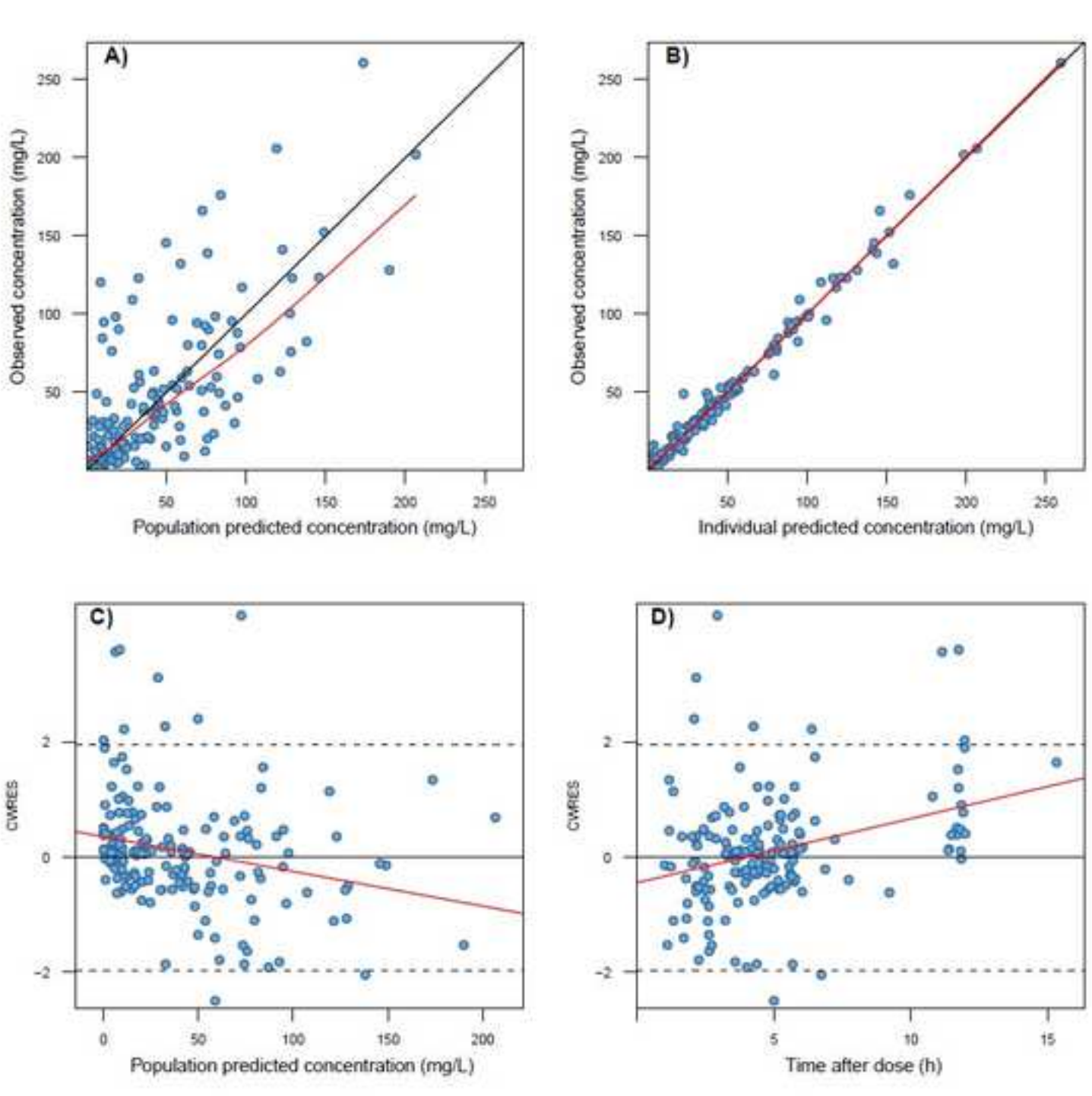

Fig. 2

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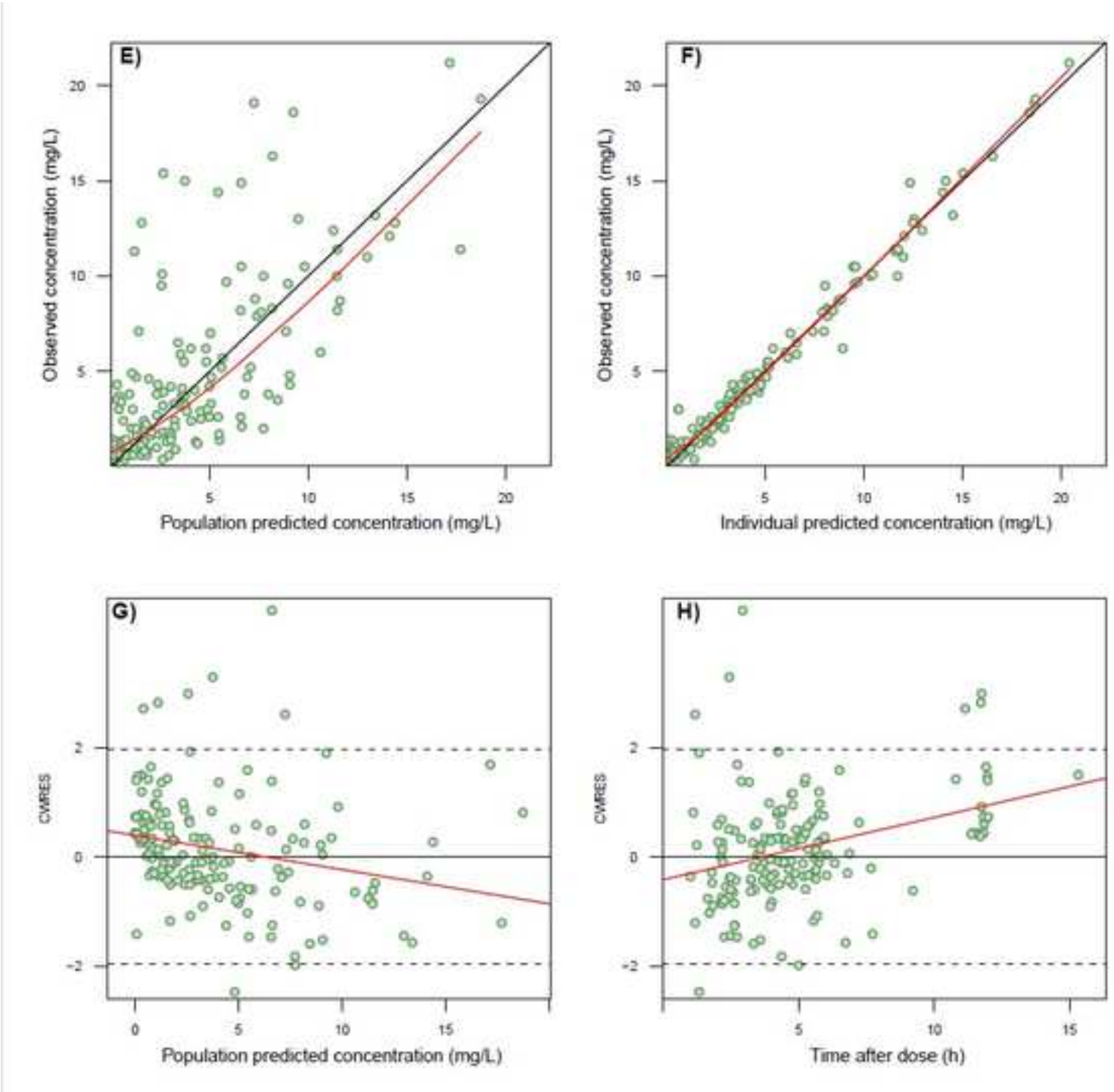

Fig.3

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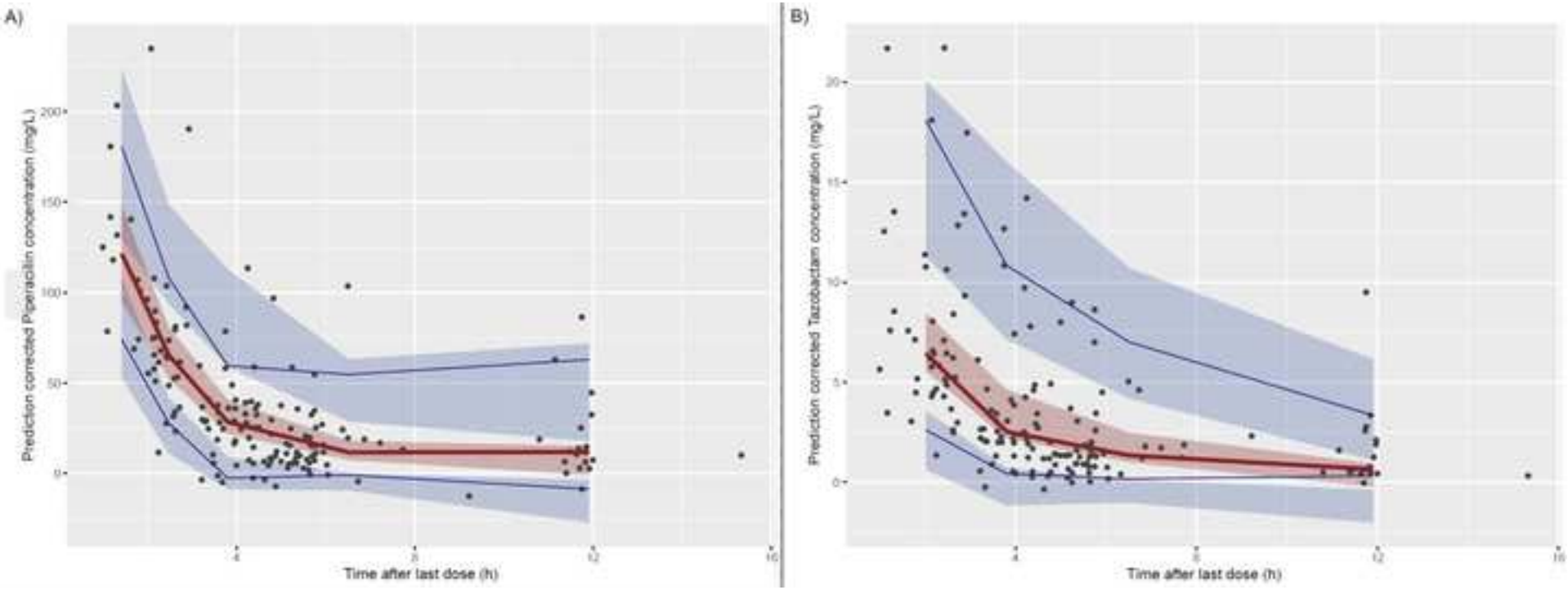

Supplementary Fig.1

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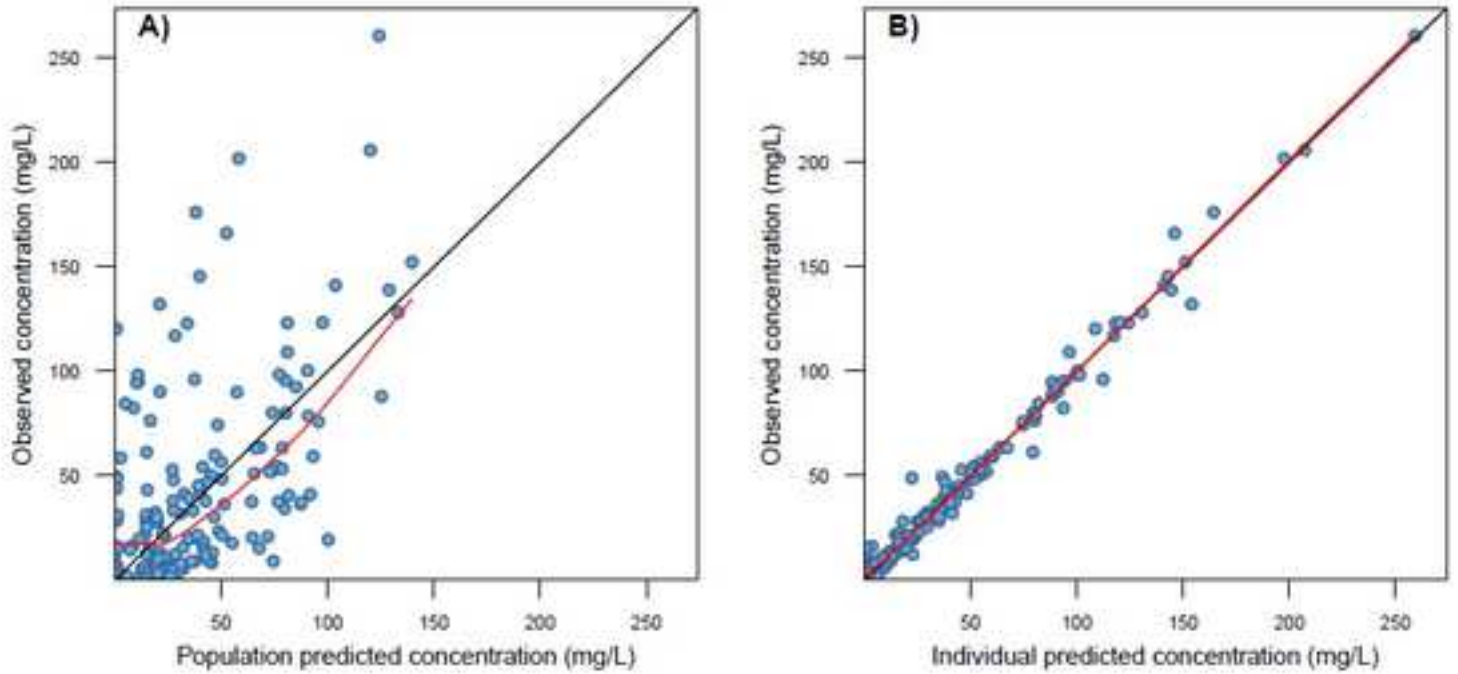

Supplementary Fig.2

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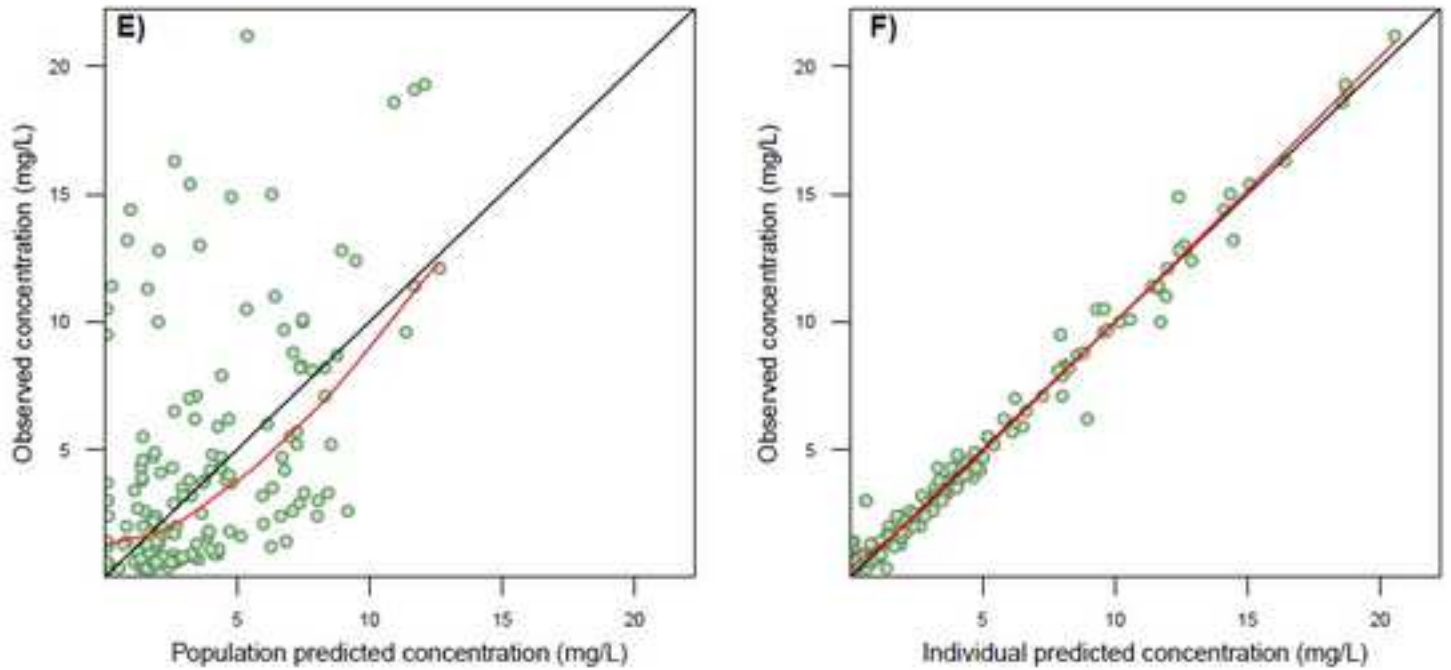

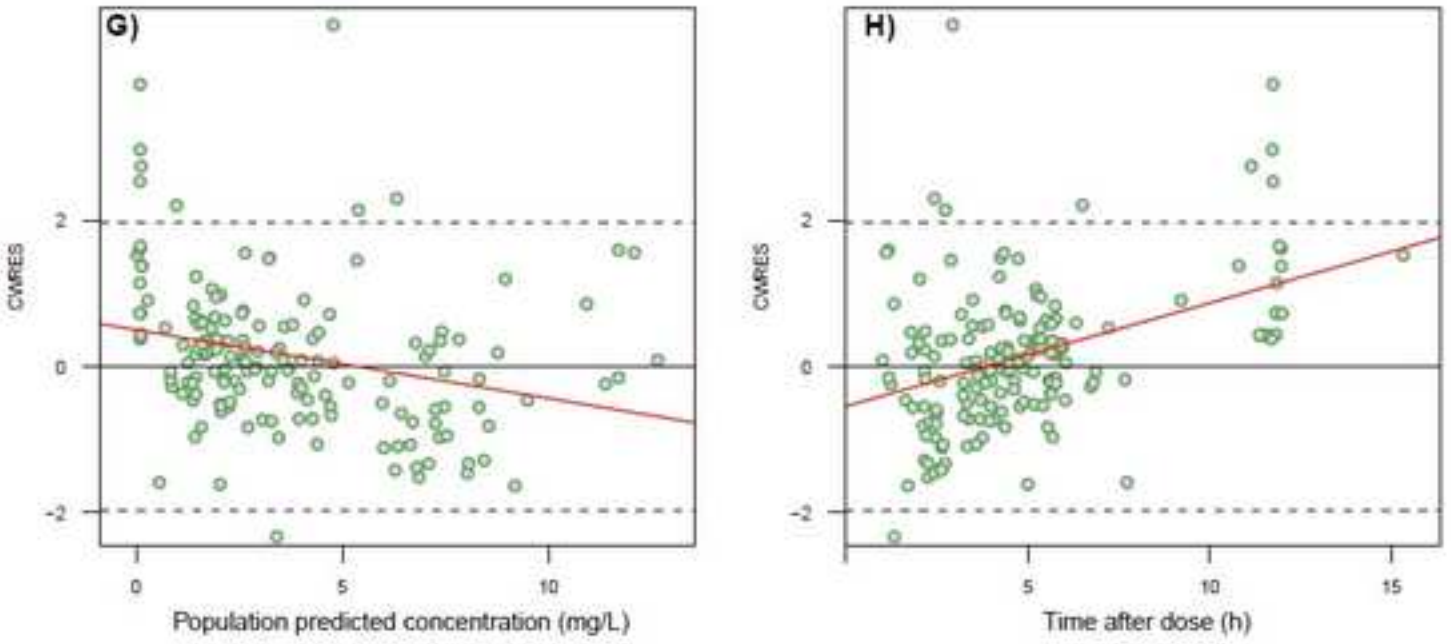

1. Clinical Pharmacokinetic Study Checklist
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Checklist of Information to be Included When Reporting a Clinical Pharmacokinetic Study[a]

	Checklist Item	
	Title/Abstract	**Reported on Page Number**
1	The title identifies the drug(s) and patient population(s) studied.	1
2	The abstract includes the name of the drug(s) studied, the route of administration, the population in whom it was studied, and the results of the primary objective and major clinical pharmacokinetic findings.	2-3
	Background	
3	Pharmacokinetic data (i.e., absorption, distribution, metabolism, excretion) that is known and relevant to the drugs being studied is described	7
4	An explanation of the study rationale is provided	6-8
5	Specific objectives or hypotheses is provided	8
	Methods	
6	Eligibility criteria of study participants is described	8
7	Information about ethical approval of the study and subjects' consent is provided.	8
8	Co-administration (or lack thereof) of study drug(s) with other potentially interacting drugs or food within this study is described.	N/A
9	Drug preparation and administration characteristics including dose, route, formulation, infusion duration (if applicable) and frequency are described.	9
10	Body fluid or tissue sampling (timing, frequency and storage) for quantitative drug measurement is described.	9
11	Validation of quantitative bioanalytical methods used in the study is described in detail or described briefly and referenced.	10-11
12	Pharmacokinetic modeling methods, observed and derived parameters along with the formulas, and software used are described.	11-12
13	Formulas for calculated variables (such as creatinine clearance, body surface area, AUC, and adjusted body weight) are provided or referenced.	9
14	The specific body weight used in drug dosing and pharmacokinetic calculations are reported (i.e., ideal body weight vs. actual body weight vs. adjusted body weight)	9
15	Statistical methods including software used are described	11
	Results	
16	Study withdrawals or subjects lost-to-follow up (or lack thereof) are reported.	14
17	Quantification of missing or excluded data is provided if applicable.	N/A
18	All relevant variables that may explain inter- and intra-patient pharmacokinetic variability (including: age, sex, end-organ function, ethnicity, weight or BMI, health status or severity of illness, and pertinent co-morbidities) are provided with appropriate measures of variability.	15

19	Results of pharmacokinetic analyses are reported with appropriate measures of variability and precision (such as range, standard deviation, 95% confidence interval, etc.)	14-17
20	Studies in patients receiving extracorporeal drug removal (i.e., dialysis) should report the mode of drug removal, type of filters used, duration of therapy and relevant flow rates.	N/A
21	In studies of drug bioavailability comparing two formulations of the same drug, F (bioavailability), AUC, C_{max} (maximum concentration) and t_{max} (time to maximum concentration) should be reported.	N/A
	Discussion/Conclusion	
22	Study limitations describing potential sources of bias and imprecision where relevant should be described	22
23	The relevance of study findings (applicability, external validity) is described	17-22
	Other Information	
24	Funding sources and conflicts of interest for the authors are disclosed.	4

[a] Adapted from: Kanji S, Hayes M, Ling A, et al. Reporting Guidelines for Clinical Pharmacokinetic Studies: The ClinPK Statement. Clin Pharmacokinet. 2015. DOI 10.1007/s40262-015-0236-8.

Supplementary Information
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Clinical Pharmacokinetics

Supplementary information File of:

Evaluation of standard dosing regimens for Piperacillin-Tazobactam in Mexican patients with severe infections using a population pharmacokinetic approach

1. Ana S. Rodríguez-Báez [1], Silvia Romano-Moreno [1], Arturo Ortiz-Álvarez [2], Fidel Martínez-Gutiérrez [1], Rosa C. Milán-Segovia [1], Susanna E. Medellín-Garibay [1].
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Supplementary information file, Figure S1. Goodness-of-fit plots for the structural population pharmacokinetic model of piperacillin in patients with severe infections. (A, B) including identity line. Conditional weighed residuals (CWRES) versus population observed concentrations (C) and time after last dose of the structural model (D).

Supplementary information file, Figure S2. Goodness-of-fit plots for the structural population pharmacokinetic model of tazobactam in patients with severe infections. (E, F) including identity line. Conditional weighed residuals (CWRES) versus population observed concentrations (G) and time after last dose of the structural model (H).

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Evaluation of standard dosing regimens for Piperacillin-Tazobactam in Mexican patients with severe infections using a population pharmacokinetic approach

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Abstract

Piperacillin-tazobactam a combination of a β-lactam antibiotic with a β-lactamase inhibitor frequently used in critically ill patients to treat moderate to severe infections due to its broad-spectrum antibacterial activity. This population develop pathophysiological changes that increased the variability in treatment response, leading to a 30% of probability of target attainment. Therefore, the aim of this study was to characterize the pharmacokinetics parameters of piperacillin-tazobactam in Mexican patients with severe infections and describe the covariates with significant influence on drug disposition and excretion to propose individualized dosing regimens achieving therapeutic targets. An observational analytical study was performed on 67 patients (aged>18 years) with known or suspected severe infection receiving piperacillin-tazobactam treatment at Hospital Central "Dr. Ignacio Morones Prieto." Sample were collected at the steady state, and plasma concentrations were quantified through Liquid Chromatography coupled to Mass Spectrometry. Population pharmacokinetic analysis was performed by nonlinear mixed-effects modeling. Internal validation was performed by bootstrap and visual predictive check (n=1000); moreover, external validation was carried out to evaluate the predictive capacity of final models by an *a priori* approach using a different group of patients. A total of 166 and 40 plasma concentrations were available for model development and external validation, respectively. Piperacillin-tazobactam pharmacokinetics was best described by a one-compartment open model with exponential interindividual variability associated with clearance and distribution volume; a homoscedastic model error was chosen. Creatinine clearance demonstrated a significant influence on piperacillin-tazobactam clearance. Additionally, piperacillin clearance decreased by 56% in patients with human immunodeficiency virus. Internal

validation indicates the stability and accuracy of the final models, moreover the external validation showed a mean prediction error 2.35 μg/mL of (95% confidence interval,-0.37,5.08) for piperacillin and -1.92 μg/mL (95% confidence interval, -4.20,0.36) for tazobactam, respectively. In conclusion, population pharmacokinetic models have been developed and validated for piperacillin and tazobactam. The dosing recommendations in patients with severe infections should consider the renal function of the patient, and close monitoring is needed in patients with human immunodeficiency virus to avoid the risk of toxicity.

Manuscript word count: 4209 words

Keywords: Pharmacometrics, Piperacillin-tazobactam, Population pharmacokinetics, Severe infections. Special populations.

Key points

- A population pharmacokinetic analysis was conducted to evaluate clinical and anthropometric covariates that may explain the variability observed in Piperacillin-Tazobactam pharmacokinetics of Mexican patients.
- Creatinine clearance and HIV infection should be considered to improve Piperacillin-tazobactam treatment and thus propose dosage regimens based on this population.
- Model-informed precision dosing approach for dose optimization and maximizing Piperacillin-tazobactam PK/PD target attainment could be applied to Mexican patients.

Declarations

Competing Interests

The authors declare no conflicts of interest.

Funding

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Ethics approval

All procedures performed in studies involving human participants were by the ethical standards of the Hospital Research and Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Research and Ethics Committee of the Hospital Central "Dr. Ignacio Morones Prieto," San Luis Potosí, Mexico (Registration number 05-20).

Consent

Written informed consent was obtained from all the patients or legally authorized representatives.

Availability of the data, code, and material

The dataset generated during the current study are available from the corresponding author on a reasonable request.

CRediT authorship contribution

Ana S. Rodríguez-Báez: Data curation, Formal Analysis, Investigation, Methodology, Software, Validation, Visualization, Writing-original draft, Writing-review & editing. **Rosa C. Milán-Segovia:** Investigation, Supervision, Visualization, Writing-review & editing. **Silvia Romano-Moreno:** Formal Analysis, Investigation, Software, Supervision, Writing-review & editing. **Emilia Barcia: Investigation,** Writing-review & editing. **Arturo Ortiz-Álvarez:** Investigation, Methodology, Supervision. **Fidel Martínez-Gutiérrez:** Investigation, Writing-review & editing. **Susanna E. Medellín-Garibay:** Conceptualization, Data curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing-original draft, Writing-review & editing.