Abstracts of the V Ibero-American Pharmacometrics Network (RedIF) Congress, Bogotá D.C., Colombia, April 24th - 26th, 2024

Organized by:

Universidad Nacional de Colombia and the Ibero-American Pharmacometrics Network (RedIF)

Scientific Committee

Dr. Bibiana Verlindo, Professor, Universidade Federal do Rio Grande do Sul (Brasil)

Dr. Darlene Santiago, Professor, Puerto Rico University (Puerto Rico)

Dr. Gonzalo Suárez, Professor, Universidad de la República (Uruguay)

Dr. Manuel Ibarra, Professor, Universidad de la República (Uruguay)

Dr. Marcela Aragón, Professor, Universidad Nacional de Colombia (Colombia)

Dr. Mauricio García, Professor, Pontificia Universidad Católica de Chile (Chile)

Dr. Teresa Dalla Costa, Professor, Universidade Federal do Rio Grande do Sul (Brasil)

Dr. Victor Mangas, Professor, Universidad de Valencia (España)

Organizing Committee

Dr. Marcela Aragón, Professor, Universidad Nacional de Colombia (Colombia)

Dr. Bibiana Verlindo, Professor, Universidade Federal do Rio Grande do Sul (Brasil)

Dr. Maritza Rojas, Professor, Universidad Nacional de Colombia (Colombia)

Dr. Izabel Almeida Alves, Professor, Universidade Federal de Bahia (Brasil)

Dr. Paola Cárdenas, Independed consultant

Dr. Gina Domínguez, Professor, Universidad del Atlántico (Colombia)

Dr Andrés Zuluaga, Professor, Universidad de Antioquia (Colombia)

Dr. Diana Sinuco, Professor, Universidad Nacional de Colombia (Colombia)

Dr. Constain H. Salamanca, Professor, Universidad Nacional de Colombia (Colombia)

MSc. Sandra Echeverry, PhD. Student, Universidad Nacional de Colombia (Colombia)

Miss. Karen Lancheros, Pharmacist

Oral presentations

Piperacillin/tazobactam target attainment in neonatal intensive care unit patients

Frida Sofía Boer Pérez[1]*, Silvia Romano Moreno[1], Ma. Victoria Lima Rogel[2], Susanna Edith Medellín Garibay[1], Ana Ruth Mejía Elizondo[2], Paula Schaiquevich[3], Ana Socorro Rodríguez Baez[1], Cristian Jazmín Rodríguez Pinal[1], Rosa del Carmen Milán Segovia[1]

[1] Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México

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

[3] Hospital Pediátrico Dr. Juan P. Garrahan, Buenos Aires, Argentina

*E-mail: A239034@alumnos.uaslp.mx.com

Summary

Piperacillin/tazobactam has been used extensively for late-onset neonatal sepsis treatment, although safety and pharmacokinetic (PK) data in this population are limited [1]. The present work aims to evaluate the pharmacokinetic/pharmacodynamic (PK/PD) target attainment of piperacillin/tazobactam in preterm and term Mexican neonates with severe infections. A total of 65 piperacillin concentrations from 25 neonatal intensive care unit (NICU) patients were determined by liquid chromatography/tandem mass spectrometry (LC/MS/MS). The overall median value (range) postnatal age, gestational age, and body weight were 14 (8-28) days, 34.2 (28-41.1) weeks, and 1760 (995-3430) grams, respectively. The attainment of the PK/PD target (70% fT>MIC, free drug concentration above minimum inhibitory concentration during 70% of the dosing interval) was evaluated for different MICs using the individual Bayesian estimates method in NONMEM VII. A significant difference was found in piperacillin concentrations observed at 70% of the dosing interval between the very preterm (49.8 mg/L) and term neonates (23.7 mg/L) (p=0.041). 72% and 88% of preterm and term neonates achieved the PK/PD target for a MIC of 16 mg/L, however, of each category, respectively, 56% and 12% attained the PK/PD target for a MIC of 32 mg/L. Potential toxicity piperacillin concentration >150 mg/L was observed in 44% of our population [2]. In neonates with life-threatening infections, the rapid pathophysiological fluctuations and organic immaturity can difficult to achieve the PK/PD target. The importance

of this study lies in the necessity to monitor the piperacillin plasma concentrations in NICU patients to optimize antibiotic therapy and minimize the risk of toxicity.

Ethical approval

The present study was approved by the Comité en Ética e Investigación del Hospital Central "Dr. Ignacio Morones Prieto" with the registration code: CONBIOETICA-24- CEI-001-20160227.

Financial support and acknowledgements

This project is supported by Mexico's Consejo Nacional de Ciencia y Tecnología through the student grant number: 745752.

References

1. C.I.B. Barker, K. Kipper, D.O. Lonsdale, K. Wright, G. Thompson, M. Kim, M.A. Turner, A. Johnston, M. Sharland, J.F. Standing, The neonatal and paediatric pharmacokinetics of antimicrobials study (NAPPA): Investigating amoxicillin, benzylpenicillin, flucloxacillin and piperacillin pharmacokinetics from birth to adolescence, *J. Antimicrob. Chemother.*, **78**, 2148-2161 (2023). Doi: https://doi.org/10.1093/jac/dkad196

2. M.C. Quinton, S. Bodeau, L. Kontar, Y. Zerbib, J. Maizel, M. Slama, K. Masmoudi, A.S. Lemaire-Hurtel, Y. Bennis, Neurotoxic concentration of piperacillin during continuous infusion in critically ill patients, *Antimicrob. Agents Chemother.*, **61**, 614 (2017). Doi: https://doi.org/10.1128/aac.00654-17

Guiding methotrexate rescue therapy through a population pharmacokinetic model in brazilian pediatric patients with osteosarcoma

Laura Ben Olivo[1]*, Pricilla de Oliveira Henz[1], Sophia Wermann[1], Bruna Bernar Dias[1], Gabriel Osorio Porto[1], Amanda Valle Pinhatti[2,3], Lauro José Gregianin[3], Teresa Dalla Costa[1], Bibiana Verlindo de Araújo[1,2]

[1] Pharmacokinetics and PK/PD Modeling Laboratory, Pharmaceutical Sciences Graduate Program, Federal University of Rio Grande do Sul, 2752 Ipiranga Ave., Santana, RS 90610-000 Porto Alegre, Brazil

[2] Medical Sciences Graduate Program, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

[3] Pediatric Oncology Service, Hospital de Clínicas de Porto Alegre, Department of Pediatrics, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

*E-mail: lauraolivo96@gmail.com

Summary

Methotrexate (MTX) is part of the Brazilian Osteosarcoma Treatment Group protocol. Itpresents high interindividual variability and is subject to therapeutic drug monitoring (TDM) [1, 2]. The administration of MTX is associated with several cases of toxicity which have been diminished due to the concomitant administration with leucovorin rescue therapy [3]. This work aimed to develop a population pharmacokinetic model (POPPK) of MTX in Brazilian children with osteosarcoma (OS) to support the prevention of several adverse effects. Pediatric patients with OS who received MTX as part of cancer treatment were included in the study. The model was developed using retrospective data from TDM, NONMEM 7.4 (Icon®), ADVAN3 TRANS4 and FOCE-I. Interindividual (IIV) and interoccasion (IOV) variabilities were analyzed between subjects. Several demographic and biochemical covariates were tested to explain variabilities. Data fitted in a two-compartment model, using 216 MTX cycles from 32 patients (5-18 y.o) with OS. Serum creatinine was added in clearance to explain the variabilities associated with this parameter. Body surface area was added in peripheral volume as a covariate. Clearance estimate was 15.6 L/h and intercompartmental clearance was 0.208 L/h. The volume of the central compartment was 87.1 L and for the peripheral volume was 5.89 L.

The model adequately describes MTX exposure in Brazilian children with OS. The model was used to predict MTX plasma concentrations, guide rescue therapy, and prevent toxicity exposure.

Ethical approval

The study was approved by the Ethics Committee in Human Research of Hospital de Clínicas de Porto Alegre (4.260.110 in 10/21/2021).

Financial support and acknowledgements

This work was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES, Finance Code 001) and by the PPSUS/FAPERGS, Rio Grande do Sul, Brazil (#21/2551–0000065-1). Acknowledgments to Coordination for the Improvement of Higher Education Personnel (CAPES) and Hospital de Clínicas de Porto Alegre (HCPA).

References

1. A.S. Petrilli, B. de Camargo, V.O. Filho, P. Bruniera, A.L. Brunetto, R. Jesus-Garcia, O.P. Camargo, W. Pena, P. Péricles, A. Davi, J.D. Prospero, M.T.S. Alves, C.R. Oliveira, C.R.D. Macedo, W.L. Mendes, M.Teresa A. Almeida, M.L. Borsato, T.M. dos Santos, J. Ortega, E. Consentino, Results of the Brazilian osteosarcoma treatment group studies III and IV: prognostic factors and impact on survival, *J. Clin. Oncol.*, **24**, 1161-1168 (2006). Doi: https://doi.org/10.1200/JCO.2005.03.5352

2. A.A. Senerchia, C.R. Macedo, S. Ferman, M. Scopinaro, W. Cacciavillano, E. Boldrini, V.L. Lins de Moraes, G. Rey, C.T. de Oliveira, L. Castillo, M.T. Almeida, M.L. Borsato, E. Lima, D. Lustos, J.H. Barreto, T. El-Jaick, S. Aguiar, A. Brunetto, L. Greggiani, H. Cogo-Moreira, A. Atallah, A.S. Petrilli, Results of a randomized, prospective clinical trial evaluating metronomic chemotherapy in nonmetastatic patients with high-grade, operable osteosarcomas of the extremities: A report from the Latin American Group of Osteosarcoma Treatment, *Cancer*, **123**, 1003-1010 (2017). Doi: https://doi.org/10.1002/cncr.30411

1. K.R. Crews, T. Liu, C. Rodriguez-Galindo, M. Tan, W.H. Meyer, J.C. Panetta, M.P. Link, N.C. Daw, High-dose methotrexate pharmacokinetics and outcome of children and young adults with osteosarcoma, *Cancer*, **100**, 1724-1733 (2004). Doi: https://doi.org/10.1002/cncr.20152

Population pharmacokinetics of meropenem in critically ill children and young adults

Ronaldo Morales Junior[1*], Tomoyuki Mizuno[1,2], Kelli Paice[1,3], Kathryn Pavia[1,3], Peter Tang[2], Rhonda Jones[3], Abigayle Gibson[3], Erin Stoneman[3], Calise Curry[4], Jennifer Kaplan[2,3], Sonya Tang Girdwood[1,2,4]

[1] Division of Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[2] Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

[3] Division of Critical Care Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

[4] Division of Hospital Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

*E-mail: ronaldo.moralesjunior@cchmc.org

Summary

Meropenem, a β-lactam antibiotic widely prescribed for severe infections, poses dosing challenges in critically ill patients due to highly variable pharmacokinetics. We aim to develop a population pharmacokinetic model of meropenem for critically ill pediatric and young adult patients. Pediatric intensive care unit patients receiving meropenem 20-40 mg/kg Q8h as a 30-minute infusion were prospectively followed for clinical data collection and scavenged opportunistic plasma sampling [1]. Meropenem concentrations were measured using high-performance liquid chromatography. Nonlinear mixed effects modeling was conducted using Monolix®. Allometric body weight scaling was included with fixed exponents to account for body size differences. Data from 48 patients, aged 1 month to 30 years, with 296 samples, were described using a two-compartment model with first-order elimination. Inter-individual variabilities were estimated for clearance (CL) and central volume of distribution (V1), but could not be estimated for intercompartmental clearance (Q) or peripheral volume (V2). Creatinine clearance and percentage of fluid overload were identified as covariates on CL and V1, respectively. The maturation function for glomerular filtration rate [2] was incorporated to accommodate

developmental changes in renal clearance. The final parameters were estimated with good precision: CL 13.22 L/h/70 kg$^{0.75}$, Q 1.78 L/h/70 kg$^{0.75}$, V1 16.45 L/70 kg, and V2 7.66 L/70 kg. The goodness-of-fit plots showed no model misspecification. Bootstrap results confirmed the final model's stability. In conclusion, a meropenem PK model for critically ill pediatric patients was successfully developed accounting for patients' renal function, fluid status, body size- and age-related development. It will be applied for optimal dosing simulations and model-informed precision dosing.

Ethical approval

The study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board, which granted a waiver of consent (Protocol 2018-3245).

Financial support and acknowledgements

This work was supported by the National Institute of General Medical Sciences of the National Institute of Health under award number R35GM146701-01.

References

1. S.C. Tang Girdwood, P.H. Tang, M.E. Murphy, A.R. Chamberlain, L.A. Benken, R.L. Jones, E.M. Stoneman, J.M. Kaplan, A.A. Vinks, Demonstrating feasibility of an opportunistic sampling approach for pharmacokinetic studies of β-lactam antibiotics in critically ill children, *J. Clin. Pharmacol.*, **61**, 565-573 (2020). Doi: https://doi.org/10.1002/jcph.1773

2. M.M. Rhodin, B.J. Anderson, A.M. Peters, M.G. Coulthard, B. Wilkins, M. Cole, E. Chatelut, A. Grubb, G.J. Veal, M.J. Keir, N.H.G. Holford, Human renal function maturation: a quantitative description using weight and postmenstrual age, *Pediatr. Nephrol.*, **24**, 67-76 (2009). Doi: https://doi.org/10.1007/s00467-008-0997-5

Model-informed development of gastroretentive furosemide formulations with physiologically based biopharmaceutics modeling

María Luisa Rodríguez[1]*, Santiago Palma[2], Pietro Fagiolino[1], Manuel Ibarra[1]

[1] Pharmaceutical Sciences Department, Faculty of Chemistry, Universidad de la República, Uruguay

[2] Pharmaceutical Sciences Department, Faculty of Chemical Sciences, Universidad Nacional de Córdoba, Argentina

*E-mail: mluisar@fq.edu.uy

Summary

Furosemide is a potent diuretic widely used in clinical practice; however, it has a narrow absorption window restricted to the upper part of the gastrointestinal tract. To improve its oral bioavailability and diuretic effect, controlled-release gastroretentive systems are being developed [1]. In this study, we employed physiologically based biopharmaceutics modeling (PBBM) to predict the *in vivo* behavior of gastroretentive formulations, aiming to aid the development of effective furosemide pharmaceutical dosage forms. This includes integrating formulation parameters estimated from *in vitro* dissolution testing into a PBPK model [2]. A validated PBPK model for furosemide in dogs [3] was adapted to humans in PK-Sim® and MoBi® [4], utilizing literature pharmacokinetic data post intravenous and oral administration [5]. The model was optimized for plasma and urinary excretion profiles based on individual sex. Model predictions were validated with published plasma pharmacokinetic profiles post immediate and modified dosage forms in men and women [6-9]. The PBBM approach described furosemide pharmacokinetics and product performance in both men and women. The model was applied to simulate the performance of multiple-unit floating drug delivery systems developed, System I (SI) and System II (SII), and compare it to the immediate-release reference formulation after a single 40 mg oral dose. The predicted Test/Reference GMR for AUC in men (n=1000) were 1.00 for AUC0-inf (90%CI 0.89-1.14) for SI and 1.30 for AUC0-inf (90%CI 1.17-1.50) for SII. *In silico* predictions suggest that the developed SII would exhibit higher bioavailability relative to the immediate release reference formulation of furosemide, making it a promising candidate for further *in vivo* studies.

Financial support and acknowledgements

Postgraduate student María Luisa Rodríguez receive funding from the CAP (Postgraduate Academic Committee) postgraduate scholarship (UdelaR) and the economic rate for postgraduate students of the Basic Sciences Development Program (PEDECIBA).

References

1. F. Mentre, CPT: Pharmacometrics & Systems Pharmacology 2.0, *CPT Pharmacometrics Syst. Pharmacol.*, **8**, 197 (2019). Doi: https://doi.org/10.1002/psp4

2. C. Valiante *et al.*, Tesis de maestría, Universidad de la República, Uruguay, 2022.

3. Open Systems Pharmacology. URL: http://www.open-systems-pharmacology.org. Accessed 14 Dec 2023

4. H. Britz, N. Hanke, M.E. Taub, T. Wang, B. Prasad, É. Fernandez, P. Stopfer, V. Nock, T. Lehr, Physiologically based pharmacokinetic models of probenecid and furosemide to predict transporter mediated drug-drug interactions, *Pharm. Res.*, **37**, 250 (2020). Doi: https://doi.org/10.1007/s11095-020-02964-z

5. L. Magallanes, P. Fagiolino, M. Vázquez, N. Fotaki, M. Ibarra, M. Lorier, V. Bértola, A. Barindelli, Influence of food and sex on the pharmacokinetics and pharmacodynamics of furosemide, *Curr. Topics Pharmacol.*, **20**, 45-56 (2016).

6. Y. Akiyama, N. Nagahara, E. Nara, M. Kitano, S. Iwasa, I. Yamamoto, J. Azuma, Y. Ogawa, Evaluation of oral mucoadhesive microspheres in man on the basis of the pharmacokinetics of furosemide and riboflavin, compounds with limited gastrointestinal absorption sites, *J. Pharm. Pharmacol.*, **50**, 159-166 (1998). Doi: https://doi.org/10.1111/j.2042-7158.1998.tb06171.x

7. E.A. Klausner, E. Lavy, D. Stepensky, E. Cserepes, M. Barta, M. Friedman, A. Hoffman, Furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage form administration to healthy volunteers, *J. Clin. Pharmacol.*, **43**, 711-720 (2003). Doi: https://doi.org/10.1177/0091270003254575

8. M. Neumann, C. Heimhardt, K. Seidlitz, M. Koziolek, F. Schneider, C. Schiller, U. Hanke, M. Anschütz, C. Knopke, F. Donath, R. Thoma, C. Brätter, B. Schug, H. Franke, W. Weitschies, Development of a furosemide-containing expandable system for gastric retention, *J. Control Release*, **338**, 105-118 (2021). Doi: https://doi.org/10.1016/j.jconrel.2021.08.026

Physiologically-based pharmacokinetics modelling to predict drug concentration in human milk: a contribution from the conception project

Julia Macente[1]*, Nina Nauwelaerts[1], Justine Marine Badée[2], Rodolfo Hernandes Bonan[3], Miao-Chan Huang[1], Martje Van Neste[1], Karel Allegaert[1], Frederico Severino Martins[1], Pieter Annaert[1,3]

[1] KU Leuven, Leuven, Belgium

[2] Novartis Institutes for BioMedical Research, Basel, Switzerland

[3] BioNotus GCV, Niel, Belgium

*E-mail: julia.macente@kuleuven.be

Summary

Physiologically-based Pharmacokinetic (PBPK) modelling emerges as a highly valuable tool to predict drug concentration in human milk, and estimates the daily infant dosage (DID), and subsequently, the infants systemic exposure [1]. This study aimed to develop and evaluate the performance of lactation PBPK models to predict drug concentrations in human milk and the relative infant dose (RID, %) of sertraline, sildenafil, nevirapine and valproic acid. An adult healthy volunteer (HV) PBPK model was developed, reproduced or adapted [2-4] and validated using Simcyp v21 software. The validated adult HV model was extended to lactating women. Drug transfer into human milk was parameterized using the perfusion-limited model, with the milk-to-plasma ratio calculated using log-transformed phase distribution model by Atkinson and Begg [5]. The DID (mg/kg/day) received via breastfeeding and the RID, was calculated relying on the average (C_{ave}, milk) predicted concentration in human milk. The adult HV models established exhibited a good prediction (<2-fold) compared to observed data, qualifying as base for lactating women's PBPK models. The lactation PBPK models resulted in good prediction for the selected drugs. The RID was low (<10%) for all compounds. In addition, the DID was compared to the common therapeutic infant dosage, revealing <10% when compared to the therapeutic usage. The PBPK models effectively describe plasma and milk concentrations, simulations revealed a low infant systemic exposure compared to maternal exposure. Ongoing efforts to establish a non-clinical

workflow for (*in vitro*, and) PBPK-based predictions (permeability-limited model) of drug transfer into human milk are in progress.

Financial support and acknowledgements

This work has received support from the EU/EFPIA (Innovative Medicines initiative). Joint Undertaking ConcePTION grant No. 821520. The research leading to these Results was conducted as part of the ConcePTION consortium. This abstract only reflects the personal views of the stated authors.

References

1. N. Nauwelaerts, J. Macente, N. Deferm, R. Hernandes Bonan, M.C. Huang, M. Van Neste, D. Bibi, J. Badee, F.S. Martins, A. Smits, K. Allegaert, T. Bouillon, P. Annaert. Generic workflow to predict medicine concentrations in human milk using physiologically-based pharmacokinetic (PBPK) Modelling-A contribution from the ConcePTION project, *Pharmaceutics*, **15**, 1469 (2023). Doi: https://doi.org/10.3390/pharmaceutics15051469

2. A. Almurjan, H. Macfarlane, R.K.S. Badhan, The application of precision dosing in the use of sertraline throughout pregnancy for poor and ultrarapid metabolizer CYP 2C19 subjects: A virtual clinical trial pharmacokinetics study, *Biopharm. Drug Dispos.*, **42**, 252-262 (2021). Doi: https://doi.org/10.1002/bdd.2278

3. J. Macente, N. Nauwelaerts, F.M. Russo, J. Deprest, K. Allegaert, B. Lammens, R. Hernandes Bonan, J.M. Turner, S. Kumar, A. Diniz, F.S. Martins, P. Annaert, PBPK-based dose finding for sildenafil in pregnant women for antenatal treatment of congenital diaphragmatic hernia, *Front. Pharmacol.*, **14**, 1068153 (2023). Doi: https://doi.org/10.3389/fphar.2023.1068153

4. T.M. Conner, V.C Nikolian, P.E. Georgoff , M.P. Pai, H.B. Alam, D. Sun, R.C. Reed, T. Zhang, Physiologically based pharmacokinetic modeling of disposition and drug-drug interactions for valproic acid and divalproex, *Eur. J. Pharm. Sci.*, **111**, 465-481 (2018). Doi: https://doi.org/10.1016/j.ejps.2017.10.009

5. E.J. Begg, H.C. Atkinson, Modelling of the passage of drugs into milk, *Pharmacol. Ther.*, **59**, 301-310 (1993). Doi: https://doi.org/10.1016/0163-7258(93)90072-l

Enhancing tacrolimus precision dosing with multimodel methods

Martin Umpiérrez[1]*, Cecilia Maldonado[1], Oscar Noboa[2], Sebastian Wicha[3], Manuel Ibarra[1]

[1] Pharmaceutical Sciences Department, Faculty of Chemistry- Universidad de la República, Montevideo, Uruguay

[2] Nephrology Center, Faculty of Medicine- Universidad de la República, Montevideo, Uruguay

[3] Department of Clinical Pharmacy, University of Hamburg, Hamburg, Germany

*E-mail: martinumpierrezbattaglino@gmail.com

Summary

Tacrolimus (FK), an essential immunosuppressant, demands dose titration due to its narrow therapeutic index and high intra- and inter-individual variability [1, 2]. In this context, Model-Informed Precision Dosing (MIPD) [3] holds the potential of overcoming limitations of traditional therapeutic drug monitoring. However, the effectiveness of this approach can be hindered by significant inter-model variability. Utilizing a single model for a target population, either developed in-house or adopted from the literature, may fail to account for individual variations. Here, we explored multi-model approaches, Model Selection Algorithm (MSA) and Model Averaging Algorithm (MAA) [4] for FK MIPD. These methods use a single-model (MSA) or a combined-model forecast (MAA) for each patient, using a weighed selection based on the fit of individual models to observed data. Twenty-one population pharmacokinetic models were selected through systematic review and implemented in TDMxR [5].The accuracy and precision of single-models, MSA and MAA predictions were evaluated using data from 49 renal transplant patients (328 observations) collected in 6 occasions. Metrics such as relative bias (rBIAS) and mean absolute prediction error (MAPE) [6] were implemented. MSA and MAA consistently outperformed individual models in both precision and accuracy. Remarkably, MSA and MAA combining the five models with the poorest individual performance with data up to the first occasion yielded lower rBIAS (-15.2 and -10.6%) relative to individual models which showed results as high as 66.9% (Vadcharavivad) [7] or -55.9% (Han) [8]. Our study highlights the potential of these algorithms in replacing traditional approaches for implementing MIPD with FK, alleviating resource-intensive processes of in-house model development and external evaluation.

Ethical approval

This work was approved by the Ethics Committee of the Hospital de Clínicas Dr. Manuel Quintela (Approved 03/2021)

Financial support and acknowledgements

This work is supported by the Agencia Nacional de Investigación e Innovación and by Comisión Sectorial de Investigación Científica Investigación + Desarrollo (CSIC 1+D).

References

1. R. Venkataramanan, A. Swaminathan, T. Prasad, A. Jain, S. Zuckerman, V. Warty, J. McMichael, J. Lever, G. Burckart, T. Starzl, Clinical pharmacokinetics of tacrolimus, *Clin. Pharmacokinet.*, **29**, 404-430 (1995). Doi: https://doi.org/10.2165/00003088-199529060-00003

2. C.E.Staatz, S.E. Tett, Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation, *Clin. Pharmacokinet.*, **43**, 623-653 (2004). Doi: https://doi.org/10.2165/00003088-200443100-00001

3. R.J. Keizer, R.T. Heine, A. Frymoyer, L.J. Lesko, R. Mangat, S. Goswami, Model-informed precision dosing at the bedside: scientific challenges and opportunities, *CPT Pharmacometrics Syst. Pharmacol.*, 7, 785-787 (2018). Doi: https://doi.org/10.1002/psp4.12353

4. D.W. Uster, S.L. Stocker, J.E. Carland, J. Brett, D.J.E. Marriott, R.O. Day, S.G. Wicha, A model averaging/selection approach improves the predictive performance of model-informed precision dosing: Vancomycin as a case study, *Clin. Pharmacol. Ther.*, **109**, 175-183 (2021). Doi: https://doi.org/10.1002/cpt.2065

5. S.G. Wicha, M.G. Kees, A. Solms, I.K. Minichmayr, A. Kratzer, C. Kloft, TDMx: a novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine, *Int. J. Antimicrob. Agents*, **45**, 442-444 (2015). Doi: https://doi.org/10.1016/j.ijantimicag.2014.12.010

6. C.Y. Zhao, Z. Jiao, J.J. Mao, X.Y. Qiu, External evaluation of published population pharmacokinetic models of tacrolimus in adult renal transplant recipients, *Br. J. Clin. Pharmacol.*, **81**, 891-907 (2016). Doi: https://doi.org/10.1111/bcp.12830

7. S. Vadcharavivad, S. Praisuwan, N. Techawathanawanna, W. Treyaprasert, Y. Avihingsanon, Population pharmacokinetics of tacrolimus in Thai kidney transplant patients: comparison with similar data from other populations, *J. Clin. Pharm. Ther.*, **41**, 310-328 (2016). Doi: https://doi.org/10.1111/jcpt.12396

8. N. Han, S. Ha, H.Y. Yun, M.G. Kim, S.I. Min, J. Ha, J.I. Lee, J.M. Oh, I.W. Kim, Population pharmacokinetic-pharmacogenetic model of tacrolimus in the early period after kidney transplantation, *Basic Clin. Pharmacol. Toxicol.*, **114**, 400-406 (2014). Doi: https://doi.org/10.1111/bcpt.12176

Poster presentations

Relative bioequivalence of ivermectin 1%: single vs. combined formulation with fluazuron 12.5% by subcutaneous administration on cattle

Diego Robaina[1]*, Gonzalo Suárez[1]

[1] Departmento de Clínica y Hospital Veterinario, Universidad de la República, Montevideo, Uruguay

*E-mail: diego.robaina@fvet.edu.uy

Summary

Ivermectin (IVM) is the first Macrocyclic Lactone developed for animals. Differences in formulations account for changes in plasma kinetics and parasite exposure [1]. The objective of this study was to check for IVM bioequivalence using two formulations. Six Hereford cows (weight 372 ± 34 kg) and six Hereford heifers (weight 295 ± 33 kg) were randomized into two groups (three cows and three heifers per group). Group A (IVM 1 %, 0.2 mg/kg) and group B (a combined formulation of IVM and Fluazuron [IVM 1%, 0.2 mg/kg + Fluazuron 12.5%, 12.5 mg/kg]), both by subcutaneous route on the side of the neck (single dose). Blood samples were collected until 29 days after dosing. Non-compartmental approach showed bioequivalence for IVM between formulations, with Cmax ratio of 1.1 (CI90: 1.00 – 1.21, ANOVA, P = 0.077) and AUC0-t ratio of 0.99 (CI90: 0.93 – 1.05, ANOVA, P = 0.85) with Tmax (2.5 ± 2.3 and 1.6 ± 0.8 days (Mann-Whitney U test, P = 0.79) for A and B, respectively). The pharmacokinetic model has one compartment, linear elimination with first-order absorption and lag time; formulation was added as covariable for the absorption rate and lag time, weight was covariable on volume of distribution. We conclude that both IVM 1% formulations (alone or combined with fluazuron 12.5%), are bioequivalent in cattle. Carrying out bioequivalence studies are of great importance to ensure interchangeability between formulations.

Ethical approval

The experimental study was approved by the Comisión Honoraria de Experimentación Animal, Universidad de la República, Uruguay (CHEA, No. 506-1493294137).

Financial support and acknowledgements

Financial Support was granted from Universidad de la República.

References

1. D. Robaina, S. Alvariza, G. Suárez, Bioequivalence of two novel formulations of ivermectin 1% combined with fluazuron 12.5% for subcutaneous administration in cattle, *J. Pharm. Pharmacogn. Res.*, **9**, 88-97 (2021).

Modeling and simulation focusing on the chronopharmacokinetics of gentamicin in dogs

Karina Krauss Ferraz Vasconcelos[1]*, Kevellyn Silveira Gomes Martins[1], Naira Fernanda Dias da Silva[1], Lillian Pereira Gouvêia[1], Sibely Aiva Flores[1], Lucas Wamser Fonseca Gonzaga[1]

[1] Faculdade de Zootecnia e Medicina Veterinária, Universidade Federal de Lavras, Lavras, Minas Gerais, Brazil

*E-mail: karina.ferraz2007@gmail.com

Summary

Gentamicin is an aminoglycoside used to treat dogs with sepsis and bacterial infections, with chronotherapy being an alternative to increase efficacy and reduce side effects considering the impact of the circadian rhythm on pharmacokinetics (PK) [1]. The objective was to build a PK model to optimize gentamicin doses according to the administration schedule. The model was built using the Monolix2023 software based on plasma concentration data, at two different times, obtained from a chronopharmacokinetic study [2]. The best-fitting model was exported to the Simulix2023 software, in which different protocols were simulated (2, 4, 6 and 8 mg/kg) for both times. An MIC range of 0.016 to 32 μg/mL and the PK/PD index of Cmax/MIC=10 [3] were used to calculate the probability of target attainment (PTA). A 2-compartment intravenous linear elimination model was efficient in predicting plasma concentration. Administration time was inserted as a categorical covariate, correlating with clearance and volume of the peripheral compartment. For bacterias with a MIC of up to 0.5 μg/mL, all protocols achieved a PTA ≥ 90. The dose of 6 mg/kg and 8 mg/kg, recommended for sepsis in dogs [4], reached a PTA ≥ 90 for bacterias with MIC of up to 2 μg/mL at both administration times. For MICs up to 4 μg/mL, the nighttime dose of 8mg/kg was the only one that reached the PTA. Therefore, the model was efficient in predicting the ideal dose according to the MIC of the bacteria and the time of administration.

Ethical approval

Since this is an *in silico* study, no animals were used.

Financial support and acknowledgements

This study was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

References

1. Y. Yang, L.A. Lindsey-Boltz, C.M. Vaughn, *et al.*, Circadian clock, carcinogenesis, chronochemotherapy connections, *J. Biol. Chem.*, **297**, 101068 (2021). Doi: https://doi.org/10.1016/j.jbc.2021.101068

2. N. Widerhon, D. Díaz, E. Picco, M. Rebuelto, T. Encinas, J.C. Boggio, Chronopharmacokinetic study of gentamicin in dogs, *Chronobiology International*, **22**, 731-739 (2005). Doi: https://doi.org/10.1080/07420520500179738

3. G. Santana, *et al.*, *Manual de Terapêutica em Animais Domésticos*, Manole, 2021.

4. D.C. Plumb, *Plumb's Veterinary Drug Handbook*, 6th ed., Wiley Blackwell, 2008.

Physiology-based pharmacokinetic modeling of dexmedetomidine in healthy dogs

Lillian Pereira Gouvêia[1]*, Lucas Wamser Fonseca Gonzaga[1], Karina Krauss Ferraz Vasconcelos[1], Naira Fernanda Dias da Silva[1], Sibely Aiva Flores[1], Marcos Ferrante[1]

[1] Faculdade de Zootecnia e Medicina Veterinária, Universidade Federal de Lavras, Lavras, Minas Gerais, Brazil

*E-mail: gouveialillian@gmail.com

Summary

Pharmacokinetic modeling based on physiology (PBPK) aims to estimate the concentration of drugs in the blood and other tissues [1]. Dexmedetomidine has been used intravenously as an adjunct to anesthesia in dogs [2]. Therefore, the objective was to develop a physiologically-based pharmacokinetic (PB/PK) model to predict the plasma concentration after intravenous administration of dexmedetomidine in dogs. The model was developed with the assistance of PK-SIM® software (OPEN SYSTEMS PHARMACOLOGY), version 11.2. Plasma profiles of dexmedetomidine previously published in the literature were employed. The drug's physicochemical data were obtained from the PubChem database. Pharmacokinetic data were divided into a construction group and a validation group. The model was refined based on observed data from pharmacokinetic studies and evaluated using the geometric mean fold error (GMFE), calculated based on area under the curve from the first to the last point (AUCt-end) values. A sensitivity analysis was conducted to identify the impact of model parameters on AUCt- end and maximum concentration (Cmax) and suggest possible future adjustments. The model demonstrated satisfactory predictive performance with a GMFE value of 1.95, indicating acceptable accuracy under a double-error criterion [3]. Four datasets were used, two for model construction and two for validation. In the sensitivity analysis, changes in hepatic clearance, muscle volume, and hematocrit variables were observed to affect AUCt-end and Cmax values, suggesting potential future applications for the model. The model efficiently predicted the pharmacokinetics of dexmedetomidine in dogs, making it applicable for various purposes in the future.

Ethical approval

Since this is an *in silico* study, no animals were used.

Financial support and acknowledgements

This study was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and by Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG).

References

1. L. Kuepfer, C. Niederalt, T. Wendl, J.-F. Schlender, S. Willmann, J. Lippert, M. Block, T. Eissing, D. Teutonico, Applied concepts in PBPK modeling: How to build a PBPK/PD model, *CPT Pharmacometrics Syst. Pharmacol.*, **5**, 516-531 (2016). Doi: https://doi.org/10.1002/psp4.12134

2. O.L. Levionnois, A. Barbarossa, A. Barhi, J. Siegenthaler, T.F. Pleyers, M. Guidi, C. Spadavecchia, M. Raillard, Enantiospecific pharmacokinetics of intravenous dexmedetomidine in beagles, *J. Vet. Pharmacol. Therap.*, **45**, 366-372 (2022). Doi: https://doi.org/10.1111/jvp.13063

3. L. Kovar. A. Weber, M. Zemlin, Y. Kohl, R. Bals, B. Meibohm, D. Selzer, T. Lehr, Physiologically-based pharmacokinetic (PBPK) modeling providing insights into fentanyl pharmacokinetics in adults and pediatric patients, *Pharmaceutics*, **12**, 908 (2020). Doi: https://doi.org/10.3390/pharmaceutics12100908

PBPK modeling for propofol dose optimization in dogs with hepatic impairment

Lucas Wamser Fonseca Gonzaga[1]*, João Bosco Costa Coelho[1], Beatriz Monte Egito[1], Lillian Pereira Gouveia[1], Frederico Severino Martin[2], Marcos Ferrante[1]

[1] Faculdade de Zootecnia e Medicina Veterinária, Universidade Federal de Lavras, Lavras, Minas Gerais, Brazil

[2] Faculdade de ciências farmacêuticas da Universidade de São Paulo, São Paulo, Brazil

*E-mail: lucaswamserfg@gmail.com

Summary

A PBPK model allows predicting the concentration of a medication in different tissues over time and can be used to simulate and optimize various therapeutic protocols in both healthy and diseased individuals [1]. With this objective, a PBPK model was created to predict propofol doses in dogs with hepatic dysfunction. The model was developed using PK-SIM® software (OPEN SYSTEMS PHARMACOLOGY), version 11.2, based on pharmacokinetic data obtained from the literature. Physicochemical data of the drug were sourced from the PubChem database. The model's evaluation was based on the geometric mean fold error (GMFE) of the area under the curve (AUCt-end). Individuals with hepatic impairment were simulated by reducing hepatic clearance to mimic 20%, 40%, 60%, and 80% reductions in hepatic function. Populations were simulated, and adjustments to the protocols were made based on the area under the curve from 0 to 3 hours (AUC0-3) [2]. The model for healthy dogs showed good predictive performance, evidenced by the GMFE ranging from 0.8 to 1.25, meeting the double error criterion [3]. The simulated regimen for healthy dogs of 5mg/kg (administered as a bolus) followed by continuous infusion at a rate of 0.13mg/kg/min was sufficient and ensured that all simulated subjects reached the target plasma concentration. Dogs with 80% and 60% hepatic impairment required adjustments in the infusion rate to ensure that individuals did not exceed the therapeutic window. The results presented in the manuscript demonstrate the effectiveness and practicality of a PBPK model for propofol in dogs, with a particular focus on hepatic impairment.

Ethical approval

Since this is an *in silico* study, no animals were used.

Financial support and acknowledgements

This study was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), and by Fundação de Amparo a Pesquisa de Minas Gerais (FAPEMIG).

References

1. L. Kuepfer, C. Niederalt, T. Wendl, J.-F. Schlender, S. Willmann, J. Lippert, M. Block, T. Eissing, D. Teutonico, Applied concepts in PBPK modeling: How to build a PBPK/PD model, *CPT Pharmacometrics Syst. Pharmacol.*, **5**, 516-531 (2016). Doi: https://doi.org/10.1002/psp4.12134

2. P.L. Toutain, A. Autefage, M. Oukessou, M. Alvinerie, Pharmacokinetics of methylprednisolone succinate, methylprednisolone, and lidocaine in the normal dog and during hemorrhagic shock, *J. Pharm. Sci.*, **76**, 528-534 (1987). Doi: https://doi.org/10.1002/jps.2600760708

3. L. Kovar. A. Weber, M. Zemlin, Y. Kohl, R. Bals, B. Meibohm, D. Selzer, T. Lehr, Physiologically-based pharmacokinetic (PBPK) modeling providing insights into fentanyl pharmacokinetics in adults and pediatric patients, *Pharmaceutics*, **12**, 908 (2020). Doi: https://doi.org/10.3390/pharmaceutics12100908

Pharmacokinetic modeling applied to the optimization of methadone dosing regimen in dogs

Naira Fernanda Dias da Silva[1]*, Karina Krauss Ferraz Vasconcelos[1], Lillian Pereira Gouvêia[1], Sibely Aiva Flores[1], Kevellyn Silveira Gomes Martins[1], Lucas Wamser Fonseca Gonzaga[1]

[1] Faculdade de Zootecnia e Medicina Veterinária, Universidade Federal de Lavras, Lavras, Minas Gerais, Brazil

*E-mail: nairafernandadias@gmail.com

Summary

Methadone is a widely used opioid analgesic in the management of pain in small animals [1]. However, there are few studies relating its analgesic effect to its plasma concentration over time. Therefore, the aim was to create a pharmacokinetic (PK) model for intravenous methadone administration in dogs, in order to establish more effective drug dosing regimens for this species. Plasma concentration data for methadone from *in vivo* studies were used to construct the PK model [2-4]. The model was developed using "Monolix 2023R1 software, Lixoft SAS, a Simulations Plus Company", by testing different models; the structural model choice relied on graphical analysis within the program. The analgesic duration of methadone for different doses and repetitions was predicted using "Simulx 2023R1 software, Lixoft SAS, a Simulations Plus Company", based on methadone concentration values that remained above the minimum plasma concentration (17 $ng{\cdot}ml^{-1}$) for analgesia obtained from an *in vivo* study [5]. The PK model fell within the 90% prediction interval, allowing the correlation of drug dose to plasma concentration over time and the estimation of analgesic effect duration from the model in the Simulx software. The intermittent administration protocol of 0.3 mg/kg every 3 hours kept the population at a dosage near or above the minimum concentration for analgesia, taking into account the half-life interval of approximately 2 hours for reduced exposure. Thus, this model can be employed for simulating different doses of methadone and assessing its analgesic effect, as well as exploring dosing regimen possibilities in dogs.

Ethical approval

Since this is an *in-silico* study, no animals were used.

Financial support and acknowledgements

This study was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

References

1. T. Elwell-Cuddy, M. Li, B. KuKanich, Z. Lin, The construction and application of a population physiologically based pharmacokinetic model for methadone in Beagles and Greyhounds, *J. Vet. Pharmacol. Ther.*, **41**, 670-683 (2018). Doi: https://doi.org/10.1111/jvp.12676

2. C. Ingvast-Larsson, A. Holgersson, U. Bondesson, A.S. Lagerstedt, K. Olsson, Clinical pharmacology of methadone in dogs, *Vet. Anaesth. Analg.*, **37**, 48-56 (2010). Doi: https://doi.org/10.1111/j.1467-2995.2009.00476.x

3. B. Kukanich, B.D.X. Lascelles, M.G. Papich, Pharmacokinetics of morphine and plasma concentrations of morphine-6-glucuronide following morphine administration to dogs, *J. Vet. Pharmacol. Ther.*, **28**, 371-376 (2005). Doi: https://doi.org/10.1111/j.1365-2885.2005.00661.x

4. N. Schmidt, K. Brune, K.M. Williams, G. Geisslinger, Stereoselective pharmacokinetics of methadone in beagle dogs, *Chirality*, **6**, 492-495 (1994). Doi: https://doi.org/10.1002/chir.530060608

5. T. Amon, S.B.R. Kästner, M. Kietzmann, J. Tünsmeyer, Plasma levels of a methadone constant rate infusion and their corresponding effects on thermal and mechanical nociceptive thresholds in dogs, *BMC Vet. Res.*, **17**, 35 (2021). Doi: https://doi.org/10.1186/s12917-020-02735-3

PBPK modeling to predict *in vivo* performance of floating 3D printed inks containing ricobendazole in dogs

Marianela Lorier[1]*, María Eugenia Barberis[2], Juan Pablo Real[2], Manuel Ibarra[1]

[1] Department of Pharmaceutical Sciences, Faculty of Chemistry, Universidad de la República, Montevideo, Uruguay

[2] Research and Development Unit in Pharmaceutical Technology (UNITEFA), CONICET and Department of Pharmacy, Faculty of Chemical Sciences. Universidad Nacional de Córdoba, Córdoba, Argentina

*E-mail: mlorier@fq.edu.uy

Summary

Ricobendazole is a widely used antiparasitic which exhibits low oral bioavailability due to poor solubility at intestinal pH. Floating formulations may increase Ricobendazole gastric residence time enhancing its dissolution. This study aimed to simulate the *in vivo* performance of floating printlets to identify a suitable candidate for a pilot pharmacokinetic study in dogs and subsequently validate the predictions with the experimental data. A PBPK model was developed in PK-Sim® 11.1 using previously published pharmacokinetic data for oral powder formulations as a training dataset [1]. The model was further refined with data obtained after the administration of a micronized powder, the selected 3D printed floating formulation (T1), and a capsule containing the ink (DS1), to six dogs. Gastro-floating was implemented by setting Tablet Delay Factor to a value close to cero. T1 was selected for the pilot study due to its higher predicted bioavailability. Dissolution of DS1 and T1 was characterized by a varying pH *in vitro* study. Optimization of the drug's pH-dependent solubility profile was necessary to describe *in vivo* plasma concentration levels. The developed PBPK model adequately predicted the mean relative area under the curve and maximum plasma concentration between T1 and DS1 (1.66 vs. 1.56 and 1.48 vs. 1.50, respectively). DS1 and T1 exhibited better *in vivo* performance than initially predicted. This may be primarily attributed to enhanced solubility at gastric and intestinal pH levels, as well as extended gastric residence time. Gastroretention would lead to a 20% increase in bioavailability.

Ethical approval

Animal procedures and management protocols were approved by the Catholic University of Cordoba (UCC) Ethical Committee and were in compliance with the guidelines of the US National Research Council's for the Care and Use of Laboratory Animals (NRC-USA, 2011).

References

1. A. J. Paredes, N.M. Camacho, L. Schofs, A. Dib, M.P. Zarazaga, N. Litterio, D.A. Allemandi, S. Sánchez Bruni, C. Lanusse, S.D. Palma, Ricobendazole nanocrystals obtained by media milling and spray drying: Pharmacokinetic comparison with the micronized form of the drug, *Int. J. Pharm.*, **585**, 119501 (2020). Doi: https://doi.org/10.1016/j.ijpharm.2020.119501

Covariates affecting potassium bromide apparent clearance in dogs

Silvana Alvariza[1]*, Vernadette Bianchinotti[1], Micaela Sturchio[1], Diego Robaina[1], Gonzalo Suárez[1]

[1] Pharmacology and Therapeutics Unit, School of Veterinary Medicine, Universidad de la República,

Montevideo, Uruguay

*E-mail: silvana.alvariza@fvet.edu.uy

Summary

Potassium bromide KBr is a first line drug for treatment of canine epilepsy, demanding precise dosage control due to its narrow therapeutic window. Monitor its serum levels is crucial for effective treatments. Our study analyzed thirty predose serum samples from dogs treated with KBr alone or in conjunction with phenobarbital. In this study, we analyzed thirty predose serum samples from dogs receiving KBr alone or with phenobarbital, using Monolix® software to investigate factors influencing KBr elimination clearance. We examined the impact of age, sex, phenobarbital consumption, body weight (WT), serum urea (sUr), and creatinine concentration (sCr) on apparent clearance (CL/F). Employing a one-compartment model with fixed absorption rate constant and volume of distribution, WT, sex, and Ur were found to significantly affect CL/F of KBr ($p< 0.001$, $p<0.05$, and $p<0.001$ respectively). Our findings suggest that CL/F increases with higher WT and sUr levels and decreases in male dogs, with males exhibiting a 26% lower CL/F than females. The correlation between CL/F and sUr may stem from bromide's tubular excretion and reabsorption processes, with glomerular filtration playing a minor role in elimination.

Ethical approval

This research was approved by the Committee of Ethics in the Use of Animals (CEUA-FVET) of the School of Veterinary Medicine – Protocol number 799

Financial support and acknowledgements

Financial Support: funds from the Pharmacology and Therapeutics Unit

References

1. P.A. March, M. Podell, R.A. Sams, Pharmacokinetics and toxicity of bromide following high-dose oral potassium bromide administration in healthy Beagles, *J. Vet. Pharmacol. Ther.*, **25**, 425-432 (2002). Doi: https://doi.org/10.1046/j.1365-2885.2002.00440.x

2. J.H. Rossmeisl, K.D. Inzana, Clinical signs, risk factors, and outcomes associated with bromide toxicosis (bromism) in dogs with idiopathic epilepsy, *J. Am. Vet. Med. Assoc.*, 234, 1425-1431 (2009). Doi: https://doi.org/10.2460/javma.234.11.1425

Pharmacokinetic and pharmacodynamic modeling for *in vitro* evaluation of cloxacillin against *Corynebacterium pseudotuberculosis*

Marcos Ferrante[1]*, Larissa Alexsandra Felix[1], Maria Leticia Carneiro Rodrigues[2], Ana Milena César Lima[2], Viviane Maria Dias Costa[2], Patrícia Yoshida Faccioli-Martins[2]

[1] Faculdade de Zootecnia e Medicina Veterinária, Universidade Federal de Lavras, Lavras, Minas Gerais, Brazil

[2] Embrapa Caprinos e Ovinos, Sobral, Ceará, Brazil

*E-mail: marcos.ferrante@ufla.com

Summary

Current treatment of *Corynebacterium pseudotuberculosis* does not result in bacteriological cure and has low biosafety, making it necessary to develop new therapeutic strategies. Therefore, the objective of this study was to determine the epidemiological cutoff point and the PK/PD index of cloxacillin against *C. pseudotuberculosis* based on the *in vitro* bacterial time-kill curve. The minimum inhibitory concentration (MIC) and the time-kill curve were studied in the Cation-adjusted Miller Hinton broth. The epidemiological cut-off point was determined from the MIC distribution [1]. A sigmoid E_{max} model was used to determine the PK/PD index that best described the dose-response profile observed in the time-kill curves. PK/PD (PDT) values were established for bacteriostatic (E=0), bactericidal (E= 3 log10) and eradication (E= -4 log10) activity [2]. The MIC distribution of 35 isolates ranged from 4 to 16 μg/mL with an ECOFF of 16 μg/mL (IC 99.9%). Cloxacillin showed a time-dependent profile represented by the PK/PD indice T>MIC, that is the time that the concentration was above MIC (R^2=0.92). However, in this study the PDT value was established for the area under the curve divided by MIC (AUC/MIC) too. PDT values for the %T>MIC bactericidal (E= 3 log10) and eradication activity were 39% and 51%, respectively, and, for the AUC/MIC were 33.65 h and 46.07 h. This study is a necessary step towards the development of more effective drugs with less emergence of antimicrobial resistance.

Ethical approval

Since this is an *in silico* study, no animals were used.

Financial support and acknowledgements

This study was funded by a Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq - 448011/2014-0), FAPEMIG - APQ-01168-21, FUNCAP BP5-0197-00148.01.00/22, DCR-CNPq/Funcap 04854900/2022 and EMBRAPA (SEG 20.20.03.002.00.00).

References

1. J. Turnidge, G. Kahlmeter, G. Kronvall, Statistical characterisation of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values, *Clin. Microbiol. Infect.*, **12**, 418-425 (2006). Doi: https://doi.org/10.1111/j.1469-0691.2006.01377.x

2. Y.F. Zhou, Z. Sun, R.L. Wang, J.G. Li, C.Y. Niu, X.A. Li, Y.Y. Feng, J. Sun, Y. H. Liu, X.P. Liao, Comparison of PK/PD targets and cutoff values for danofloxacin against *Pasteurella multocida* and *Haemophilus parasuis* in piglets, *Front. Vet. Sci.*, **9**, 811967 (2022). Doi: https://doi.org/10.3389/fvets.2022.811967

Pharmacokinetic and pharmacodynamic integration of enrofloxacin in broiler for colibacillosis treatment

Larissa Alexsandra Felix[1]*, Beatriz Monte Egito[1], Bruna Christina Fernandes Soares[1], Diego Diaz[2], Sheila Rezler Wosiack[3], Marcos Ferrante[1]

[1] Faculdade de Zootecnia e Medicina Veterinária, Universidade Federal de Lavras, Lavras, Minas Gerais, Brazil

[2] Faculty of Veterinary Science, Universidad Nacional del Litoral, Santa Fe, Argentina

[3] Departamento de Medicina Veterinária, Universidade Estadual de Maringá, Umuarama, Paraná, Brazil

*E-mail: felix_larissaa@outlook.com

Summary

Enrofloxacin is widely used in poultry production for the treatment of respiratory and enteric infections [1]. The aim of this study was to perform a pharmacokinetic/pharmacodynamic (PK/PD) integration to establish therapeutic protocols for enrofloxacin in broilers for the treatment of colibacillosis. A PK model of enrofloxacin in broilers was constructed using Monolix 2023R1 software based on literature data [2]. The best-fit model was used as the basis for PK/PD integration, with the area under the curve divided by the minimum inhibitory concentration (AUC/MIC) as the PK/PD index. The target values (PDT) were 9.74, 21.29 and 32.13, considering bacteriostatic, bactericidal and eradication action, respectively [3]. A MIC range of 0.004 to 256 μg/mL was used [4-7]. Three doses of enrofloxacin were simulated: 10, 20 and 50 mg/kg, single dose, by gavage. The probability of target achievement (PTA) for each of the protocols was assessed according to a distribution of MICs. The recommended dose of 10 mg/kg achieves a PTA ≥ 90 only for bacteria with an MIC up to 0.06μg/mL for eradication. However, the 20 mg/kg dose could achieve a PTA of 94% for bacteria with a MIC of 0.125 μg/mL for eradication. This is still a preliminary model, but it has already demonstrated the need for dose adjustment in the face of increasing MICs due to antimicrobial resistance.

Ethical approval

Since this is an *in silico* study, no animals were used.

Financial support and acknowledgements

This study was funded by a Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Conselho Nacional de Desenvolvimento Científico e Tecnológico and Undergraduate Research Scholarship Program of UFLA.

References

1. R. Temmerman, L. Pelligand, W. Schelstraete, G. Antonissen, A. Garmyn, M. Devreese, Enrofloxacin dose optimization for the treatment of colibacillosis in broiler chickens using a drinking behaviour pharmacokinetic model, *Antibiotics* (Basel), **10**, 604 (2021). Doi: https://doi.org/10.3390/antibiotics10050604

2. M.C. Kruse, Thesis, 2008.

3. X. Xiao, X. Chen, K. Yan, L. Jiang, R. Li, Y. Liu , M. Wang, Z. Wang, PK/PD integration and pharmacodynamic cutoff of cefquinome against cow mastitis due to *Escherichia coli*, *J. Vet. Pharmacol. Ther.*, **45**, 83-91 (2022). Doi: https://doi.org/10.1111/jvp.13012

4. T.M. Huang, T.L. Lin, C.C. Wu, Antimicrobial susceptibility and resistance of chicken *Escherichia coli*, *Salmonella* spp., and Pasteurella multocida isolates, *Avians Dis.*, **53**, 89-93 (2009). Doi: https://doi.org/10.1637/8268-021608-Reg.1

5. M. Vanni, V. Meucci, R. Tognetti, P. Cagnardi, C. Montesissa, A. Piccirillo, A.M. Rossi, D. Di Bello, L. Intorre, Fluoroquinolone resistance and molecular characterization of gyrA and parC quinolone resistance-determining regions in *Escherichia coli* isolated from poultry, *Poult. Sci.*, **93**, 856-863 (2014). Doi: https://doi.org/10.3382/ps.2013-03627

6. K. Sang, H.H. Hao, L.L. Huang, X. Wang, Z.H. Yuan,Pharmacokinetic-pharmacodynamic modeling of enrofloxacin against *Escherichia coli* in broilers, *Front. Vet. Sci.*, **2**, 80 (2016). Doi: https://doi.org/10.3389/fvets.2015.00080

7. R. Temmerman, A. Garmyn, G. Antonissen, G. Vanantwerpen, M. Vanrobaeys, F. Haesebrouck, M. Devreese, Evaluation of fluoroquinolone resistance in clinical avian pathogenic Escherichia coli isolates from Flanders (Belgium), *Antibiotics* (Basel), **9**, 800 (2020). Doi: https://doi.org/10.3390/antibiotics9110800

Population modeling to study the pharmacokinetics of rutin in an extract of calyces from *Physalis peruviana* in New Zealand white rabbits

Gina Paola Domínguez Moré[1,2]*, Cláudia Maria Oliveira Simões[3], Diana Marcela Aragón[1]

[1] Departamento de Farmacia, Universidad Nacional de Colombia, Bogotá, D.C, Colombia

[2] Facultad de Química y Farmacia, Universidad del Atlántico, Puerto Colombia, Atlántico, Colombia

[3] Programa de Pós-Graduação em Farmácia, Universidade Federal de Santa Catarina, Florianópolis, SC, Brazil

*E-mail: ginadominguez@mail.uniatlantico.edu.co

Summary

A hydroethanolic extract of calyces from *P. peruviana* rich in rutin (quercetin-*3-O*-rutinoside), has shown hypoglycemic activity [1] and produced significant changes in the pharmacokinetics of the pure compound, in rats [2]. This work aimed to study the pharmacokinetics of rutin in the extract, compared to that of the pure compound, in New Zealand White rabbits, a non-rodent species, using population pharmacokinetics (popPK) modeling. The animals (n = 5) received intravenous or oral doses (0.37 to 500 mg/kg) of either the extract or pure rutin. Blood samples were collected for up to 48 h, and the plasma concentrations of rutin and quercetin (rutin metabolite) were quantified using a validated bioanalytical method [3]. The popPK modeling was carried out in Monolix 2019R, incorporating the rutin source as a covariate. The intravenous rutin profile was fitted to a model of two compartments with first-order elimination. The population parameters values for volume of central compartment and elimination rate constant increased (β 0.678 and 0.625, respectively), but the distribution to peripherical compartment rate constant decreased (β –0.634), due to the extract. Orally, the dominant compound in plasma was quercetin which exhibited a double absorption profile with two absorption rate constants, ka1 and ka2. The model showed that the extract produces a decrease of ka1 and an increase of ka2 (β –0.949 and 3.53, respectively). The two popPK models

developed effectively characterized rutin and quercetin pharmacokinetics in the extract (AIC< 1300) and confirmed the variability of the parameters with respect to the pure compound in animal species.

Ethical approval

The study was approved by the ethics committee of the science faculty of the Universidad Nacional de Colombia (Act 06, 2015, project 40831, 22 June 2015).

Financial support and acknowledgements

Authors thanks Universidad Nacional de Colombia and Universidad del Atlántico (Colombia) for their financial support.

References

1. S. Echeverry, I.H. Valderrama, G.M. Costa, L.F. Ospina-Giraldo, D.M. Aragón, Development and optimization of microparticles containing a hypoglycemic fraction of calyces from *Physalis peruviana*, *J. App. Pharm. Sci.*, **8**, 10-18 (2018). Doi: https://doi.org/10.7324/JAPS.2018.8502

2. D. Moré, G. Paola, M.I. Cardona, P.M. Sepúlveda, S.M. Echeverry, C.M. Oliveira Simões, D.M. Aragón, Matrix effects of the hydroethanolic extract of calyces of *Physalis peruviana* L. on rutin pharmacokinetics in Wistar rats using population modeling, *Pharmaceutics*, **13**, 535 (2021). Doi: https://doi.org/10.3390/pharmaceutics13040535

3. G. Domínguez, *Estudio farmacocinético de quercetina-3-O-rutinósido a partir de un extracto estandarizado de cálices de Physalis peruviana en dos modelos animales*, Ph. D. thesis, Universidad Nacional de Colombia, 2020.

Sex, drugs, & PBPK: an assessment of relevant men-women physiologic differences representation in PK-Sim and GastroPlus

Marianela Chavarría-Rojas[1,2]*, Marianela Lorier[3], Manuel Ibarra[3]

[1] Graduate Program in Chemistry, Faculty of Chemistry, Universidad de la República, Montevideo, Uruguay

[2] Industrial Pharmacy Department, Faculty of Pharmacy, Universidad de Costa Rica, San José, Costa Rica

[3] Department of Pharmaceutical Sciences, Faculty of Chemistry, Universidad de la República, Montevideo, Uruguay

*E-mail: marianela.chavarria@ucr.ac.cr

Summary

Physiologically based pharmacokinetic (PBPK) modelling is well-established in model- informed drug development [1]. Its integration in biopharmaceutical applications, involving drug products *in vitro* characterization is gaining traction in generic and controlled-release formulations development. Additionally, it supports risk assessment and alternative bioequivalence approaches in regulatory submissions [2, 3]. While PBPK models enable the evaluation of intrinsic and extrinsic factors affecting drug exposure, the impact of sex-related differences in gastrointestinal tract (GIT) physiology on bioavailability and bioequivalence remains underexplored [1, 2]. This work includes a comprehensive review of sex-related differences impacting pharmacokinetics, particularly drug absorption. Through literature and software revision, we assessed how these differences are represented in predefined anatomical and physiological parameters in PK-Sim® and Gastroplus® PBPK models for virtual populations of Caucasian men and women aged 18-50. Finally, we explore how these differences might affect pharmacokinetic predictions. Key physiological factors with reported sex-related differences, such as GIT pH, transit times, and enzyme and transporters expression, were found to be inadequately reflected in PBPK platforms. For instance, reported gastric pH values (2.16±0.09 for men, 2.79±0.18 for women) [4] are not differentiated in PK-Sim (pH=2.00) and Gastroplus (pH=1.30). Similar discrepancies exist between reported duodenal pH (6.75±0.63 for men, 7.16±0.29 for women) [4] and the included value (pH=6) in both platforms. These parameters

can be manually defined, considering that failing to incorporate sex-related differences may lead to simulation errors, particularly for females, impacting bioavailability and bioequivalence predictions. This research emphasizes the importance of refining PBPK models to better reflect sex-related disparities in GIT physiology, enhancing predictive accuracy and applicability across populations.

Financial support and acknowledgements

Financial support MCR is funded by a scholarship from the Universidad de Costa Rica, granted through the Office of International Affairs and External Cooperation (OAICE) under the contract OAICE-33-2023.

References

1. A. Golhar, M. Pillai, P. Dhakne, N. Rajput, T. Jadav, P. Sengupta, Progressive tools and critical strategies for development of best fit PBPK model aiming better *in vitro-in vivo* correlation, *Int. J. Pharm.*, **643**, 123267 (2023). Doi: https://doi.org/10.1016/j.ijpharm.2023.123267

2. C.G. Wilson, L. Aarons, P. Augustijns, J. Brouwers, A.S. Darwich, T. De Waal, G. Garbacz, S. Hansmann, D. Hoc, A. Ivanova, M. Koziolek, C. Reppas, P. Schick, M. Vertzoni, J.A. García-Horsman, Integration of advanced methods and models to study drug absorption and related processes: An UNGAP perspective, *Eur. J. Pharm. Sci.*, **172**, 106100 (2022). Doi: https://doi.org/10.1016/j.ejps.2021.106100

3. S. Subhani, C. Kim, P. Muniz, M. Rodriguez, S. van Os, E. Suarez, R. Cristofoletti, S. Schmidt, V. Vozmediano, Application of physiologically based absorption and pharmacokinetic modeling in the development process of oral modified release generic products, *Eur. J. Pharm. Biopharm.*, **176**, 87-94 (2022). Doi: https://doi.org/10.1016/j.ejpb.2022.05.007

4. A.C. Freire, A.W. Basit, R. Choudhary, C.W. Piong, H.A. Merchant, Does sex matter? The influence of gender on gastrointestinal physiology and drug delivery, *Int. J. Pharm.*, **415**, 15-28 (2011). Doi: https://doi.org/10.1016/j.ijpharm.2011.04.069

Can inhaled cannabis users accurately evaluate impaired driving ability? A PKPD model

Nicolas Simon[1], Bibiana Cardozo[1]*, Sarah Hartley, Islam Amine Larabi, Jean Claude Alvarez

[1] Department of Clinical Pharmacology, Aix Marseille University, SESSTIM

*E-mail: bibiana.cardozo@etu.univ-amu.fr

Summary

The aim of this investigation is to study the effect of inhaled cannabis on self-assessed predicted driving ability and its relation to reaction times and driving ability on a driving simulator. Participants: 30 healthy males aged 18–34, divided into 15 chronic (1–2 joints/day) and 15 occasional (1–2 joints/week) users. Assessments included self-rated driving confidence (visual analog scale), vigilance (Karolinska), reaction time (mRRT, psychomotor vigilance test), driving ability (SDLP on a York driving simulator), and blood THC concentrations. Measurements were taken before and at intervals after controlled inhalation of placebo, 10mg, or 30mg of THC mixed with tobacco in a cigarette. A population pharmacokinetic/pharmacodynamic analysis was conducted using non-linear mixed-effects modeling in NONMEM version 7.4.1 (26) with the gfortran 4.6.0 compiler. The Wings for NONMEM version 743 served as a "front end" for the NONMEM program [Holford]. Graphical analysis utilized R software version 3.4.2. The first order conditional estimate (FOCE) method with the interaction option was used. Cannabis consumption (at 10 and 30mg) led to a marked decrease in driving confidence over the first 2 h which remained below baseline at 8 h. Driving confidence was related to THC dose and to THC concentrations in the effective compartment with a low concentration of 0.11 ng/ml for the EC50 and a rapid onset of action (T1/2 37min). Driving ability and reaction times were reduced by cannabis consumption. Driving confidence was shown to be related to driving ability and reaction times in both chronic and occasional consumers. Cannabis consumption leads to a rapid reduction in driving confidence which is related to reduced ability on a driving simulator.

Ethical approval

Data used for medialization were obtained from the Study of the Relationship Between Dose-concentration-effect of Delta-9-tetrahydrocannabinol (THC) and the Ability to Drive in Chronic or Occasional Cannabis Users (VIGICANN).

The study was approved by the local Ethics Commitee (CPP Ile-de-France XI: NP 13039), all participants gave their accord to participate in the study by signing an informed consent. Clinical trial registration: ClinicalTrials.gov, identifier: NCT02061020.

Financial support and acknowledgements

Financial Support: Funding for the Ph.D. thesis was provided by the Ministry of Sciences of Colombia. Additional support came from Aix-Marseille University, Faculty of Medicine, SESSTIM group.

References

5. S. Hartley, N. Simon, B. Cardozo, I.A. Larabi, J.C. Alvarez, Can inhaled cannabis users accurately evaluate impaired driving ability? A randomized controlled trial, *Frontiers in Public Health*, **11**, 1234765 (2023). Doi: https://doi.org/10.3389/fpubh.2023.1234765

Application of a pharmacometrics model by assessing the efficacy of amphotericin B deoxycholate

Laiz Campos Pereira [1,2]*, Valdeene Vieira dos Santos[1,2], Matheus Antônio da Hora Borges[1,2], Jackeline Marley dos Santos Araújo[1,2], Luisa Oliveira Samtos[1,2], Rafaela Ferreira Santos Marques[1], Izabel Almeida Alves[1], Francine Johansson Azeredo[2,3]

[1] Laboratory of Pharmacokinetics and Pharmacometrics, Faculty of Pharmacy, Federal University of Bahia, Salvador, Brazil

[2] Pharmacy Graduate Program, Federal University of Bahia, Salvador, Brazil

[3] Center for Pharmacokinetics & System Pharmacology, Department of Pharmaceutics, University of Florida, Orlando, Florida, United States of America

*E-mail: laiz.campos08@gmail.com

Summary

Amphotericin B (AmB) is a drug used to treat invasive candidiasis, and it is considere one of the oldest antifungals employed in clinical practice [1, 2]. In Brazil, AmB deoxycholate is more cost-effective, and only this formulation is provided by the Public Health System [3]. A better understanding of the pharmacokinetic/pharmacodynamic (PK/PD) parameters of AmB deoxycholate is needed to optimize the treatment with this antifungal [4]. The study aims to develop a pharmacokinetic-pharmacodynamic (PK/PD) model to delineate the efficacy of AmB deoxycholate against *Candida albicans*. The modeling was carried out using the Monolix ® software, with the analyzed data obtained from studies featuring static time-kill curves previously conducted by our research group. Among the models evaluated to characterize the antifungal effect of AmB, the modified Emax model was the most descriptive, in which a parameter (*alpha*) was added to signify the delay in the growth of *C. albicans*, both in the presence and absence of the drug. From this model, the parameters related to the potency (kmax) and effectiveness (EC50) of the AmB were obtained. The results were as follows: k0 = 5.52 ± 0.2 h^{-1}; kmax = 0.42 ± 0.11 h^{-1}; EC50 = 0.2 ± 0.06 μg/mL and *alpha* = 1.11 ± 0.29. These results demonstrate that the model employed was considered the best to describe the fungicidal activity of AmB. Therefore, it can be used as a tool for simulating alternative dosage regimens and contribute significantly to optimizing AmB dosage.

Financial support and acknowledgements

Financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001. CNPq Grant number 407600/2016-7.

References

1. A.M. Tortorano, A. Prigitano, G. Morroni, L. Brescini, F. Barchiesi, Candidemia: Evolution of drug resistance and novel therapeutic approaches, *Infect. Drug Resist.*, **14**, 5543-5553 (2021). Doi: https://doi.org/10.2147/IDR.S274872

2. A. Lemke, A.F. Kiderlen, O. Kayser, Amphotericin B, *Appl. Microbiol. Biotechnol.*, **68**, 151-162 (2005). Doi: https://doi.org/10.1007/s00253-005-1955-9

3. H.H. Lobo Borba, L.M. Steimbach 1, B. Salgado Riveros, F. Stumpf Tonin, V. Lins Ferreira, B.A. de Queiros Bagatim, G. Balan, R. Pontarolo, A. Wiens, *Mycoses*, **61**, 754-763 (2018). Doi: https://doi.org/10.1111/myc.12801

4. N.J. Onufrak, A. Forrest, D. Gonzalez, Pharmacokinetic and pharmacodynamic principles of anti-infective dosing, *Clin. Therap.*, **38**, 1930-1947 (2016). Doi: https://doi.org/10.1016/j.clinthera.2016.06.01

Simulation of pharmacokinetic properties of naringenin, curcumin and β-carotene

Jessica Cruz-Mora[1]*, Marisín Pecchio[2], Johant Lakey-Beitia[1,3]

[1] Center for Biodiversity and Drug Discovery, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología (INDICASAT AIP), Clayton, City of Knowledge, Panama City 0843-01103, Panama

[2] Center for Academic Affairs and Collaboration, Instituto de Investigaciones Científicas y Servicios de Alta Tecnología (INDICASAT AIP), Clayton, City of Knowledge, Panama City 0843-01103, Panama

[3] Sistema Nacional de Investigación (SNI), SENACYT, Panama City 0816-02852, Panama

*E-mail: jessicacruzmora128@gmail.com

Summary

Naringenin, curcumin and β-carotene are natural products that in recent years have demonstrated a wide range of potential therapeutic properties such as neuroprotective activity, anti-aggregation and antioxidants [1-4]. Our research group is interested in improving the neuroprotective activity of these 3 compounds through synthetic modification of their structures. The aim of this study was to predict *in silico* the physicochemical properties and to simulate the pharmacokinetic behavior of each compound after an oral administration of 10 mg. SwissADME and ADMET Predictor software were used to predict the physicochemical properties. The estimated logP for naringenin, curcumin and β-carotene were 2.42, 3.62 and 9.75, respectively. The ADMET parameters (absorption, distribution, metabolism, excretion and toxicity) of the compounds were estimated with ADMET Predictor. The bioavailable fraction values for naringenin, curcumin and β-carotene were 93.5%, 85.1% and 0.065%. The low bioavailability estimated with β-carotene is consistent with the insolubility in water reported in the literature [5]. In addition, half-life results were obtained for naringenin (5 h), curcumin (8 h) and β-carotene (30 h). The participation of the hepatic enzyme CYP3A4, Caco-2 cells and albumin are highly involved in the pharmacokinetic processes of these compounds [1-3]. This project allowed us to validate a workflow that will be used for the understanding of

the ADMET properties of synthetic compounds in association with the knowledge of pharmacological potency, will support us in the identification of pharmacokinetically more acceptable derivatives for future *in vivo* studies.

Financial support and acknowledgements

We are grateful for the support of SENACYT for project FID23-003 and the National Research System (SNI).

References

1. J. Adiwidjaja, A.J. McLachlan, A.V. Boddy, Curcumin as a clinically-promising anti-cancer agent: pharmacokinetics and drug interactions, *Expert Opin. Drug Metab. Toxicol.*, **13**, 953-972 (2017). Doi: https://doi.org/10.1080/17425255.2017.1360279

2. R. Joshi, Y.A. Kulkarni, S. Wairkar, Pharmacokinetic, pharmacodynamic and formulations aspects of Naringenin: An update, *Life Sciences*, **215**, 43-56 (2018). Doi: https://doi.org/10.1016/j.lfs.2018.10.066

3. T. Bohn, C. Desmarchelier, S.N. El, J. Keijer, E. van Schothorst, R. Rühl, P. Borel, β-Carotene in the human body: metabolic bioactivation pathways - from digestion to tissue distribution and excretion, *Proc. Nutr. Soc.*, **78**, 68-87 (2019). Doi: https://doi.org/10.1017/S0029665118002641

4. Z. Nouri,Fakhri, F.F. El-Senduny, N. Sanadgol, G.E. Abd-ElGhani, M.H. Farzaei, J.T. Chen, On the neuroprotective effects of naringenin: Pharmacological targets, signaling pathways, molecular mechanisms, and clinical perspective, *Biomolecules*, **9**, 690 (2019). Doi: https://doi.org/10.3390/biom9110690

5. National Center for Biotechnology Information, PubChem Compound Summary for CID 5280489, Beta-Carotene, URL: https://pubchem.ncbi.nlm.nih.gov/compound/Beta-Carotene. Accessed 2024.

PD modeling of artesunate-mefloquine association effect in mice

Valdeene Vieira Santos[1]*, Laiz Campos Pereira[1], Aline Morena Lourenço dos Santos Miranda[2], Helenita Costa Quadros[3], Mariana da Cruz Borges Silva[2], Diogo Rodrigo de Magalhães Moreira[2], Francine Johansson Azeredo[3]

[1] Pharmacy Post Graduate Program, College of Pharmacy, Federal University of Bahia, Salvador, Bahia, Brazil

[2] Instituto Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Bahia, Brazil

[3] Center for Pharmacometrics & System Pharmacology, College of Pharmacy, University of Florida, Orlando, Florida, United States of America

*E-mail: valdeene.vieira@ufba.br

Summary

The artesunate-mefloquine (ARMQ) association treats malaria caused by *Plasmodium falciparum* [1]. Pharmacokinetic/pharmacodynamic (PK/PD) modeling for drug association establishes the effect-time relationship, analyzing the interaction of drugs administered together [2]. To compose the PK/PD model, preclinical PD studies and modeling can be used to describe the concentration-effect relationship of drugs. With this, time-to-event analysis (TTE) and determination of parasitemia were performed. The efficacy of the ARMQ association was evaluated using survival (TTE) and the Thompson test in mice infected with *P. berghei* after administration of 100 mg/kg and 55 mg/kg of AR and MQ, respectively (n=6/group). For TTE analysis, untreated AR and ARMQ groups of animals were observed for 30 days. Survival analysis was performed using the MonolixSuite™ software, using treatment as a covariate. The Thompson test determined parasitemia using flow cytometry on days 5, 6, 7, 8, and 9 after infection. As a result, in the TTE analysis, the Weibull model was chosen as it better describes the survival curve of the data, and the covariate analysis identified that the ARMQ is significant in the Te_pop parameter, with an estimate of 13.66 h, p_pop 4.39 and beta Te_ARMQ of 0.77 h. The probability of survival after treatment with ARMQ for 7, 15, and 30 days was 94.4%, 88.9%, and 14.9%, respectively. Parasitemia in the ARMQ group decreased when compared to the untreated group. Therefore, it can be concluded that the ARMQ association increases survival and reduces parasitemia of infected animals.

Ethical approval

All procedures were reviewed and approved by the Committee on Ethics in the Use of Animals of Instituto Gonçalo Moniz (015/2022).

Financial support and acknowledgements

We thank CNPq for grant number 440227/2022-4S and FAPESB for the scholarship support.

References

1. Brasil, Guia de tratamento da malária no Brasil 2º edição, Ministério da Saúde, 2021.

2. M.J. Brill, A.N. Kristoffersson, C. Zhao, E.I. Nielsen, L.E. Friberg, Semi-mechanistic pharmacokinetic-pharmacodynamic modelling of antibiotic drug combinations, *Clin. Microbiol. Infect.*, **24**, 697-706 (2018). Doi: https://doi.org/10.1016/j.cmi.2017.11.023

PBPK modeling in drug development for rare diseases: A systematic review of FDA approvals

Karen Dayana Lancheros Porras[1], Diana Marcela Aragón Novoa[1]*

[1] Department of Pharmacy, Universidad Nacional de Colombia, Bogotá D.C., Colombia

*E-mail: dmaragonn@unal.edu.co

Summary

Currently, there are more than 10,000 rare diseases worldwide, and the majority represent an unmet medical need [1, 2]. However, due to the nature of these diseases and limited number of patients, it is impractical to develop new drugs using traditional models [3]. Physiologically Based Pharmacokinetic (PBPK) modeling is presented as a valuable tool for drug development in this context, enabling the prediction of systemic drug exposure by integrating *in vitro* information, the physicochemical properties of the drug, and physiological factors [4]. The aim of this work was to assess the use of PBPK in the U.S Food and Drug Administration agency (FDA) applications for novel orphan drugs from 2018 to 2023. Data on yearly approved drugs were sourced from the FDA's novel drug approvals annual reports. For each drug, the Application Review Files available in the FDA's approved drug database were reviewed, focusing on the PBPK modeling section. It was found that 50 orphan drugs employed PBPK modeling in their approval process, and after the FDA review, only 5 models were considered completely inadequate, mainly because of a lack of validation data and uncertainty regarding the enzymatic contribution. The primary approved use (60%) was for the treatment of oncological diseases, particularly those with specific genetic variations, and the main application of PBPK modeling was to predict drug interactions mediated by enzymes (63%). PBPK modeling supported studies at the clinical trial stage, fulfilling a crucial role in both the development and regulatory approval processes for new treatments in rare diseases.

Financial support and acknowledgements

Acknowledgements to the Universidad Nacional de Colombia for making possible the development of the present review and to the professors involved for their guidance and support.

References

1. Global Genes. Rare diseases: Facts and statistics, 2023. URL: http://globalgenes.org/rare-diseases-facts- statistics/. Accessed November 18, 2023.

2. P. Kaufmann, A.R. Pariser, C. Austin, From scientific discovery to treatments for rare diseases - the view from the National Center for Advancing Translational Sciences - Office of Rare Diseases Research, *Orphanet J. Rare Dis.*, **13**, 196 (2018). Doi: https://doi.org/10.1186/s13023-018-0936-x

3. M.J. Field, T.B. Boat, *Rare diseases and orphan products: Accelerating research and development*, Institute of Medicine (US) Committee on Accelerating Rare Diseases Research and Orphan Product Development, 2010. Doi: https://doi.org/10.17226/12953

4. F. Wu, Y. Mousa, K. Raines, C. Bode, Y. Chung Tsang, R. Cristofoletti, H. Zhang, T. Heimbach, L. Fang, F. Kesisoglou, A. Mitra, J. Polli, M.J. Kim, J. Fan, B.S. Zolnik, D. Sun, Y. Zhang, L. Zhao, Regulatory utility of physiologically-based pharmacokinetic modeling to support alternative bioequivalence approaches and risk assessment: A workshop summary report, *CPT Pharmacometrics Syst. Pharmacol.*, **12**, 585-597 (2023). Doi: https://doi.org/10.1002/psp4.12907

Two-step *in vitro-in vivo* correlation for development a predictive flow through cell dissolution method for carbamazepine modified release tablet

Laura Carvajal Barbosa[1], Marcela Aragón Novoa[1]*

[1] Department of Pharmacy, Universidad Nacional de Colombia, Bogotá D.C., Colombia

*E-mail: dmaragonn@unal.edu.co

Summary

The development of an *in vitro-in vivo* correlation (IVIVC) aims to use *in vitro* dissolution data to predict the *in vivo* performance of a drug product [1]. This correlation is not only useful for achieving a biowaiver in bioequivalence (BE) studies but also for successful generic drug product development [2]. The aim of this work was to develop an *in vivo* predictive flow-through cell dissolution method for a modified release carbamazepine tablet (Tegretol® Retard) in a local pharmaceutical company. For this purpose, an experimental design was employed to optimize the dissolution method minimizing the prediction error of the Area Under the Curve (AUC_{0-t}) and Cmax. Three factors at three levels were evaluated: sodium lauryl sulfate concentration in dissolution media, the amount of glass beads, and flow rate. The IVIVC was developed using a deconvolution with the Wagner-Nelson equation, followed by a two-step scaling approach, and a reconvolution [3]. The two-step approach was carried out by constructing a Levy plot, scaling up the dissolution profiles and plotting them against the absorption profile. The obtained IVIVC models were then used to predict the absorbed fractions. Fifteen dissolution profiles and IVIVC models were obtained under different conditions, with AUC_{0-t} and Cmax prediction errors ranging from -64% to -8%. With the optimized dissolution method, an IVIVC was achieved with an r^2= 0.9905, predicting errors of -6.08% for the AUC_{0-t} and -1.93% for Cmax. The developed and optimized dissolution method was challenged with immediate-release carbamazepine tablets (Tegretol® IR) and proved to be discriminative. In conclusion, an *in vivo* predictive flow-through cell dissolution method was developed in a local pharmaceutical company as a tool for the development of generic modified release carbamazepine products.

Financial support and acknowledgements

Pharmacy Department of the Universidad Nacional de Colombia and Pharmetique Labs.

References

1. Y. Lu, S. Kim, K. Park, *In vitro-in vivo* correlation: Perspectives on model development, *Int. J. Pharm.*, **418**, 142148 (2011). Doi: https://doi.org/10.1016/j.ijpharm.2011.01.010

2. B. Sánchez-Dengra, I. González-García, M. González-Álvarez, I. González-Álvarez, M. Bermejo, Two-step *in vitro-in vivo* correlations: Deconvolution and convolution methods, which one gives the best predictability? Comparison with one-step approach, *Eur. J. Pharm. Biopharm.*, **158**, 185-197 (2021). Doi: https://doi.org/10.1016/j.ejpb.2020.11.009

3. M.C. Gohel., R.K. Parikh, P.Y. Aghara, S.A. Nagori, R.R. Delvadia, M.R. Dabhi, Application of simplex lattice design and desirability function for the formulation development of mouth dissolving film of salbutamol sulphate, *Curr. Drug Deliv.*, **6**, 486-494 (2009). Doi: https://doi.org/10.2174/156720109789941696

Evaluation of the dissolution behavior of etodolac tablets using a physiologically based biopharmaceutics modeling approach

Larissa Lopes Rodrigues Gomide[1], Marcelo Dutra Duque[1]*

[1] Universidade Federal de São Paulo - UNIFESP, Institute of Environmental, Chemical and Pharmaceutical Sciences, Diadema, São Paulo, Brazil

*E-mail: marcelo.duque@unifesp.br

Summary

Etodolac is an acidic molecule (pKa 4.65) with pH-dependent solubility and classified as a BCS class II drug [1]. Due to its low solubility, it is important to understand if different dissolution media could lead to different results on its predicted bioavailability. In order to evaluate such influence, a Physiologically Based Biopharmaceutics Model (PBBM) was developed and validated. Methods: Experimental dissolution tests were carried out using the reference drug product in Brazil, Flancox 400mg, at four different dissolution pH values 5.5, 6.0, 6.4 and 6.8 using USP apparatus II at 50 rpm and a PBBM for etodolac using GastroPlus® version 9.8.3. The *in vitro* dissolution profiles were modeled in GastroPlus® using the Z-factor dissolution model, and virtual bioequivalence (VBE) studies were run in comparison to Lodine, FDA's etodolac reference drug product. As expected, for each pH different dissolutions profiles were observed, as well as different Z-factor values. These values were used to run ten VBE trials for each pH condition, and all were within the 0.8 -1.25 acceptance criteria. These results showed similar predicted *in vivo* dissolution behavior of the evaluated drug product, with high probability to be bioequivalent to the FDA's reference drug product, Lodine. Although etodolac is a BCS class II drug, under pH conditions above its pKa, it behaves as a BCS class I drug, according to the predictions and virtual bioequivalences.

Financial support and acknowledgements

The authors would like to thank Simulations Plus Inc., (Lancaster, CA, USA) for providing GastroPlus® software.

References

1. X. Hu, Y. Gong, Z. Cao, Z. Huang, J. Sha, Y. Li, T. Li, B. Ren, Solubility, Hansen solubility parameter and thermodynamic properties of etodolac in twelve organic pure solvents at different temperatures, *J. Mol. Liq.*, **316**, 113779 (2020). Doi: https://doi.org/10.1016/j.molliq.2020.113779

Physiology-based pharmacokinetic evaluation of tafenoquine drug-drug interactions

Luisa Oliveira Santos[1]*, Francine Johansson Azeredo[1,2]

[1] Graduate Program in Pharmacy, Federal University of Bahia, Salvador, Bahia, Brazil

[2] Center for Pharmacometrics & Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, Florida, FL, United States of America

*E-mail: santos.luisa@ufba.br

Summary

Physiology-Based Pharmacokinetics (PBPK) uses models and simulations combining physiology, population, drug substance, and product characteristics to mechanistically describe the pharmacokinetic behaviors of a drug [1]. PBPK has become a promising tool for drug interaction potential evaluation [2]. Malaria is an acute febrile infectious disease transmitted by the bite of the female Anopheles mosquito [3]. In South America, 77% of the global cases accumulate, most related to the etiological agent *Plasmodium vivax*. This species has evolutionary forms that remain dormant in the liver [4, 5]. Tafenoquine (TQ) is an 8-aminoquinoline analog of primaquine that appears promising due to its administration in a single dose. However, being a prodrug, there are concerns regarding its drug-drug interactions [6]. A PBPK model for TQ was developed in the PK-SIM® software (v.11) utilizing previously published studies. The model was created based on a healthy male European individual considering CYP2D6 as the predominant metabolizing enzyme. For some parameters that could not be informed from experimental data or were present to be relevant after sensitivity analyses, parameter identification based on plasma concentration-time profiles was performed using a subset of the available clinical studies (training dataset) for model optimization. The predicted Cmax value fell within the 2-fold acceptance criteria with an overall geometric mean fold error (GMFE) of 1.09. The mean relative deviations (MRD) for all plasma concentration was 1.29 falling within 2-fold of the corresponding concentration observed. Model still needs improvement and training with different doses so then it can be used for drug interaction evaluation regarding the CYP2D6 enzyme.

Financial support and acknowledgements

Financed by the Fundação de Amparo à Pesquisa do Estado da Bahia – Finance code 916/2023.

References

1. FDA, The Use of Physiologically Based Pharmacokinetics Analyses, 2020. URL: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-physiologically-based-pharmacokinetic-analyses-biopharmaceutics-applications-oral-drug-product, Accessed 2024.

2. C. Wagner, Y. Pan, V. Hsu, V. Sinha, P. Zhao, Predicting the Effect of CYP3A Inducers on the pharmacokinetics of substrate drugs using physiologically based pharmacokinetic (PBPK) modeling: An analysis of PBPK submissions to the US FDA, *Clin. Pharmacokinet.*, **55**, 475-483 (2016). Doi: https://doi.org/10.1007/s40262-015-0330-y

3. E.M. Braga, *et al.*, *Livro Parasitologia Humana*, 13 ed., Atheneu, 2016.

4. WHO, World Malaria Report, 2023. URL: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2023. Accessed 2024.

5. Brasil, Guia de tratamento da malária no Brasil, 2021. URL: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/svsa/malaria/tratamento. Accessed 2024.

PBPK modeling of 3D-printed benznidazole formulations for individualized Chagas disease treatment

Patricia Rega[1,2*], María Sol Magi[3,4], Lucía Lopez-Vidal[3,4], Álvaro Jimenez Kairuz[4], Santiago Daniel Palma[3,4], Juan Pablo Real[3,4], Manuel Ibarra[1]

[1] Department of Pharmaceutical Sciences, Faculty of Chemistry. Universidad de la República. Montevideo, Uruguay

[2] Postgraduate Program, Faculty of Chemistry, Universidad de la República, Montevideo, Uruguay

[3] Investigation Unit and Pharmaceutical Technology Development, CONICET. Universidad Nacional de Córdoba, Argentina

[4] Department of Pharmaceutical Sciences, Faculty of Chemical Sciences, Universidad Nacional de Córdoba, Argentina

*E-mail: patriciarega@fq.edu.uy

Summary

Benznidazole (BNZ) is a first-line drug used against Chagas disease, a neglected tropical disease associated with ten thousand deaths and seven million annual infections. The treatment implies the administration of high doses of BNZ over extended periods, often leading to the appearance of severe adverse events that compromise patient adherence. Consequently, the development of innovative technologies, such as 3D-printed solid pharmaceutical forms, emerges as a promising strategy to individualize the pharmacotherapy and improve BNZ safety and efficacy. 3D inks advantages includes providing specific drug release properties and enabling a customized dose [1]. This work aimed to inform decision-making in the preclinical development stage by predicting the pharmacokinetic performance of two printlets (immediate release and extended release) in dogs, and subsequently projecting a third formulation containing a mixture of both inks. A physiologically based pharmacokinetic model (PBPK) for BNZ in dogs was developed using reported data including *in vitro* drug dissolution and *in vivo* pharmacokinetics after administration of Abarax® (immediate release formulation) and a modified release formulation based on ionic polymers combination (IPC) [2], which were later used in the production of one

of the inks. Sensitivity analyses were conducted to evaluate variables affecting BNZ bioavailability, including *in vivo* dissolution profile, absorption time, and a gastro-retentive delivery system implementation. Single and multiple dose plasma profiles were simulated for the formulation of interest. The combination of gastro-retention and IPC as a solubility enhancer was predicted to improve BNZ bioavailability, resulting in a desirable therapeutic profile. This formulation strategy holds promise for personalized medicine design.

Financial support and acknowledgements

Financial support was received from the National Postgraduate Scholarship Program of ANII (Agencia Nacional de Innovación e Investigación-Uruguay), grant POS_NAC_2022_1_174151).

References

1. J. Goole, K. Amighi, 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems, *Int. J. Pharm.*, **499**, 376-394 (2016). Doi: https://doi.org/10.1016/j.ijpharm.2015.12.071

2. M.C. García, M.L. Guzman, M.A. Himelfarb, N.J. Litterio, M.E. Olivera, A. Jimenez-Kairuz, Preclinical pharmacokinetics of benznidazole-loaded interpolyelectrolyte complex-based delivery systems, *Eur. J. Pharm. Sci.*, **122**, 281-291 (2018). Doi: https://doi.org/10.1016/j.ejps.2018.07.005

Physiology-based pharmacokinetic modeling to optimize intravenous lidocaine infusion in dogs with hemorrhagic shock

Sibely Aiva Flores[1]*, Bárbara Fernandes Dorante[1], Vivian Aparecida Malta[1], Bruna Christina Fernandes Soares[1], Lucas Wamser Fonseca Gonzaga[1], Marcos Ferrante[1]

[1] Faculdade de Zootecnia e Medicina Veterinária, Universidade Federal de Lavras, Lavras, Minas Gerais, Brazil

*E-mail: sibelyaflores@gmail.com

Summary

Lidocaine, when administered intravenously, can promote analgesia in dogs [1]. Eventually, patients in critical condition may present other conditions adjacent to the pain, such as hemorrhagic shock, leading to the need to adjust the dose of analgesics in this situation [2]. This study aims to create a physiologically based pharmacokinetic model (PBPK) to optimize the lidocaine infusion protocol for dogs in hemorrhagic shock. The model was developed in the PK-SIM® software (OPEN SYSTEMS PHARMACOLOGY), version 11.2 based on pharmacokinetic data obtained in the literature. Physicochemical data of the drug were obtained from the PubChem database. The model was evaluated by the geometric mean fold error (GMFE) of the area under the curve (AUCt-end) [3]. Therefore, it was resized to predict doses in patients with hemorrhagic shock based on a pharmacokinetic study [2]. The administration of a 2 mg/kg/h infusion was simulated to compare and adjust the infusion rate based on the area under the curve values from 0 to 3 hours (AUC0-3h) of the two individuals. A GMFE value of 1.42 was observed, indicating a good predictive value when considering a double error criterion. The simulated protocols revealed AUC0-2h values of 473.56 μmol·min/L for healthy patients and 850.7 μmol·min/L for shock patients. When adjusting the infusion rate to 1.1 mg/kg/h, the AUC0-2h value of shock patients was reduced to 467.89 μmol·min/L. With this model, it was possible to suggest an adjustment in the lidocaine infusion rate for patients in shock to minimize possible adverse effects of lidocaine.

Ethical approval

Since this is an in silico study, no animals were used.

Financial support and acknowledgements

This study was funded by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and by Fundação de Amparo a Pesquisa de Minas Gerais (FAPEMIG).

References

1. P. Raušer. H. Němečková, M. Mrázová, J. Václavíková, L. Novák, Influence of fentanyl, ketamine, and lidocaine on tear production in healthy conscious dogs, *Top Companion Anim. Med.*, **46**, 100615 (2022). Doi: https://doi.org/10.1016/j.tcam.2021.100615

2. P. L. Toutain. A. Autefage, M. Oukessou, M. Alvinerie, Pharmacokinetics of methylprednisolone succinate, methylprednisolone, and lidocaine in the normal dog and during hemorrhagic shock, *J. Pharm. Sci.*, **76**, 528-534 (1987). Doi: https://doi.org/10.1002/jps.2600760708

3. L. Kovar. A. Weber, M. Zemlin, Y. Kohl, R. Bals, B. Meibohm, D. Selzer, T. Lehr, Physiologically-based pharmacokinetic (PBPK) modeling providing insights into fentanyl pharmacokinetics in adults and pediatric patients, *Pharmaceutics*, **12**, 908 (2020). Doi: https://doi.org/10.3390/pharmaceutics12100908

Evaluation of the dissolution behavior of the lysosomotropic drug amlodipine using physiologically based biopharmaceutics modeling (PBBM)

Jose Perez-Urizar[1,2*], Porfirio de La Cruz[1], Larissa Lopes Rodrigues Gomide[3], Marcelo Dutra Duque[3]

[1] Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México [2] FS Scientia Pharma S.A. de C.V., San Luis Potosí, México

[3] Department Pharmaceutical Sciences, Universidade Federal de São Paulo-UNIFESP, Institute of Environmental, Chemical and Pharmaceutical Sciences, Diadema, São Paulo, Brazil

*E-mail: jpurizar@uaslp.mx

Summary

Amlodipine (AML) is a weak base drug (pKa 9.1) classified as a BCS class I drug. The aim of this study was to develop and validate a PBBM to evaluate the dissolution behavior of AML when administered orally. GastroPlus® software was used to build a compartmental pharmacokinetic (PK) model based on intravenous (IV) and oral administration data. Lysosomal trapping of the drug was evaluated using MembranePlus™ software by testing different pHs in the lysosomes. The model was validated by comparing the obtained PK data with different literature data, and it was used to evaluate different dissolution profiles [1, 2] of the reference drug product Norvasc® 5 mg. The predicted/observed (P/O) ratio values for Cmax, Tmax and AUC, were within the 0.8-1.25 acceptance range for the IV 10 mg infusion and for the 5 mg tablet used to build the model, and for 5 mg and 10 mg tablets from different literature. AML showed to be trapped by the lysosomes, with a fraction unbound to the enterocytes of 1.3%. The calculated Z-factor values for the dissolution profiles of Norvasc® 5 mg tablets were 4.98E-4, 4.05E-4, and 4.96E-4 mL/mg/s, for pH 1.2, 4.5, and 6.8, respectively. The results showed that lysosomal trapping is responsible for the long Tmax (>6h) of AML, and the three dissolution test conditions evaluated can be used as biopredictive, since similar predicted *in vivo* behavior was observed independent of the dissolution profile used in the model.

Financial support and acknowledgements

The authors would like the thank Simulations Plus Inc., (Lancaster, CA, USA) for providing the software GastroPlus® and MembranePlus™ as academic license, and to Consejo Potosino de Ciencia y Tecnología for financial support via FME/2023/SE-08/17 project.

References

1. A.N. Zaid, S. Natur, A. Qaddomi, M. Abualhasan, R. Al-Ramahi, N. Shraim, S. Khammash, N. Jaradat, Formulation and bioequivalence of two Valsartan/Amlodipine immediate release tablets after a single oral administration, *Pak. J. Pharm. Sci.*, **27**, 755-762 (2014).

2. A.N. Zaid, N. Shraim, A. Radwan, N. Jaradat, S. Hirzallah, I. Issa, A. Khraim, Does GastroPlus support similarity and dissimilarity factors of *in vitro-in vivo* prediction in biowaiver studies? A lower strength amlodipine as a model drug, *Drug Res.* (Stuttg), **68**, 625-630 (2018). Doi: https://doi.org/10.1055/a-0611-4927

Advancing horizons in PBPK modeling: A review of patent from 2013 to 2024

Brian Sebastian Correa Barrera[1], Karen Lancheros[1], Izabel Almeida Alves[2], Diana Marcela Aragón Novoa[1]*

[1] Departamento de Farmacia, Universidad Nacional de Colombia, Bogotá D.C., Colombia

[2] Faculdade de Farmácia, Universidade Federal de Bahia, Salvador-BA, Brazil

*E-mail: dmaragonn@unal.edu.co

Summary

Physiologically-Based Pharmacokinetic (PBPK) models have emerged as a powerful mathematical framework integrating physiological and pharmacological insights to predict PK profiles across diverse compounds [1, 2]. Despite advancements, accurately characterizing substance behavior and translating findings to human contexts remains a challenge due to inter-individual variabilities and substance complexities [3]. This study aims to evaluate recent patents concerning PBPK modeling. Data were retrieved from the Espacenet patents database spanning 2000 to 2023 using the keyword "PBPK" Screening criteria encompassed titles, summaries, and content pertinent to PBPK modeling. Sixteen patents were identified, primarily applied in toxicology, bioequivalence, and drug development decision support. Notably, 44% of PBPK patents focused on enhancing *in vitro* test understanding and *in vivo* extrapolation, while 25% addressed toxic risk assessment and 13% targeted anticancer drugs. PBPK models proved beneficial for drugs with narrow therapeutic margins or inadequate *in vitro* data, facilitating predictive physiological and metabolic insights using *in vitro* information. This study underscores PBPK modeling's adaptability in predicting physiological and metabolic responses to diverse compounds, particularly those with toxic potential, thereby enhancing drug development decision-making processes.

Ethical approval

This study did not involve experimentation on cells, animals, or human subjects.

Financial support and acknowledgements

Acknowledgments to Universidad Nacional de Colombia for making possible the development of this research.

References

1. D. Deepika, V. Kumar, The role of "Physiologically Based Pharmacokinetic Model (PBPK)" new approach methodology (NAM) in pharmaceuticals and environmental chemical risk assessment, *Int. J. Environ. Res. Public Health*, **20**, 3473 (2023). Doi: https://doi.org/10.3390/ijerph20043473

2. K.D. Lancheros, I.A. Alves, D.M. Aragon, PBPK modeling as an alternative method of interspecies extrapolation that reduces the use of animals: A systematic review, *Current Medicinal Chemistry*, **31**, 102-126 (2024). Doi: https://doi.org/10.2174/0929867330666230408201849

3. H. Jones, K. Rowland-Yeo, Basic concepts in physiologically based pharmacokinetic modeling in drug discovery and development, *CPT Pharmacometrics Syst. Pharmacol.*, **2**, e63 (2013). Doi: https://doi.org/10.1038/psp.2013.41

Prediction of *in vivo* behaviour of metformin-loaded PLGA nanoparticles

Dalia Elena Lopera[1,2]*, Marisin Pecchio[1,2]

[1] Facultad de Farmacia, Universidad de Panamá, Ciudad de Panamá, Panamá

[2] Instituto de Investigaciones Científicas y Servicios de Alta Tecnología AIP (INDICASAT AIP), Ciudad de Panamá, País de Panamá

*E-mail: daliamariafar@gmail.com

Summary

Metformin is the drug of first choice in the treatment of type II diabetes. To maintain effective concentrations of metformin in plasma, repeated doses are necessary. Nanoparticles appear to be able to improve the pharmacokinetics of many substances, and in many cases have the ability to efficiently cross biological barriers. Therefore, applying this new technology in the administration of drugs such as metformin points to improvements in their therapeutic profile [1]. A PK model was developed from a physiological model with the use of the *in silico* program, PK-Sim® [2, 3], using data from *in vitro* dissolution of three metformin -loaded PGLA nanoparticle with a size of less than 300 nm, obtained from the *in vitro* dissolution profile, achieving predictions for absorption, distribution, metabolism and excretion (ADME). The first priori predictions were made, to human population, in normal Mexican adult women, without modifying the transporter systems and enzymes responsible for metabolism in man. Simulations were performed with simple and advanced administration protocols. The most favorable simulations were obtained with the advanced administration protocol, at an initial dose of 5000 mg, orally, with three repetitions. The results suggest that the prepared nanoparticles could be promising for oral administration of metformin. The application of this approach physiologically based pharmacokinetic (PK) modeling is very interesting to describe the development of a new PGLA metformin nanoparticle formulation without resorting to *in vivo* assays. Changes that have the greatest impact on single-dose administration and elimination half-life can be predicted.

References

1. G.G. Graham, J. Punt, M. Arora, R.O. Day, M.P. Doogue, J.K. Duong, T.J. Furlong, J.R. Greenfield, L.C. Greenup, C.M. Kirkpatrick, J.E. Ray, P. Timmins, K.M. Williams, Clinical pharmacokinetics of metformin, *Clin. Pharmacokinet.*, **50**, 81-98 (2011). Doi: https://doi.org/10.2165/11534750-000000000-00000

2. PK-SIM® y MOBI® para PBPK, GitHub. Open-Systems-Pharmacology, 2019.

3. L. Kuepfer, C. Niederalt, T. Wendl, J.F. Schlender, S. Willmann, J. Lippert, M. Block, T. Eissing, D. Teutonico, Applied concepts in PBPK modeling: How to build a PBPK/PD model, *CPT Pharmacometrics Syst. Pharmacol.*, **5**, 516-531 (2016). Doi: https://doi.org/10.1002/psp4.12134

Impact of the differences *in vitro* dissolution on the albendazole pharmacokinetics parameters

Nelly Norma Castro-Torres[1]*, Iliana González-Hernández[1], Lourdes Mayet-Cruz[2], José Becerril-Vega[2], Helgi Jung-Cook[2]

[1] Laboratorio de Neurobioquímica y conducta, Instituto Nacional de Neurología y Neurocirugía MVS, Ciudad de México, México

[2] Laboratorio de Biofarmacia, División de Estudios de posgrado Facultad de química, Universidad Nacional Autónoma de México, Ciudad de México, México

*E-mail: nelly.castro@innn.edu.mx

Summary

Except for Brazil and Mexico, in Latin America a bioequivalence study is not required for generic albendazole products, however they must comply with a dissolution requirement. The aim of the present study was to evaluate if differences in the *in vitro* dissolution of albendazole tablets could be related to *in vivo* pharmacokinetic differences. For the *in vitro* evaluation 3 Mexican generic products containing 200 mg of albendazole (ALB) and the innovator product, were selected. Study was performed according to the Mexican Pharmacopeia [1]. Differences were found in the mean dissolution time (MDT) and in the f2 test. For the *in vivo* study, the product with the lowest similarity factor was selected. Study was performed in 12 healthy volunteers who received a dose of 400 mg of ALB in a crossover design. ALB and its main metabolite albendazole sulfoxide (ALBSO) were determined using a previously validated LC/MS/MS assay. A high interindividual variability was found both for the reference and the test products. No significant differences ($P<0.05$) were found in maximum concentration (Cmax) and area under the curve (AUC) for ALB or ALBSO, and therefore a relation *in vitro-in vivo* was not found. To explain the variability, a nonlinear mixed-effects modeling approach was employed using Monolix 2021R1 software. The best model was a one compartment with double absorption peaks and lag time. Results showed that due to the high variability in albendazole absorption and the double peak phenomena, the pharmacopeia dissolution test would not be representative of the *in vivo* behavior of the drug products.

Ethical approval

Protocol 19/18 approved by the Investigation Committee of the Instituto Nacional de Neurologia, MVS.

Financial support and acknowledgements

Financial Support. The authors thankfully acknowledge Facultad de Química, UNAM (grant number PAIP 50009137) and CONACYT (grant number 229785) for providing financial support.

References

1. Farmacopea de los Estados Unidos Mexicanos, Undécima edición, México, Secretaría de Salud, Vol III, 2018, pp. 2095-2097.

Mechanistic insights into amlodipine oral absorption

Porfirio de la Cruz Cruz[1]*, Mauricio García Alcalde[2], Ángel Antonio Vértiz Hernández[3], José Trinidad Pérez Urizar[4,5]

[1] Doctorado Institucional en Ingeniería y Ciencia de Materiales, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México

[2] Departmento de Farmacia, Escuela de Química y Farmacia, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Santiago, Chile

[3] Coordinación Académica Región Altiplano, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México

[4] Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, San Luis Potosí, México

[5] FS Scientia Pharma S.A. de C.V., San Luis Potosí, México

*E-mail: porfirio1104@hotmail.com

Summary

Amlodipine (AML) is the only dihydropyridine with a slow absorption, resulting in prolonged Tmax (6-8 h), most likely due to its basic pKa=9.1. Although models have been successfully developed, they overlooked the mechanisms behind this phenomenon. Even though this could be explained by the recently introduced lysosomal trapping (Hypothesis 1: H1), it may also relate to a potential slow intestinal permeability (Hypothesis 2: H2). In this work, we developed and validated a PBPK model using GastroPlus® to assess H1 and H2. Lukacova's method was used to model AML distribution, calculating the blood- to-plasma ratio from published equations [1, 2]. Renal clearance was fit to 1.6 L/h [3]. CYP3A4 Km and Vmax were simultaneously fit to match intravenous profiles, while CYP3A5 Vmax was set to 10% that of CYP3A4 [4]. For H1, permeability (Peff=1.9x10^{-4} cm/s) was calculated from ka [5] and fraction trapped was calculated to 1.17% using Henderson-Hasselbach. For H2, Peff was decreased to target a borderline An=0.85 assuming no trapping. Both internal and external validations showed r^2>0.94 and RMSE <9.17. After oral dose simulation, neither approach correctly predicted Tmax (1.1 and 2.0 h, H1 and

H2, *vs* 8.0 h observed). Nonetheless, H2 performed comparatively better than H1 in predicting Cmax (prediction errors of 53 and 284%, respectively). Results suggest that deeper mechanistic understanding is needed to model AML oral absorption, although the H2 seemed to provide closer predictions. Therefore, further knowledge on regional absorption may be to improve predictions for this and other similar drugs.

Financial support and acknowledgements

The authors would like the thank Simulations Plus Inc., (Lancaster, CA, USA) for providing the software GastroPlus® as academic license, and to Consejo Potosino de Ciencia y Tecnología for financial support via FME/2023/SE-08/17 project.

References

1. C. Tannergren, H. Jadhav, E. Eckernäs, J. Fagerberg, P. Augustijns, E. Sjögren, Physiologically based biopharmaceutics modeling of regional and colon absorption in humans, *Eur. J. Pharm. Biopharm.*, **186**, 144-159 (2023). Doi: https://doi.org/10.1016/j.ejpb.2023.03.013

2. A.P. Beresford, D. McGibney, M.J. Humphrey, P.V. Macrae, D.A. Stopher, Metabolism and kinetics of amlodipine in man, *Xenobiotica*, **18**, 245-254 (1988). Doi: https://doi.org/10.3109/00498258809041660

3. J.K. Faulkner, D. McGibney, L.F. Chasseaud, J.L. Perry, I.W. Taylor, The pharmacokinetics of amlodipine in healthy volunteers after single intravenous and oral doses and after 14 repeated oral doses given once daily, *Br. J. Clin. Pharmacol.*, **22**, 21-25 (1986). Doi: https://doi.org/10.1111/j.1365-2125.1986.tb02874.x

4. Y. Zhu, F. Wang, Q. Li, M. Zhu, A. Du, W. Tang, W. Chen, Amlodipine metabolism in human liver microsomes and roles of CYP3A4/5 in the dihydropyridine dehydrogenation, *Drug Metab. Dispos.*, **42**, 245-249 (2014). Doi: https://doi.org/10.1124/dmd.113.055400

5. J.T. Flynn, M.C. Nahata, J.D. Mahan Jr, R.J. Portman, Population pharmacokinetics of amlodipine in hypertensive children and adolescents, *J. Clin. Pharmacol.*, **46**, 905-916 (2006). Doi: https://doi.org/10.1177/0091270006289844

Novel and simple method to back-calculate plasma concentrations in two-compartmental models

Mauricio A. García[1]*, Pablo M. González[2]

[1] Departamento de Farmacia, Escuela de Química y Farmacia, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Santiago, 7820436, Chile

[2] Innovation and Biopharmaceutical Evaluation Center (IBECenter), Recoleta, Santiago, Chile

*E-mail: magarci3@uc.cl

Summary

Pharmacometrics is the discipline that quantifies the interaction between the drug product and the patient through modelling. Among pharmacokinetic (PK) models, compartmental are the simplest and perhaps most used in pharmaceutical industry. Level A *in vivo-in vitro* correlation (IVIVC) is the highest standard were fraction dissolved and absorbed are correlated point-by-point. Although mechanistical PBPK software have recently emerged, compartmental deconvolution is still highly used due to its simplicity and fewer number of assumptions. Validation of the IVIVC requires reconstructing plasma profiles from *in vitro* dissolution. In 2005, Gohel *et al.* [1] published one equation for one- compartment PK. However, no method was reported two-compartment cases. In this poster, we derived a novel and simple method to reconstruct plasma profiles after Loo- Riegelman's deconvolution, which can be easily solved. Validation was achieved by both numerical back-calculation of plasma profiles and applicating the equation to a real IVIVC case for levonorgestrel as model drug. Back-calculation of plasma levels was not only accomplished, but also this method was successfully applied to correlate *in vitro* dissolution and *in vivo* absorption of two contraception formulations with levonorgestrel and ethynyl estradiol, which failed the bioequivalence for the former drug. Prediction errors (PE) for Cmax and AUC parameters were below 15% for each formulation, with average PE being below 10%, thus fulfilling the regulatory requirements for IVIVC validation. This tool may be a valuable asset for small generic companies that not always can afford expensive software.

Ethical approval

Clinical trial was approved by the Independent Ethics Committee (IEC) (protocol HP8814-03, Version: 2 .0, and date of approval 04 December 2021), in accordance with the Declaration of Helsinki.

Financial support and acknowledgements

Financial Support was received from "Proyecto de Inserción Académica (PIA)" no 3915-1004-301-81, Pontificia Universidad Católica de Chile.

References

1. J.C. Loo, S. Riegelman, New method for calculating the intrinsic absorption rate of drugs, *J. Pharm. Sci.*, **57**, 918-928 (1968). Doi: https://doi.org/10.1002/jps.2600570602

Approximation to the population PK/PD model of a self-emulsifying delivery system of an extract from *Physalis peruviana*

Cristian Sneyder Castellanos Sánchez[1], Maria Isabel Cardona[1], Gina Paola Domínguez Moré[1,2], Diana Marcela Aragón[1]*

[1] Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Bogotá, Colombia

[2] Centro de servicios farmacéuticos y monitoreo de fármacos. Programa de Farmacia, Facultad de Química y Farmacia, Universidad del Atlántico, Puerto Colombia, Colombia

*E-mail: dmaragonn@unal.edu.co

Summary

The hydroalcoholic extract of *Physalis peruviana* has poor oral bioavailability due to low solubility and permeability [1, 2]. To improve the bioavailability and hypoglycemic activity of rutin, the major flavonoid on the extract, a self-emulsifying delivery system (SEDDs) was developed. This study aims to conduct population pharmacokinetic and pharmacodynamic (PK/PD) modeling of the extract formulated with SEDDs and evaluated through an oral glucose test in Wistar rats. The PK/PD model, developed using Monolix software (Lixoft®, Paris, France) was chosen based on the observation of graphs, Akaike information criterion (AIC) values and precision of the estimated parameters. The final popPK exhibit two compartments, dual uptake of order 1 and order 0, a time delay for the second uptake, and Michaelis-Menten elimination. These results could be explained because high plasma levels of rutin (from extracts) after oral administration of SEDDs cause changes in the rate of metabolic processes such as transport into the intestinal lumen and active tubular secretion may become saturated [3, 4]. Our pharmacodynamic model suggests an indirect stimulation mechanism for rutin, sice rutin stimulate calcium channels to promote glucose reuptake into muscles [5, 6]. SEDDs significantly enhance extract bioavailability, with 12 times greater potency than unformulated extract.

Ethical approval

The study was approved by the Ethics Committee of the Science Faculty of Universidad Nacional de Colombia (Act 06, 2015, project 40831, 22 June 2015).

Financial support and acknowledgements

To the Universidad Nacional de Colombia and Lixoft for the academic license of Monolix software.

References

1. G.P. Domínguez Moré, M.I. Cardona, P.M. Sepúlveda, S.M. Echeverry, C.M. Oliveira Simões, D.M. Aragón, *Pharmaceutics*, **13**, 535 (2021). Doi: https://doi.org/10.3390/pharmaceutics13040535

2. M.I. Cardona. G.P. Dominguez, S.M. Echeverry, I.H. Valderrama, A. Bernkop-Schnürch, M. Aragón, Enhanced oral bioavailability of rutin by a self-emulsifying drug delivery system of an extract of calyces from *Physalis peruviana*, *J. Drug Deliv. Sci. Technol.*, **66**, 102797 (2021). Doi: https://doi.org/10.1016/j.jddst.2021.102797

3. D. Muñoz-Reyes. A.I. Morales, M. Prieto, Transit and metabolic pathways of quercetin in tubular Cells: Involvement of its antioxidant properties in the kidney, *Antioxidants* (Basel), **10**, 909 (2021). Doi: https://doi.org/10.3390/antiox10060909

4. X. Chen, O.Q.P. Yin, Z. Zuo, M.S.S. Chow, Pharmacokinetics and modeling of quercetin and metabolites, *Pharm. Res.*, **22**, 892-901 (2005). Doi: https://doi.org/10.1007/s11095-005-4584-1

5. V. D. Kappel, L. Zanatta, B.G. Postal, F.R.M. Barreto Silva, Rutin potentiates calcium uptake via voltage-dependent calcium channel associated with stimulation of glucose uptake in skeletal muscle, *Arch. Biochem. Biophys.*, **532**, 55-60 (2013). Doi: https://doi.org/10.1016/j.abb.2013.01.008

6. M.A. Felmlee, M.E. Morris, D.E. Mager, Mechanism-based pharmacodynamic modeling, *Computational Toxicology*, **1**, 583-600 (2012).

Improvement type 2 diabetes treatment with vildagliptin using population pharmacokinetic and pharmacodynamic modeling

Bruna Bernar Dias[1]*, Laura Ben Olivo[1], Bibiana Verlindo de Araújo[1]

[1] Pharmaceutical Sciences Graduate Program, Federal University of Rio Grande do Sul, Brazil

*E-mail: b.bernardias@gmail.com

Summary

Diabetes is a chronic metabolic disease [1, 2]. Previous studies demonstrated vildagliptin (VDG) concentration in plasma in healthy and diabetic animals are the same, but tissue penetration in healthy subjects is reduced compared to diabetic rats [3, 4]. To understand VDG distribution and PK/PD we used a population-based approach via NONMEM®v.7.4. PK/PD analysis simulated free tissue concentrations in diabetic patients after doses of 25, 50 and 100 mg once and twice daily with DPP-4 inhibition described by an Emax model. Four-compartment model with linear elimination described data, with bidirectional transport between tissues and central compartment, diabetes influencing Q1 and Qout,liver, with CL: 2.7 L/h/kg (5%RSE), V1: 1.1 L/kg (9%RSE), Q1,healthy: 0.338 L/h/kg (21%RSE), Q1,diabetic: 2.61 L/h/kg (21%RSE), V2: 1.85 L/kg (12 %RSE). Tissue parameters were: Vmuscle: 2.5L/kg (26%RSE), Qin,muscle: 2.0 L/h/kg (0.8%RSE), Qout,muscle: 14.3 L/h/kg (23 %RSE) and Vliver: 2.2 L/kg (48 %RSE), Qin,liver: 1.38 L/h/kg (31 %RSE), Qout,liver,healthy: 218 L/h/kg (53 %RSE), Qout,liver,diabetic: 19.7 L/h/kg (49 %RSE). Model was translated from mice to humans using data from previously published model developed for humans [5]. Muscle and liver Qin and Qout were used to simulate the prediction expected tissue levels in patients. Free tissue concentrations following once-daily dosing did not cause DPP-4 inhibition across all dosing intervals, whereas 50 and 100 mg twice-daily dose produced sufficient DPP-4 inhibition for adequate hypoglycemic effect during the whole interval of dose. This first investigation of free tissue exposure and effect of VDG demonstrate plasma concentrations are not useful to predict tissue effect of VDG and dose administered twice daily can lead to better treatment results in type 2 diabetes.

Ethical approval

This study was approved by the Ethics Committee in Animal Use from the Federal University of Rio Grande do Sul (UFRGS/CEUA #20352).

Financial support and acknowledgements

The authors acknowledge Coordination of Superior Level Staff Improvement (CAPES) for the scholarship.

References

1. Y. Zheng, S.H. Ley, F.B. Hu, Global aetiology and epidemiology of type 2 diabetes mellitus and its complications, *Nat. Rev. Endocrinol.*, **14**, 88-98 (2017). Doi: https://doi.org/10.1038/nrendo.2017.151

2. M.A. Nauck, J. Wefers, J.J. Meier, Treatment of type 2 diabetes: challenges, hopes, and anticipated successes, *Lancet Diabetes Endocrinol.*, **9**, 525-544 (2021). Doi: https://doi.org/10.1016/S2213-8587(21)00113-3

3. C. De Andrade, Dissertação de mestrado, UFRGS, 2013.

4. C. de Andrade, G. de Araújo Lock, M.C. Pigatto, S.E. Haas, T. Dalla Costa, B. Verlindo de Araújo, Validation of LC-MS/MS method applied to evaluation of free tissue concentrations of vildagliptin in diabetic rats by microdialysis, *Biomed. Chromatogr.*, **28**, 1722-1727 (2014). Doi: https://doi.org/10.1002/bmc.3212

5. C.B. Landersdorfer, Y.L. He, W.J. Jusko, Mechanism-based population pharmacokinetic modelling in diabetes: vildagliptin as a tight binding inhibitor and substrate of dipeptidyl peptidase IV, *Br. J. Clin. Pharmacol.*, **73**, 391-401 (2012). Doi: https://doi.org/10.1111/j.1365-2125.2011.04108.x

A software tool for a priori model-informed dose selection of tacrolimus for solid organ transplant recipients

Yannick Hoffert[1]*, Nada Dia[1], Erwin Dreesen[1]

[1] KU Leuven, Department of Pharmaceutical and Pharmacological Sciences, Leuven, Belgium

*E-mail: yannick.hoffert@kuleuven.be

Summary

Tacrolimus concentrations are not available before start of therapy and in resource-limited settings, preventing *a posteriori* model-informed precision dosing (MIPD). Still, population pharmacokinetics (popPK) models can be used for *a priori* (covariate-based) model-informed dosing. PopPK models were collected in a systematic literature review and code was reconstructed. For each graft type, the model with the highest sample/patient ratio was selected. The tool was developed into a web application using the *Shiny* package in R (v1.7.4), where simulations are performed using the *mrgsolve* package (v4.3.0). Four models were integrated, covering a broad range of covariates [1–4]. After selecting a popPK model and providing dosing details, the user can determine the clinical relevance of covariates using a novel and rational probability of target attainment (PTA)- based approach, including PTA *versus* covariate plots and receiver operating characteristic (ROC) curves. Dose finding can be guided by a user-defined PTA target and the area under the ROC curve (AUROC). An AUROC >0.5 indicates clinical relevance of the covariate, hence covariate-based dosing may be investigated. User- specified virtual patients (*i.e.*, covariates sets) can be inspected using predicted tacrolimus exposure and PTA over time plots. Results were cross-validated against NONMEM. The beta version of the tool can be accessed at https://hyannick.shinyapps.io/app_tac_simulator/. Our tool provides an objective and efficient framework for simulation-based assessment of the clinical relevance of covariates for *a priori* popPK model-informed dosing of tacrolimus. It enables the investigation of individualized dosing right from the first dose and is useful in settings where MIPD is not routinely/frequently performed.

Financial support and acknowledgements

Yannick Hoffert is supported by a doctoral research grant from the Research Foundation – Flanders, Belgium (1SHAA24N).

References

1. X. Cai. H. Song, Z. Jiao, H. Yang, M. Zhu, C. Wang, D. Wei, L. Shi, B. Wu, J. Chen, Population pharmacokinetics and dosing regimen optimization of tacrolimus in Chinese lung transplant recipients, *Eur. J. Pharm. Sci.*, **152**, 105448 (2020). Doi: https://doi.org/10.1016/j.ejps.2020.105448

2. R. Kirubakaran, S. Hennig, B. Maslen, R.O. Day, J.E. Carland, S.L. Stocker, Evaluation of published population pharmacokinetic models to inform tacrolimus dosing in adult heart transplant recipients, *Br. J. Clin. Pharmacol.*, **88**, 1751-1772 (2022). Doi: https://doi.org/10.1111/bcp.15091

3. J.Y. Lee, H.J. Hahn, I.J. Son, K.S. Suh, N.J. Yi, J.M. Oh, W. G. Shin, Factors affecting the apparent clearance of tacrolimus in Korean adult liver transplant recipients, *Pharmacotherapy*, **26**, 1069-1077 (2006). Doi: https://doi.org/10.1592/phco.26.8.1069

4. Z. Lu, P. Bonate, J. Keirns, Population pharmacokinetics of immediate- and prolonged-release tacrolimus formulations in liver, kidney and heart transplant recipients, *Br. J. Clin. Pharm.*, **85**, 1692-1703 (2019). Doi: https://doi.org/10.1111/bcp.13952

A quantitative systems pharmacology model of valproic acid-induced hyperammonemia for pediatric and adult patients

Alejandra Schiavo[1,2]*, Cecilia Maldonado[1], Marta Vázquez[1], Pietro Fagiolino[1], Iñaki F. Trocóniz[3,4], Manuel Ibarra[1]

[1] Department of Pharmaceutical Sciences, Faculty of Chemistry, Universidad de la República, Montevideo, Uruguay

[2] Graduate Program in Chemistry, Faculty of Chemistry, Universidad de la República, Montevideo, Uruguay

[3] Pharmacometrics and Systems Pharmacology Research Unit, Department of Pharmaceutical Technology and Chemistry, School of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain

[4] IdiSNA, Navarra Institute for Health Research, Pamplona, Spain

*E-mail: schiavoma@fq.edu.uy

Summary

Valproic acid (VPA) induces hyperammonemia (HA) in adults and pediatric patients. We aimed to enhance a previous Quantitative Systems Pharmacology model of VPA developed in Simulx® [1], focusing on characterizing age- and sex-related differences in VPA-induced HA. A virtual population (n=2000) aged 0 to 40 years was created in PK- Sim®. Individual patients were categorized into three groups: i) toddlers (0-2 y/o); ii) children (3-14 y/o); iii) adults (15-40 y/o, 50% women). Following literature reports, sex and age were introduced as covariates affecting VPA clearance and inputs of carnitine, ammonia, and fatty acid. We simulated the pharmacokinetic profiles of a delayed-release (Reference) and an extended-release (Test) formulations containing VPA. Model extrapolation to the pediatric population was assessed comparing predicted outputs with reported data [2-4]. HA incidence was predicted for each formulation under a 500q12 VPA, further stratifying by age. Our findings supported Test's objective to achieve a lower HA incidence compared to Reference (odds ratio = 0.88). They also indicated that VPA treatment was safer in pediatric patients. Interestingly, only these patients received preventive L-carnitine supplementation (CS). Moreover, women exhibited 15% higher HA incidence than men when receiving Reference. We conclude that admin-

istering an L- carnitine dose equal to double the VPA dose, with the same inter-dose interval, effectively maintains ammonia levels at baseline for adults and pediatrics. This supplementation does not significantly impact unbound VPA concentrations, indicating that the treatment efficacy should not be affected. This conclusion aligns with the preventive CS practice implemented at the Uruguayan pediatric Hospital Pereira Rossell.

References

1. A. Schiavo, C. Maldonado, M. Vázquez, P. Fagiolino, I.F. Trocóniz, M. Ibarra, Quantitative systems pharmacology Model to characterize valproic acid-induced hyperammonemia and the effect of L-carnitine supplementation, *Eur. J. Pharm. Sci.*, **183**, 106399 (2023). Doi: https://doi.org/10.1016/j.ejps.2023.106399

2. B.B. Serrano, M.J. García Sánchez, M.J. Otero, D.S. Buelga, J. Serrano, A. Domínguez-Gil, Valproate population pharmacokinetics in children, *J. Clin. Pharm. Therap.*, **24**, 73-80 (1999). Doi: https://doi.org/10.1046/j.1365-2710.1999.00202.x

3. J.C. Cloyd, An overview of antiepileptic drug therapy, *Am. J. Hosp. Pharm.*, **50**(12 SUPPL. 5), S3-S4 (1993).

4. E. Yukawa, T. Honda, S. Ohdo, S. Higuchi, T. Aoyama, Detection of carbamazepine-induced changes in valproic acid relative clearance in man by simple pharmacokinetic screening, *J. Pharm. Pharmacol.*, **47**, 751-756 (1997). Doi: https://doi.org/10.1111/j.2042-7158.1997.tb06106.x

Population pharmacokinetics of tenofovir/emtricitabine among transwomen at HIV risk on oral prep and feminizing hormone therapy: Analysis of potential interactions on prep

Vitória Berg Cattani[1]*, Emilia Jalil[1], Thiago Torres[1], Sandra Cardoso[1], Leonardo Eksterman[1], Cristiane Castro[1], Bruna Bernar Dias[2], Laila Monteiro[1], Erin Wilson[3], Bibiana Araujo[2], Valdilea Veloso[1], Beatriz Grinsztejn[1], Rita Estrela[1]

[1] Evandro Chagas National Institute of Infectious Diseases INI Fiocruz, Rio de Janeiro, Brazil

[2] Pharmacy Graduate Program, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

[3] Department of Epidemiology and Biostatistics, University of California, San Francisco, United States

*E-mail: vitoria.berg@ini.fiocruz.br

Summary

Interactions between feminizing hormone therapy (FHT) and oral pre-exposure prophylaxis (PrEP): tenofovir disoproxil fumarate (TFV) and emtricitabine (FTC) could negatively affect PrEP outcomes among transwomen [1]. We aimed to develop a PopPK model using TFV and FTC plasma PK data from our trans-specific oral PrEP study (PrEParadas) to evaluate the impact of FHT on oral PrEP PK and to estimate TFV- diphosphate and FTC-triphosphate intracellular levels. PK data (24 h) from two groups of participants (using PrEP only and using PrEP plus FHT) from the PrEParadas study was used [2]. The popPK analysis employed the software NONMEM. The final model was expanded to the peripheral blood mononuclear cell compartment using formation and elimination rate constant of metabolites previously published [3]. The model was applied to estimate TFV-diphosphate and FTC-triphosphate intracellular levels for transwomen on daily oral PrEP. A two-compartment model with first-order absorption/elimination with lag time was the best model to describe TFV and FTC PK. TFV clearance (CL/F) and volume of distribution (V/F) estimated by the model were 62.5L/h (residual standard error [RSE]: 4%) and 300L (RSE 13%), respectively. Body mass index was a significant covariate influencing CL/F. FTC CL/F and V/F estimated by the model were 21.9L/h (RSE 4%) and 80.6L (RSE 8%), respectively, and body mass index and age

were significant covariates influencing CL/F. The simulated intracellular through concentrations of TFV- DP (mean: 61 fmol/10^6 cells) was of the same order as previously published for transwomen on PrEP [3]. This suggests the potential use of this model to estimate intracellular metabolite levels among transwomen on PrEP.

Ethical approval

Institutional Review Board INI/Fiocruz (CAAE: 08405912.9.1001.5262)

Financial support and acknowledgements

CNPq; FAPERJ; Brazilian Ministry of Health (SVS-MS).

References

1. J. Yager, P.L. Anderson, Pharmacology and drug interactions with HIV PrEP in transgender persons receiving gender affirming hormone therapy, *Expert Opin. Drug Metab. Toxicol.*, **16**, 463-474 (2020). Doi: https://doi.org/10.1080/17425255.2020.1752662

2. V.B. Cattani, E.M. Jalil, L. Eksterman, T. Torres, S. Wagner Cardoso, C.R.V. Castro, L. Monteiro, E. Wilson, L. Bushman, P. Anderson, V. Gonçalves Veloso, B. Grinsztejn, R. Estrela, Impact of feminizing hormone therapy on tenofovir and emtricitabine plasma pharmacokinetics: a nested drug-drug interaction study in a cohort of Brazilian transgender women using HIV pre-exposure prophylaxis, *J. Antimicrob. Chemother.*, **77**, 2729-2729 (2022). Doi: https://doi.org/10.1093/jac/dkac229

3. A. Tanaudommongkon, A. Chaturvedula, C.W. Hendrix, E.J. Fuchs, E. Shieh, R.P. Bakshi, M.A. Marzinke, Population pharmacokinetics of tenofovir, emtricitabine and intracellular metabolites in transgender women, *Br. J. Clin. Pharmacol.*, **88**, 3674-3672 (2022). Doi: https://doi.org/10.1111/bcp.15310

New insights into the effect of VKORC1 polymorphisms on model-informed precision dosing of warfarin in Caribbean Hispanics: External validation of a population PK/PD model

Karine Rodríguez-Fernández[1], Gledys Reynaldo[2], Stephanie Reyes-González[3], Camila de las Barreras[2], Leyanis Rodríguez[4], Jorge Duconge[3]*, Victor Mangas-Sanjuan[5]

[1] Dept. of Pharmacy, Pharmaceutical Technology & Parasitology, University of Valencia, Valencia, Spain

[2] Institute of Pharmacy and Foods, University of Havana, Havana, Cuba

[3] Dept. of Pharmaceutical Sciences, School of Pharmacy, University of Puerto Rico, San Juan, PR, USA

[4] Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA

[5] Interuniversity Research Institute for Molecular Recognition and Technological Development, Polytechnic University of Valencia-University of Valencia, Valencia, Spain

*E-mail: jorge.duconge@upr.edu

Summary

Warfarin, an oral anticoagulant, has been used for decades to prevent thromboembolic events. The complex interplay between *CYP2C9* and *VKORC1* genotypes on warfarin PK and PD properties is not fully understood in special sub-groups of patients. This study aimed to externally validate a population pharmacokinetic/pharmacodynamic (PK/PD) model for the effect of warfarin on international normalized ratio (INR) and to evaluate optimal dosing strategies based on the selected covariates in Caribbean Hispanic patients [1]. INR, and *CYP2C9* and *VKORC1* genotypes from 138 patients were used to develop a population PK/PD model in NONMEM. The structural definition of a previously published PK and PD models for warfarin and INR, respectively, were implemented. Simulations were conducted to determine optimal dosing strategies for each genotype combination, focusing on achieving therapeutic INR levels. Findings revealed elevated IC50 for G/G,

G/A, and A/A *VKORC1* haplotypes (11.76, 10.49, and 9.22 mg/L, respectively), in this population compared to previous reports. The model-informed precision dosing analysis recommended daily warfarin doses of 3-5 mg for most genotypes to maintain desired INR levels, although subjects with combination of *CYP2C9* and *VKORC1* genotypes *2/*2-, *2/*3- and *2/*5-A/A would require only 1 mg daily. This research underscores the potential of population PK/PD modeling to inform personalized warfarin dosing in populations typically underrepresented in clinical studies, potentially leading to improved treatment outcomes and patient safety [2]. By integrating genetic factors and clinical data, this approach could pave the way for more effective and tailored anticoagulation therapy in diverse patient groups.

Ethical approval

The study was conducted following Helsinki's declaration for human subject protection in clinical surveys (IRB approval #A4070109).

Financial support and acknowledgements

NASA EPSCoR grant # 80 NSSC19M0148, and NIGMS-NIH grant #1R16 GM149372. We want to thank the patients for voluntarily participating in the original study where data used in this analysis were gathered.

References

1. S. Reyes-González, C. de Las Barreras, G. Reynaldo, L. Rodríguez-Vera, C. Vlaar, V. Lopez Mejia, J.C.M. Monbaliu, T. Stelzer, V. Mangas, J. Duconge, Genotype-driven pharmacokinetic simulations of warfarin levels in Puerto Ricans, *Drug Metabolism and Personalized Therapy*, **35**, 4 (2020). Doi: https://doi.org/10.1515/dmdi-2020-0135

2. K. Rodríguez-Fernández, G. Reynaldo-Fernández, S. Reyes-González, C. de Las Barreras, L. Rodríguez-Vera, C. Vlaar, J.C.M. Monbaliu, T. Stelzer, J. Duconge, V. Mangas-Sanjuan, New insights into the role of VKORC1 polymorphisms for optimal warfarin dose selection in Caribbean Hispanic patients through an external validation of a population PK/PD model, *Biomed. Pharmacother.*, **170**, 115977 (2023). Doi: https://doi.org/10.1016/j.biopha.2023.115977

Predictive performance of different published models for warfarin using a Bayesian forecasting in Mexican patients with atrial fibrillation and valve replacement

Omar Rodríguez Pérez[1]*, Juan Manuel López Quijano[2], Antonio Augusto Gordillo Moscoso[3], Rodrigo Velarde Salcedo[1], Silvia Romano Moreno[1], Rosa del Carmen Milán Segovia[1], Úrsula Fabiola Medina Moreno[2], Susanna Edith Medellín Garibay[1]

[1] Facultad de Ciencias Químicas, Universidad Autónoma de San Luis Potosí, México

[2] Cardiology Department, Hospital Central "Dr. Ignacio Morones Prieto", México

[3] Facultad de Medicina, Universidad Autónoma de San Luis Potosí, México,

*E-mail: omarloops54@gmail.com

Summary

Warfarin stands out as one of the main anticoagulant drugs used in outpatients with atrial fibrillation (AF) and valve replacement (VR) [1]. Due to its high variability, multiple population models have been published to reduce the occurrence of adverse effects and improve therapeutic target attainment [2]. Most models are built using data from European and Asian populations, evidencing the lack of models with Latin-American populations. The objective of this study was to evaluate the predictive performance of different population pharmacokinetic models using Bayesian forecasting with Abbotbase PKS v1.1.0. Seven population pharmacokinetic (PK) models reporting typical PK parameters and interindividual variability were included. Warfarin plasma concentrations were monitored in 22 outpatients (14 female) aged from 33 to 72 years with aortic and mitral valve replacement (86%) and atrial fibrillation (14%). A total of 41 warfarin plasma concentrations were measured using High Performance Liquid Chromatography (mean ±SD=2.35 ± 0.94 μg/mL). *A priori* concentration estimates were calculated for all models. Mean relative prediction error (rPE) values on each model ranged from 55% to 88% and root mean square errors (RMSE) ranged from 1.31 to 2.03 μg/mL The best fitting model was reported by Lane *et al.* (2012) [3] using age and gender as covariates. Most models showed poor predictive performance when applied to the studied population. This suggests the need to build a specific model for the Mexican population since none has yet been published.

Ethical approval

The present work was approved by: "Comité de ética en Investigación y Docencia de la Facultad de Ciencias Químicas (CEID-FCQ)" with code CEID2021-014-S and "Comité Estatal de ética en Investigación en Salud" with code SLP/09-2021.

Financial support and acknowledgements

This work was promoted by the Technological Research Council of Science for a master's fellowship (781982).

References

1. X. Li, D. Li, J.C. Wu, Z.Q. Liu, H.H. Zhou, J.Y. Yin, Precision dosing of warfarin: open questions and strategies, *Pharmacogenomics J*., **19**, 219-229 (2019). Doi: https://doi.org/10.1038/s41397-019-0083-3

2. A.K. Hamberg, M. Wadelius, J.D. Lindh, M.L. Dahl, R. Padrini, P. Deloukas, A. Rane, E.N. Jonsson, A pharmacometric model describing the relationship between warfarin dose and INR response with respect to variations in CYP2C9, VKORC1, and age, *Clin. Pharmacol. Therap.*, **87**, 727-734 (2010). Doi: https://doi.org/10.1038/clpt.2010.37

3. S. Lane, S. Al-Zubiedi, E. Hatch, I. Matthews, A.L. Jorgensen, P. Deloukas, A.K. Daly, B.K. Park, L. Aarons, K. Ogungbenro, F. Kamali, D. Hughes, M. Pirmohamed, The population pharmacokinetics of R- and S-warfarin: effect of genetic and clinical factors, *Br. J. Clin. Pharmacol.*, **73**, 66-76 (2012). Doi: https://doi.org/10.1111/j.1365-2125.2011.04051.x

Pharmacokinetic characterization of isoniazid and rifampicin treatment in tuberculosis patients from Uruguay

Andrés Baptista[1,2*], Yessica Imbriago[1,2], Patricia Rega[1,2], Marianela Lorier[1], Nicolás Dell'Oca[3], Carla Molles[3], Fernanda Domínguez[3], Daniela Guicheney[4], Camila Urroz[4], Marcia Velázquez[4], Natalia Morena[4], Mercedes Perendones[4], Mercedes Corral[5], María Buroni[5],Susana Cabrera[6], Mónica Hernández[7], Mariela Contrera[7], Eduardo Reséndiz[8], Paolo Denti[8], Manuel Ibarra[1]

[1] Department of Pharmaceutical Sciences, Faculty of Chemistry, Universidad de la República, Uruguay.

[2] Graduate Program in Chemistry, Faculty of Chemistry, Universidad de la República, Uruguay

[3] Department of Genetics, Faculty of Medicine, Universidad de la República, Uruguay

[4] Medical Clinical 2, Hospital Pasteur, Administración de los Servicios de Salud del Estado, Uruguay

[5] Intensive Care Unit, Hospital Español, Administración de los Servicios de Salud del Estado, Uruguay

[6] Infectious Diseases Department, Hospital de Clínicas, Administración de los Servicios de Salud del Estado, Uruguay

[7] Comisión Honoraria para la Lucha Antituberculosa y Enfermedades Prevalentes, Uruguay

[8] Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa

*E-mail: abaptista@fq.edu.uy

Summary

Isoniazid (INH) and rifampicin (RMP) are first-line drugs for tuberculosis (TB) treatment which exhibit high intra- and interindividual pharmacokinetic variability and potentially severe adverse effects. In Uruguay, TB has a moderately rising incidence. Delayed diagnosis, among other causes, results in high hospitalization rates and a prolonged anti- TB drug regimen [1]. In this work, we aimed to characterize INH and RMP exposure by leveraging reported population pharmacokinetic (popPK) models for INH and RMP as prior information for conducting empiric Bayesian estimation of popPK parameters. We collected plasma concentrations of INH and RMP from 97 hospitalized patients (19 critically ill) under standard treatment using a limited sampling strategy (2 samples within 1-3 and 4-6 post-dosing hours). Additionally, NAT2 gene polymorphism was determined. A two-compartment model with transit compartment absorption and linear elimination, incorporating body weight and NAT2 phenotype as covariates, was found to best describe INH concentrations [2], while a one-compartment delayed first-order absorption and linear elimination, with bodyweight as covariate, best described RMP concentrations [3]. For INH, 73% of patients achieved an AUC within the target range, with a mean value of 15.9 μg·h/mL, and 46% of patients achieved a Cmax within the range, with a mean value of 3.76 μg/mL. Meanwhile, for RMP, 92% of patients achieved an AUC within the range, with a mean value of 27.0 μg·h/mL, and 20% of patients achieved a Cmax within the range, with a mean value of 6.1 μg/mL. This represents the initial phase in implementing model-informed precision dosing to optimize anti-TB treatment in Uruguay.

Ethical approval

The study was conducted according to the ICH-GCP and the normative from the Public Health Ministry from Uruguay (decree 158/2019). Additionally, the study was done following the recommendations from the World Medical Association.

Financial support and acknowledgements

The project "Evaluación farmacoterapéutica del tratamiento antituberculoso actual con rifampicina e isoniazida en pacientes críticos y moderados" is supported by the program CSIC I+D 2020, Universidad de la República.

References

1. CHLA-EP, Situación de la tuberculosis en Uruguay, 2022, 2023.

2. P. Denti, K. Jeremiah, E. Chigutsa, D. Faurholt-Jepsen, G. PrayGod, Pharmacokinetics of isoniazid, pyrazinamide, and ethambutol in newly diagnosed pulmonary TB patients in Tanzania, *PLoS One*, **10**, e0141002 (2015). Doi: https://doi.org/10.1371/journal.pone.0141002

3. N. Rockwood, G. Meintjes, M. Chirehwa, L. Wiesner, H. McIlleron, R.J. Wilkinson, P. Denti, HIV-1 coinfection does not reduce exposure to rifampin, isoniazid, and pyrazinamide in South African tuberculosis outpatients, *Antimicrob. Agents Chemother.*, **60**, 6050-6059 (2016). Doi: https://doi.org/10.1128/AAC.00480-16

Pharmacokinetic model of lamotrigine in bipolar disease patients

Priscilla Navarro Medina[1], Elba Margarita Romero Tejeda[2], Claudia Verónica Palacios Magaña[2], Edy David Rubio Arellano[3], Jaime Carmona Huerta[3,4], Nicte Selene Fajardo Robledo[2*]

[1] Doctorado en Farmacología, CUCS, Universidad de Guadalajara, Guadalajara, Jalisco, México

[2] Departamento de Farmacobiología, CUCEI, Universidad de Guadalajara, Guadalajara, Jalisco, México

[3] Departamento de Fisiología, CUCS, Universidad de Guadalajara, Guadalajara, Jalisco, México

[4] Instituto Jaliscience de Salud Mental, Guadalajara, Jalisco, Mexico

*E-mail: nicte.fajardo@academicos.udg.mx

Summary

Lamotrigine (LMT), a phenyltriazine derivative approved as anticonvulsant drug [1]. In bipolar disease (BD), the interest of LMT is as a mood stabilizer, and came from limited but robust evidence of its efficacy in the prevention of mood relapses. However, as the molecular pathogenesis and mechanistic basis of mood stabilizer strategies of BD are poorly understood [2] it is important to know course of the drug for better comprehension. In our study we included nineteen ongoing patients, Mexican women from the psychiatry service of the Mental Health Institute (SALME), the mean age was 36.4 ± 9.94 years old. They were diagnosed with Bipolar Disease type I according to the DMS IV criteria. We obtain a total of thirty-one blood samples from different times in a period of 1-3 months after treatment with 200 mg standard dose of LMT. The model was developed using MONOLIX v. 2021R1. The final model described a one- compartment model with an absorption and elimination first-order process. The residual error model was described as proportional. Given the trough steady-state, we could estimate the following parameters and RSE%. V/F = 91.33 L (13.0%) weight was added as a covariate, CL/F = 3.98 L/h (78.9%), while the absorption rate constant (ka) was set at literature values of 3.5 h^{-1} [3]. As the pharmacokinetic profile, this drug has been studied

as an epileptic drug, it is essential to propose a pharmacokinetic model of LMT in patients with bipolar disease that helps to describe and comprehend the course of the drug in this disease.

Ethical approval

This study was approved by the ethics committee "Comité de Ética en Investigación del Instituto Jalisciencie de Salud Mental" under registration number 198.

Financial support and acknowledgements

This study was developed with the financial support of the "Programa de Apoyo a la Mejora en las Condiciones de Producción de los Miembros del Sistema Nacional de Investigadores y del Sistema Nacional de Creadores de Arte (SNCA) de la Universidad de Guadalajara".

References

1. J.P. Rissardo, A.L. Fornari-Caprara, Lamotrigine-associated movement disorder: A literature review, *Neurol. India*, **69**, 1524-1538 (2021). Doi: https://doi.org/10.4103/0028-3886.333440

2. S.I. Rapoport, M. Basselin, H.W. Kim, J.S. Rao, Bipolar disorder and mechanisms of action of mood stabilizers, *Brain Res. Rev.*, **61**, 185-209 (2009). Doi: https://doi.org/10.1016/j.brainresrev.2009.06.003

3. V. Chan, R.G. Morris, K.F. Ilett, S.E. Tett, Population pharmacokinetics of lamotrigine, *Ther. Drug Monit.*, **23**, 630-635 (2001). Doi: https://doi.org/10.1097/00007691-200112000-00006

Population pharmacokinetic model of cefepime in adults with hematological malignancies and febrile neutropenia after chemotherapy

Daniel S. Parra[1*], José C. Álvarez[2,3], Sonia I. Cuervo[2,3,4#], Edelberto Silva[1,3], Jorge A. Díaz[1,3,5], Lorena L. Jiménez[3,4], Julio C. Gómez[3,4], Ricardo Sánchez[2,3,4], Jorge A. Cortés[2,5]

[1] Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia, Bogotá, Colombia

[2] Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, Colombia

[3] Grupo en Enfermedades Infecciosas en Cáncer y Alteraciones Hematológicas (GREICAH), Universidad Nacional de Colombia, Bogotá, Colombia

[4] Instituto Nacional de Cancerología (INC)—Empresa Social del Estado, Bogotá, Colombia

[5] Grupo de Investigación en Enfermedades Infecciosas, Facultad de Medicina, Universidad Nacional de Colombia, Bogotá, Colombia

[*]E-mail: dsparrag@unal.edu.co; [#]E-mail: sicuervom@unal.edu.co

Summary

Chemotherapy-induced febrile neutropenia (CIFN) induces physiological alterations with potential implications for antibiotic pharmacokinetics (PK), possibly resulting in suboptimal drug exposure and reduced effectiveness. The pharmacokinetics of cefepime (FEP) was investigated in an open-label, non-randomized, observational study. Patients with CIFN received cefepime in a dose of 2 g IV every 8 hours as 30-minute infusions. Plasma concentrations of FEP were determined using a microbiological assay. A two-compartment population PK model appropriately described the data, ith individual clearance dependent on serum creatinine levels. Monte Carlo simulation was employed to evaluate and compare various dosing regimens with different minimum inhibitory concentration (MIC) values, related to resistance cut-off points for Enterobacteriaceae. According to the simulations, increasing the daily dose of cefepime beyond 6 g daily was unnecessary to achieve a probability of target attainment (PTA) ≥ 90%. Cumulative fraction of response

(CFR) with intermittent dosing was suboptimal for empirical therapy regimens against *K. pneumoniae* and *P. aeruginosa*. Continuous infusions could be utilized in this setting to maximize exposure. Patients with high serum creatinine levels were more likely to achieve predefined pharmacokinetic/pharmacodynamic (PK/PD) targets compared to patients with low levels.

Ethical approval

All participants provided informed consent before joining the study. The research adhered to the Declaration of Helsinki and was approved by the Ethics Committee of the Faculty of Medicine at Universidad Nacional de Colombia (code: CE-005/024-14, approved on 10 April 2014) and the Institutional Review Board of Instituto Nacional de Cancerología (code: INT-OFI-006567-2014, approved on 17 September 2014).

Financial support and acknowledgements

We received support from the National Cancer Institute and obtained project funding from Inversión Nación, identified with SAP code C41030110-012. Additionally, the National University of Colombia provided resources for the project through an inter-institutional agreement between two state public institutions.

References

1. O. Lortholary, A. Lefort, M. Tod, A.M. Chomat, C. Darras-Joly, C. Cordonnier, Pharmacodynamics and pharmacokinetics of antibacterial drugs in the management of febrile neutropenia, *The Lancet: Infectious Diseases*, **8**, 612-620 (2008). Doi: https://doi.org/10.1016/S1473-3099(08)70228-7

Noncompartmental pharmacokinetic analysis of isosorbide-5-mononitrate in healthy Mexican volunteers

Ivette Guadalupe Herrera Pérez[1]*, Malena Veloz Domínguez[1], Juan Luis Gutiérrez Velázquez[1], Luis Eligio Chable Cen[1], Juan Ernesto Dávila Romero[1], Héctor Manuel González Martínez[1]

[1] Department of development and validation, Unidad Analítica, Laboratorio Cinasi S. A. de C. V., Tlaquepaque, Jalisco, México

*E-mail: ivette.hpz96@gmail.com

Summary

Oral formulations of isosorbide-5-mononitrate (5-ISMN) emerge as a treatment option for patients with angina pectoris to minimize the problems associated with isosorbide dinitrate, such as a longer elimination half-life, no first-pass metabolisms, and it has prolonged therapeutic effects and reproducible clinical effects [1, 2]. This study aimed to develop and validate a UPLC-MS/MS method for quantifying 5-ISMN in human plasma and demonstrate its application in a pilot study through noncompartmental pharmacokinetic (PK) analysis. The method adhered to national [3] regulations. This method was successfully applied to determine 5-ISMN in samples from six healthy Mexican volunteers after an oral single- dose of 60 mg. Noncompartmental PK analysis, executed with Phoenix WinNonlin software. The media ± standard deviation or median (interval) values of Cmax, Tmax, AUC0∞, clearance, half-life and elimination constant were 620.80 ± 159.35 ng/mL, 3.83 ± 0.81 h, 9560.00 ± 2693.00 (h·ng/mL), 6.84 (6.18 – 10.01) L/h and 0.1015 (0.07 – 0.11) h^{-1}, respectively. Before initiating a crucial bioequivalence study, it is advisable to conduct a preliminary investigation known as a pilot study. This preliminary study serves multiple purposes, including validating analytical methods, evaluating variability in PK, determining the required sample size for sufficient statistical power, and refining the timing of sample collection intervals. In conclusion, this information can be used to establish pharmacokinetic profiles to assess new formulations and facilitate the development of a bioequivalence study.

Ethical approval

The present work was approved by "Comité de ética en investigación y comité de investigación" with registration CONBIOETICA-19-CEI-009-20160729.

Financial support and acknowledgements

This project did not receive financial support from any institution.

References

1. T. Kosoglou, J.E. Patrick, A. Cohen, E. Radwanski, D. Christopher, M.B. Affrime, Pharmacokinetics of isosorbide-5-mononitrate after oral administration of an extended-release mononitrate formulation versus a standard dinitrate formulation, *Journal of Clinical Therapeutics*, **17**, 241-251 (1995). Doi: https://doi.org/10.1016/0149-2918(95)80022-0

2. Y. Zhou, A. Liu, R. Jia, M. Wu, N. Wu, C. Liu, Z. Han, H. Hu, H. Wang, Q. He, Determination of isosorbide-5-mononitrate in human plasma by high-performance liquid chromatography-tandem mass spectrometry and its application to a bioequivalence study, *Journal of Analytical Methods in Chemistry*, **2020**, 1753265 (2020). Doi: https://doi.org/10.1155/2020/1753265

3. Secretaría de salud, Diario Oficial de la Federación, México, 2013.

Impact of chromosomal translocations and transporter polymorphisms on population pharmacokinetics of methotrexate in children with acute lymphoblastic leukemia

Fausto Zaruma Torres[1*], Maritza Ochoa Castro[1], Enmanuel Guerrero[2,3], Andrés Andrade[2,3], Adriana Orellana[2], Catherine Acurio[4], Soledad Jiménez[4], Geovanny Barrera[5] Rodrigo Caroca[5]

[1] College of Chemical Sciences – Universidad de Cuenca, Cuenca, Ecuador

[2] College of Medical Sciences, Universidad de Cuenca, Ecuador, Cuenca, Ecuador

[3] Cancer Fighting Society Institute, Cuenca, Ecuador

[4] Cancer Fighting Society Institute, Loja, Ecuador

[5] Department of Biology, Universidad del Azuay, Cuenca, Ecuador

*E-mail: fausto.zaruma@ucuenca.edu.ec

Summary

Acute lymphoblastic leukemia (ALL) stands as the most prevalent malignant neoplasm within the pediatric population in Ecuador [1-3]. Its treatment requires high doses of methotrexate (HDMTX), whose pharmacokinetics might be influenced by chromosomal translocations (ChTr) and transporter polymorphisms. The aim of this research is to ascertain the correlation between chromosomal translocations and transporter polymorphisms with methotrexate pharmacokinetics (MTX) [2-4]. A prospective study was conducted involving 48 children (aged 1 to 17 years) diagnosed with ALL, who were treated at SOLCA Hospitals in Cuenca, Loja and Machala. These patients received HDMTX through slow infusion over 24 hours during the maintenance phase. Chromosomal translocations *12/21, 1/19* were identified using karyotype analysis, while genetic polymorphisms ABCB1*rs1128503, rs*1045642 were assessed through qPCR. Plasma concentrations of MTX were determined using enzyme immunoassay. Population pharmacokinetic (PopPK) analysis was performed using Monolix_Suite v2023R1 software, assessing the impact of covariates on intercompartmental clearance (CL), central distribution volume (V1), and peripheral distribution volume (V2). The structural two-compartment model was employed, and covariates related to both translocations

and polymorphisms did not influence. However, gender had an impact on V1 (L) = 0.59, CL (L/h) =1.02, Q (L/h) =0.04, V2 (L) = 0.0005. The results obtained indicated no association with *rs1045642*, consistent with findings in other studies [5-8], although some suggest a decrease in CL. Regarding chromosomal translocations, there are no studies related to PopPk of MTX. No association was found between the mentioned polymorphisms or ChTr and the PopPk of methotrexate. Only V1 was associated with gender, which should be considered for dose adjustments.

Ethical approval

This study was approved by the Research Ethics Committee on Human Subjects of the University of San Francisco De Quito, Quito-Ecuador (approval 2017-106E).

Financial support and acknowledgements

This work was carried out within the framework of funding provided by the University of Cuenca (UCuenca). We acknowledge the participation and support of SOLCA – Cuenca, SOLCA – Machala, SOLCA – Loja.

References

1. M. Lejman, A. Chałupnik, Z. Chilimoniuk, M. Dobosz, Genetic biomarkers and their clinical implications in B-cell acute lymphoblastic leukemia in children, *Int. J. Mol. Sci.*, **23**, 2755 (2022). Doi: https://doi.org/10.3390/ijms23052755

2. D. Bhojwani, N.D. Sabin, D. Pei, J.J. Yang, R.B. Khan, *et al.*, Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia, *J. Clin. Oncol.*, **32**, 949-959 (2014). Doi: https://doi.org/10.1200/JCO.2013.53.0808

3. G. Gervasini, S. Mota-Zamorano, Clinical implications of methotrexate pharmacogenetics in childhood acute lymphoblastic leukaemia, *Curr. Drug Metab.*, **20**, 313-330 (2019). Doi: https://doi.org/10.2174/1389200220666190130161758

4. L. Zhan, J. Lian, H. Jin, S. Wang, J. Ding, Z. Shao, ABCB1 polymorphisms and childhood acute lymphoblastic leukemia risk: A meta-analysis, *Crit. Rev. Eukaryot. Gene Expr.*, **27**, 173-181 (2017). Doi: https://doi.org/10.1615/CritRevEukaryotGeneExpr.2017019077

5. M. Hegyi, A. Arany, A.F. Semsei, K. Csordas, O. Eipel, A. Gezsi, N. Kutszegi, M. Csoka, J. Muller, D.J. Erdelyi, P. Antal, C. Szalai, G.T. Kovacs, Pharmacogenetic analysis of high-dose methotrexate treatment in children with osteosarcoma, *Oncotarget*, **8**, 9388-9398 (2017). Doi: https://doi.org/10.18632/oncotarget.11543

6. Y. Cheng, M.H. Chen, Q. Zhuang, B.J Lin, Y.Y. Chen, L. Yang, M.B. Liu, W.C Que, H.Q. Qiu, Genetic factors involved in delayed methotrexate elimination in children with acute lymphoblastic leukemia, *Pediatr. Blood Cancer*, **68**, e28858 (2021). Doi: https://doi.org/10.1002/pbc.28858

7. Radtke, O. Zolk, B. Renner, M. Paulides, M. Zimmermann, A. Möricke, M. Stanulla, M. Schrappe, T. Langer, Germline genetic variations in methotrexate candidate genes are associated with pharmacokinetics, toxicity, and outcome in childhood acute lymphoblastic leukemia, *Blood*, **121**, 5145-5153 (2013). Doi: https://doi.org/10.1182/blood-2013-01-480335

8. B. Faganel Kotnik, I. Grabnar, P. Bohanec Grabar, V. Dolžan, J. Jazbec, *Eur. J. Clin. Pharmacol.*, **67**, 993-1006 (2011). Doi: https://doi.org/10.1007/s00228-011-1046-z

A posteriori pharmacokinetic analysis in pediatric patients with acute lymphoblastic leukemia at high-dose methotrexate. Proof of concept

Juan Antonio Garzón Lamarque[1]*, Monzerrat Pardo Zepeda[2], Ana Rosa Rincón Sánchez[1], Hugo Romo Rubio[2], Fernando Sánchez Zubieta[2], Elba Margarita Romero Tejeda[3]

[1] University Center of Health Sciences (CUCS), University of Guadalajara, Guadalajara, Jalisco, Mexico

[2] Pharmacological Research Laboratory, Pediatric Oncology and Hematology Service, Hospital Civil de Guadalajara "Juan I. Menchaca" (HCJIM), Guadalajara, Jalisco, Mexico

[3] University Center of Exact Sciences and Engineering, University of Guadalajara, Guadalajara, Jalisco, Mexico

*E-mail: juan.garzon9902@alumnos.udg.mx

Summary

Methotrexate (MTX) is used to treat a variety of diseases, including lupus, arthritis, and acute lymphoblastic leukemia (ALL) [1]. The therapeutic range of MTX is highly narrow; therefore, it is necessary to maintain therapeutic concentrations to avoid the induction of hepatic and pulmonary abnormalities and myelosuppression [2]. A previously established population pharmacokinetic (popPK) model was utilized to describe the drug's time course in our patients, and a posteriori method was used to estimate typical parameters due to the limited data reported by the Hematology-oncology service of the HCJIM. Retrospective, observational, and descriptive study was performed to determine pediatric patients' clinical and anthropometric characteristics. Available concentrations of MTX infused at 2-5 g/m^2 in the plasma of 25 patients with ALL between 24 to 72 hours post-dose were determined using the ELISA technique. Sixty-six concentrations of MTX were recovered from clinical records from 2018 to 2022.The a posteriori analysis was performed with the program Monolix 2023R1 (Lixoft, France), based on the two-compartment model described by Oliveira (Cl = 7.66 L/h, V1 = 26.8 L, V2 = 8.47 L, Q = 0.218 L/h) that include as covariates renal function and factors related to body size [3]. Visual prediction checks and individual prediction graphs were performed.

Our patients' concentrations were within the 90% confidence interval of the predictions, concluding that the model's covariates improved its performance. Future prospective studies are required to develop a popPK approach in our patients to explain the time course of the drug's process in the body and link it to its therapeutic effects using a PK/PD model.

Ethical approval

This study received approval from the Ethics, Research, and Biosafety Committees of CUCS opinion CI-06323 and HCJIM with registration number 0650/23 HCJIM/2023.

Financial support and acknowledgements

We thank the Hospital Civil de Guadalajara "I. Menchaca" for providing the financial, human resources, and infrastructure necessary to implement this work.

References

1. F. Karami, S. Ranjbar, Y. Ghasemi, M. Negahdaripour, Analytical methodologies for determination of methotrexate and its metabolites in pharmaceutical, biological and environmental samples, *Journal of Pharmaceutical Analysis*, **9**, 373-391 (2019). Doi: https://doi.org/10.1016/j.jpha.2019.06.001

2. Z.L. Taylor, J. Vang, E. Lopez-Lopez, N. Oosterom, T. Mikkelsen, L.B. Ramsey, Systematic review of pharmacogenetic factors that influence high-dose methotrexate pharmacokinetics in pediatric malignancies, *Cancers*, **13**, 2837 (2021). Doi: https://doi.org/10.3390/cancers13112837

3. P. Oliveira-Henz, A. Valle-Pinhatti, L.J. Gregianin, M. Martins, M. Curra, B. Verlindo de Araújo, T. Dalla-Costa, *Pharmaceutical Research*, **40**, 1777-1787 (2023) Doi: https://doi.org/10.1007/s11095-023-03544-7

Population pharmacokinetics of tacrolimus after long-term use in adult transplant recipients in Colombia

Ivone E. Jimenez[1], Andrés Hincapié[1], María A. Montoya-Giraldo[1], Andres F. Zuluaga[1]*

[1] Departamento de Farmacologia y Toxicologia, Laboratorio Integrado de Medicina Especializada, Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia

*E-mail: andres.zuluaga@udea.edu.co

Summary

Tacrolimus, an immunosuppressant used after organ transplantation, exhibits significant pharmacokinetic variability. Population pharmacokinetic (pop-PK) models have been established to study this variability, but most focus on early liver and renal transplants. This study aimed to address the gap in knowledge by developing a nonparametric pop-PK model for tacrolimus in adult patients four and two-thirds years post-transplant. The model development utilized intensive sampling data (6 samples per day) from 9 patients. A three-compartment model with first-order absorption best described the data. Body mass index (BMI), hematocrit, time since transplant, and CYP3A5 and ABCB genotypes were identified as significant covariates influencing drug clearance and distribution volumes (allometrically scaled to BMI). The final model yielded an R-squared of 0.37, indicating a moderate fit between predicted and observed values. Additionally, the model exhibited a bias of 0.151 and an imprecision of 2.05. The final mean parameter estimates included apparent clearance (CL/F) of 0.03 L/h, apparent central volume (V/F) of 0.12 L, apparent peripheral volume (Vp/F) of 3.86 L, relative bioavailability, and absorption rate constant (Ka) of 0.42 h. While this model demonstrates potential for individualized dosage predictions, further validation with additional data and prospective evaluation are necessary.

Ethical approval

The ethical committee of the Hospital Alma Mater of Antioquia approved the study

Financial support and acknowledgements

This study was supported by MINCIENCIAS, grant number 111589786169

References

1. A. Åsberg, K. Midtvedt, M. van Guilder, E. Størset, S. Bremer, S. Bergan, R. Jelliffe, A. Hartmann, M.N. Neely, Inclusion of CYP3A5 genotyping in a nonparametric population model improves dosing of tacrolimus early after transplantation, *Transplant International*, **26**, 1198-1207 (2013). Doi: https://doi.org/10.1111/tri.12194

2. O. Campagne, D.E. Mager, K.M. Tornatore, Population pharmacokinetics of tacrolimus in transplant recipients: What did we learn about sources of interindividual variabilities? *J. Clin. Pharmacol.*, **59**, 309-325 (2019). Doi: https://doi.org/10.1002/jcph.1325

Population pharmacokinetic modeling of oral acetaminophen in healthy adults with and without obesity in Medellin, Colombia

Andres F. Zuluaga[1]*, Ivone Jiménez[1], Andrés Hincapié[1], Héctor Pérez[1], Maria A. Montoya[1], Carolina Rosero[1], Laura Vargas[1]

[1] Departamento de Farmacología y Toxicología, Laboratorio Integrado de Medicina Especializada (LIME), Facultad de Medicina, Universidad de Antioquia, Medellín, Colombia

*E-mail: andres.zuluaga@udea.edu.co

Summary

Acetaminophen remains a first-line analgesic for children and adults. Clearance (CL) and volume of distribution (Vd), which determine dosage, may differ in obese compared to non-obese individuals, suggesting at least two subpopulations better described by non-parametric approaches. We aimed to determine the population pharmacokinetics of acetaminophen in adults with and without obesity after an oral dose of 1000 mg, evaluating whether body composition affects drug kinetics. Twenty-four adults were recruited. Blood samples were collected at 0, 15, 30, 60, 90, 120, and 360 minutes after acetaminophen administration. Plasma concentrations were measured using a validated high-performance liquid chromatographic assay with ultraviolet detection. Data were analyzed using Pmetrics. A total of 144 samples were used, resulting in 21 support points. A two-compartment pharmacokinetic model with first-order elimination better described drug kinetics (R2 = 0.96 for individual obs-pred plot). Several subpopulations were identified comparing obese and non-obese populations. Fat mass was the best covariate to describe acetaminophen CL, which was 48.3 L/h/70 kg. Volume of central and peripheral compartments were 4.3 and 71.2 L, respectively. Absorption lag time and bioavailability were 13 minutes and 86%, respectively. Fat mass was an important covariate for describing acetaminophen pharmacokinetics. Dosing of acetaminophen in obese patients should consider population pharmacokinetic parameters.

Ethical approval

The protocol adhered to the principles of the Declaration of Helsinki and was reviewed, approved, and supervised by the Hospital Universitario San Vicente Fundación Ethics Committee.

Financial support and acknowledgements

This project was funded by Minciencias (Colombian Ministry of Science and Technology), grant 111589786169, and by the University of Antioquia, grant 2020-36930

References

1. J.D. Morse, I. Stanescu, H.C. Atkinson, B.J. Anderson, *Eur. J. Drug Metab. Pharmacokin.*, **47**, 497-507 (2022). Doi: https://doi.org/10.1007/s13318-022-00766-9

2. M.N. Neely, M.G. van Guilder, W. Yamada, A. Schumitzky, R. Jelliffe, Accurate detection of outliers and subpopulations with Pmetrics, a nonparametric and parametric pharmacometric modeling and simulation package for R, *Ther. Drug Monit.*, **34**, 467-476 (2012). Doi: https://doi.org/10.1097/FTD.0b013e31825c4ba6

In-vitro study of red blood cell-plasma partitioning of first-line anti-tuberculosis drugs and its relevance for model-informed precision dosing through dried blood spot sampling

Rodrigo Velarde Salcedo[1]*, Ivette Guadalupe Herrera Pérez[1], Cristian Jazmín Rodríguez Pinal[1], Arturo Ortiz Álvarez[2], Rosa del Carmen Milán Segovia[1], Silvia Romano Moreno[1], Susanna Edith Medellín Garibay[1]

[1] Facultad de Ciencias Químicas, Universidad Autónoma de Potosí, San Luis Potosí, SLP., México

[2] Hospital Central "Dr. Ignacio Morones Prieto", San Luis Potosí, SLP., México

*E-mail: rvelardesal@gmail.com

Summary

Model-informed precision dosing (MIPD) plays a key role in the success of tuberculosis (TB) treatment with first-line drugs (rifampicin – RIF, isoniazid – INH, ethambutol – ETB and pyrazinamide – PZA). While MIPD is traditionally performed with plasma drug concentrations, Dried Blood Spots (DBS) quantification is an increasingly popular alternative. However, plasma and DBS concentrations are non-concordant [1] and plasma therapeutic targets cannot be used to interpret DBS concentrations, limiting its applications in MIPD. Nonetheless, differences between DBS and plasma concentrations can be explained by drug partitioning between red blood cells and plasma. In this study the red blood cell / plasma partition coefficient ($K_{rbc/p}$) of first-line anti-TB drugs was estimated *in-vitro* to correct DBS concentrations. Spiked whole blood samples were incubated at 37 °C for 2 hours to obtain $K_{rbc/p}$ values through LC-MS/MS analysis [2]. Mean $K_{rbc/p}$ values were 1.02 ± 0.49 for RIF, 1.30 ± 0.33 for INH, 2.75 ± 0.37 for ETB and 1.05 ± 0.12 for PZA. $K_{rbc/p}$ was concentration-dependent for ETB and hematocrit- dependent for RIF. Drug concentrations were quantified on plasma and DBS samples from 15 TB patients and $K_{rbc/p}$ values were used to correct DBS concentrations [3]. Assessment with Bland-Altman plots showed good agreement between corrected DBS concentrations and plasma concentrations. Passing-Bablok regressions revealed concordance between concentrations in both matrices (except for RIF). This improvement in agreement indicates that $K_{rbc/p}$ estimation is important for pharmacometrics applications of DBS sampling, particularly for substituting plasma sampling for MIPD purposes.

Ethical approval

This study protocol was approved by the Research Committee and Ethics in Research Committee of *Hospital Central "Dr. Ignacio Morones Prieto"* (Registration number: 67- 21).

Financial support and acknowledgements

A doctorate fellowship was awarded to Rodrigo Velarde Salcedo (Grant No, 834558) by Mexico's National Council of Humanities, Science and Technology (CONAHCyT).

References

1. I.G. Herrera-Pérez, A.S. Rodríguez-Báez, A. Ortiz-Álvarez, R. Velarde-Salcedo, F.J. Arriaga-García, C.J. Rodríguez-Pinal, S. Romano-Moreno, R.C. Milán-Segovia, S.E. Medellín-Garibay, Standardization and validation of a novel UPLC-MS/MS method to quantify first line anti-tuberculosis drugs in plasma and dried blood spots, *Journal of Chromatography B*, **1228**, 123801 (2023). Doi: https://doi.org/10.1016/j.jchromb.2023.123801

2. S. Yu, S. Li, H. Yang, F. Lee, J.T. Wu, M.G. Qian, A novel liquid chromatography/tandem mass spectrometry based depletion method for measuring red blood cell partitioning of pharmaceutical compounds in drug discovery, *Rapid Communications in Mass Spectrometry*, **19**, 250-254 (2005). Doi: https://doi.org/10.1002/rcm.1777

3. C. Linder, K. Wide, M. Walander, O. Beck, L.L. Gustafsson, A. Pohanka, Comparison between dried blood spot and plasma sampling for therapeutic drug monitoring of antiepileptic drugs in children with epilepsy: A step towards home sampling, *Clinical Biochemistry*, **50**, 418-424 (2017). Doi: https://doi.org/10.1016/j.clinbiochem.2016.12.008