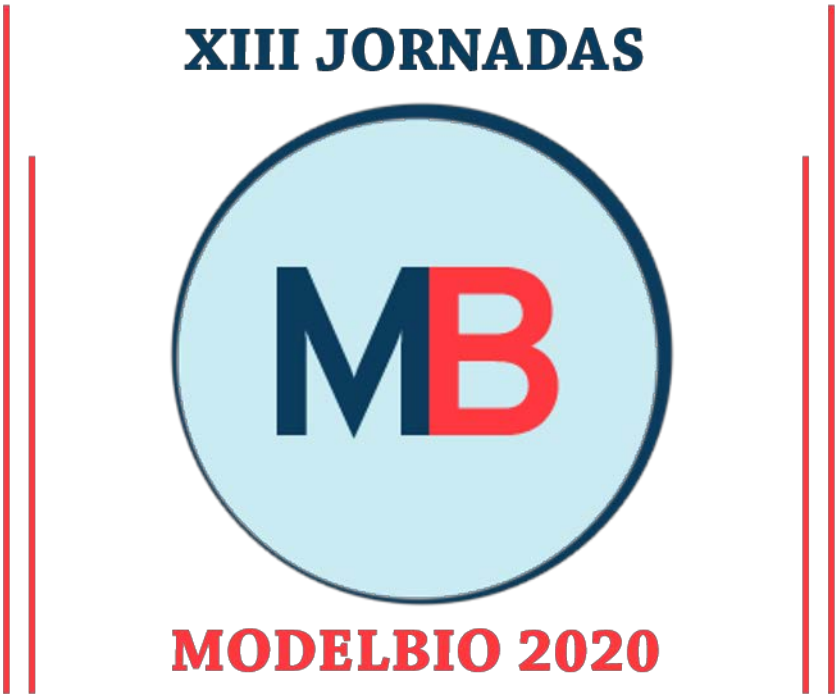
XIII Jornadas de Modelización y Simulación en Biomedicina



25-26 de noviembre de 2020

PRESENTACIÓN

Estimados compañeros y compañeras:

Es un honor daros la bienvenida a las XIII Jornadas de Modelización y Simulación en Biomedicina, que en este 2020 debían celebrarse en la Facultad de Farmacia de la Universidad del País Vasco UPV/EHU en Vitoria-Gasteiz, pero debido a la situación derivada de la pandemia por COVID-19 hemos tenido que transformar en un encuentro virtual. En estas circunstancias el comité organizador y el comité científico han trabajado con la misma ilusión y ganas para poder ofreceros un programa y un punto de encuentro interesante.

Quisiera dar las gracias a la UPV/EHU por su soporte y el apoyo técnico para poder llevar a cabo este evento, al grupo PharmaNanoGene por ofrecer su tiempo y esfuerzo y al comité científico por su trabajo para elaborar este programa.

Agradezco asimismo tener la oportunidad de contar con vuestra participación y confío en que sea una experiencia positiva y enriquecedora para todos y todas.

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Bienvenidos a MODELBIO 2020

PROGRAMA

Miércoles 25 de noviembre de 2020

15.45-16.00	**ACTO INAUGURAL** Excmo. Sr. Jon Zarate Sesma , Vicerrector de Euskera y Formación Continua
16.00-16.30	**SESIÓN DOCENTE** ***Moderadora: Alicia Rodríguez Gascón*** **IN BETWEEN THE TOP-DOWN AND BOTTOM-UP APPROACHES IN BUILDING PREDICTIVE PHARMACOKINETIC MODELS** Iñaki F. Trocóniz, Universidad de Navarra
16.30-17.15	**MODELING AND SIMULATION IN DRUG DEVELOPMENT. PRECLINICAL M&S (I)** ***Moderadora: Isabel González Álvarez*** **PBPK MODELING AND QUANTITATIVE STRUCTURE-PROPERTY RELATIONSHIPS TO PREDICT DRUG DELIVERY TO THE BRAIN** Bárbara Sánchez-Dengra, Universidad Miguel Hernández **PRECLINICAL CHARACTERIZATION OF PLASMA PROTEIN AND TISSUE BINDING OF AMIODARONE USING A POPULATION APPROACH** Karine Rodriguez-Fernandez, Universidad de Valencia **IMPLEMENTING A PHARMACOKINETIC MODEL FOR THE EVALUATION OF DRUG RELEASE FROM COATED MATRIX TABLETS** Roberto Arévalo-Pérez, Universidad de Salamanca
17.15-17.30	Pausa
17.30-18.15	**MODELING AND SIMULATION IN DRUG DEVELOPMENT. PRECLINICAL M&S (II)** ***Moderador: Carlos Fernández Teruel*** **PHARMACODYNAMIC MODELLING AND SIMULATION OF AMPHOTERICIN B TIME-KILL CURVES AGAINST *CANDIDA AURIS*** Unai Caballero, Universidad del País Vasco UPV/EHU **PHYSIOLOGICALLY-BASED PHARMACOKINETIC/PHARMACODYNAMIC MODEL OF MBQ-167 TO PREDICT TUMOR GROWTH INHIBITION IN MICE** Javier Reig-López, Universidad de Valencia **MECHANISM-BASED CHARACTERIZATION OF COMBINATION TREATMENTS IN IMMUNONCOLOGY** Aymara Sancho Araiz, Universidad de Navarra
18.15-18.30	Pausa
18.30-19.00	**CLINICAL APPLICATIONS OF POPULATION PHARMACOKINETIC MODELS (I)** ***Moderadora: Dolors Soy Muner*** **DEVELOPMENT OF A PHARMACOKINETIC MODEL TO ADJUST INTRADUODENAL ADMINISTRATION IN HUMANS** Alejandro Ruiz-Picazo, Universidad Miguel Hernández **APPLICATION OF A DUAL PBPK-POPPK MODEL BASED APPROACH ACROSS THE AGE-POPULATION OF ADULTS USING BILASTINE AS A PROBE DRUG** Valentina Lo Re, Universidad del País Vasco UPV/EHU; Dynakin S.L. Chaejin Kim, University of Florida

Jueves 26 de noviembre de 2020

16.00-16.45	**CLINICAL APPLICATIONS OF POPULATION PHARMACOKINETIC MODELS (II)** ***Moderador: J Samuel Pérez-Blanco*** **EVALUATION OF THE PREDICTIVE PERFORMANCE OF TWO POPULATION PHARMACOKINETIC MODELS OF VEDOLIZUMAB IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE** Silvia Márquez-Megías, Universidad Miguel Hernández **POPULATION PHARMACOKINETIC MODEL OF CEFTRIAXONE IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK AND CONTINUOUS VENO-VENOUS HEMODIAFILTRATION** Carla Bastida, Universidad de Barcelona **POPULATION PHARMACOKINETIC MODEL OF LEVETIRACETAM IN CRITICALLY ILL PATIENTS: ARE WE UNDERDOSING OUR PATIENTS?** Idoia Bilbao-Meseguer, Hospital Universitario Cruces; Universidad del País Vasco UPV/EHU
16.45-17.00	Pausa
17.00-17.30	**CLINICAL APPLICATIONS OF PHARMACODYNAMIC MODELING (I)** ***Moderador: Ignacio González-García*** **MODELING CARDIAC EFFECTS OF INVESTIGATIONAL COVID-19 TREATMENTS** Itziar Irurzun-Arana, Icahn School of Medicine at Mount Sinai, New York; AstraZeneca **ASSOCIATION BETWEEN HETEROGENEITY OF INDIVIDUAL TUMOR LESIONS AND OVERALL SURVIVAL ASSESSED BY MACHINE LEARNING IN FOUR METASTATIC COLORECTAL CANCER CLINICAL STUDIES** Diego Vera-Yunca, Universidad de Navarra; Merck Institute for Pharmacometrics; Instituto de Investigación Sanitaria de Navarra IdiSNA
17.30-18.00	**CLINICAL APPLICATIONS OF PHARMACODYNAMIC MODELING (II)** ***Moderador: Ricardo Nalda Molina*** **PHARMACODYNAMIC MODELLING OF MOVEMENT RESPONSE AFTER NOXIOUS STIMULUS IN PATIENTS UNDERGOING SURGERY** Nicolás Marco-Ariño, Universidad de Navarra; Instituto de Investigación Sanitaria de Navarra IdiSNA **QUANTITATIVE ASSESSMENT OF THE EXPOSURE-EFFICACY RELATIONSHIP USING MARKOVIAN ELEMENTS IN GAUCHER PATIENTS** Victor Mangas Sanjuan, Universidad de Valencia; Interuniversity Institute of Recognition Research Molecular and Technological Development
18.00-18.15	Pausa
18.15-18.45	**PONENCIA** ***Moderadora: Zinnia Parra Guillén*** **POPULATION PHARMACOKINETICS AND INTEGRATED EXPOSURE-RESPONSE ANALYSIS OF EFFICACY AND SAFETY WITH LURBINECTEDIN TO SUPPORT THE DOSE REGIMEN IN SMALL CELL LUNG CANCER** Carlos Fernández Teruel, AstraZeneca
18.45-19.00	**ENTREGA DE PREMIOS Y CLAUSURA**
19.00-20.00	**ASAMBLEA**

COMITÉ CIENTÍFICO

Carlos Fernández Teruel. AstraZeneca
Isabel González Álvarez. Universidad Miguel Hernández
Ignacio González-García. AstraZeneca
Arantxa Isla Ruiz. Universidad del País Vasco UPV/EHU
Ricardo Nalda Molina. Universidad Miguel Hernández
Zinnia Parra Guillén. Universidad de Navarra
J Samuel Pérez-Blanco. Universidad de Salamanca
Dolors Soy Muner. Hospital Clínico de Barcelona

COMITÉ ORGANIZADOR

Arantxa Isla Ruiz
Alicia Rodríguez Gascón
María Ángeles Solinís Aspiazu
Ana del Pozo Rodríguez

INDICE DE COMUNICACIONES

1 PBPK MODELING AND QUANTITATIVE STRUCTURE-PROPERTY RELATIONSHIPS TO PREDICT DRUG DELIVERY TO THE BRAIN

PONENTE: Bárbara Sánchez-Dengra

Ha estudiado Farmacia y un Máster en Biotecnología y Bioingeniería en los que, en ambos casos, fue primera de su promoción y premio extraordinario. Actualmente, es becaria FPU y se encuentra desarrollando su proyecto de tesis, como investigadora predoctoral en el grupo de "Optimización Biofarmacéutica y Disolución Biopredictiva" dirigido por la profesora Marival Bermejo de la Universidad Miguel Hernández. Además, ha realizado varias estancias internacionales y nacionales en las que ha trabajado en el desarrollo de nuevas formulaciones para la administración controlada de fármacos.

1 PBPK MODELING AND QUANTITATIVE STRUCTURE-PROPERTY RELATIONSHIPS TO PREDICT DRUG DELIVERY TO THE BRAIN

Sánchez-Dengra, Bárbara[1]*; González-Álvarez, Marta[1]; González-Álvarez, Isabel[1]; Bermejo, Marival[1]

1: Engineering: Pharmacokinetics and Pharmaceutical Technology Area. Miguel Hernandez University, Spain.

ABSTRACT

Introduction. No one can doubt about the importance of the brain in human beings and several are the examples of neurological disorders that progressively destroy the life of their patients, i.e., Alzheimer's disease, Parkinson's disease, depression or glioblastoma, among others. Because of that, researchers make uncountable efforts to find a cure for the pathologies that affect this organ, but they collide with the great wall that is the blood−brain barrier (BBB). In this sense, high throughput screening tools coupled with mathematical modeling could help to reduce the number of failures when these treatments are developed.

Objectives. The objective of this work was to develop a new *in vitro* system which in combination with a physiological-based pharmacokinetic (PBPK) model and quantitative structure-property relationships (QSPRs) would be able to predict brain concentration levels for different drugs in rat.

Methods. Firstly, *in vitro* permeability tests with three different cell lines (MDCK, MDCK-MDR1 and hCMEC/D3) were conducted and *in vitro* influx and efflux BBB clearances and the unbound fraction of drug in brain were obtained. Then, those three *in vitro* parameters, three scaling factors (SC) and other physiological parameters were used in a mathematical model to fit the plasma and brain profiles in rat for 6 different drugs. After that, the SCs of the different drugs were correlated with their lipophilicity and brain profiles were simulated using the predicted SCs. Finally, predictions were evaluated by internal validation comparing the experimental and predicted brain C_{max} and AUC.

Results. Once the percentages of predictions errors were obtained, it was seen that as the complexity of the cell line increased (MDCK < MDCK-MDR1 < hCMEC/D3), worse were the predictions. It was hypothesized that it could be due to the greater presence of

transporters in the most complex cells and their influence on the scaling factors of actively transported drugs.

Conclusions. A new PBPK model, incorporating the barrier resistance to transport, the disposition within the brain and the drug-brain binding has been developed whose best predictions were obtained with MDCK data. So this approach in combination with MDCK permeability experiments could be used as screening tool in the development of new treatments for the central nervous system.

***KEYWORDS**: Blood−brain barrier (BBB); physiological-based pharmacokinetics (PBPK); quantitative structure-property relationships (QSPRs); distribution volume in brain ($V_{u,brain}$); plasma−brain partition coefficient ($Kp_{uu,brain}$)*

2 PRECLINICAL CHARACTERIZATION OF PLASMA PROTEIN AND TISSUE BINDING OF AMIODARONE USING A POPULATION APPROACH

PONENTE: Karine Elena Rodríguez Fernández

Karine Elena Rodríguez Fernández es estudiante del programa de doctorado Biomedicina y Farmacia de la Universidad de Valencia. Realizó sus estudios de grado en Farmacia y máster en Farmacología en la Facultad de Farmacia de la Universidad de La Habana, Cuba. Desde 2019 se encuentra residiendo en España para completar sus estudios de doctorado. Actualmente está bajo la supervisión de los doctores Víctor Mangas, Mónica Climente y Elena Gras. En estos momentos se desempeña en la ejecución de su proyecto de tesis de doctorado que se titula: "Optimización posológica de Ustekinumab y Secukinumab en psoriasis", el cual se basa en el modelado farmacocinético-farmacodinámico poblacional de anticuerpos monoclonales. A su vez está participando en otros proyectos de investigación en colaboración con el Departamento de Farmacia y Tecnología Farmacéutica y Parasitología de la Facultad de Farmacia de la Universidad de Valencia.

2 PRECLINICAL CHARACTERIZATION OF PLASMA PROTEIN AND TISSUE BINDING OF AMIODARONE USING A POPULATION APPROACH

Karine Rodriguez-Fernandez[1], Elena Gras-Colomer[2], Monica Climente-Martí[1,3], Víctor Mangas-Sanjuán [1,4], Matilde Merino-Sanjuan[1,4]

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2: Department of Pharmacy, University Hospital of Manises, Valencia, Spain
3: Department of Pharmacy, University Hospital Doctor Peset of Valencia, Spain
4: Interuniversity Institute of Recognition Research Molecular and Technological Development

ABSTRACT

Introduction: Amiodarone (AM) is a benzofuran derivative which belongs to a class III of antiarrhythmic drugs. Its approved indication is for life-threatening ventricular arrhythmias. Commercially available AM presentations include intravenous (IV) and oral (OR) administrations. OR administration is indicated in patients with mild and moderate heart disease, whereas IV is preferred in advanced structural heart disease patients[1]. AM has been classified as a narrow therapeutic drug, which shows high lipophilicity in plasma and depot tissues due to the extreme affinity to lipids[2], which can explain their considerable side effects. In this sense, new technological strategies have been proposed to improve the pharmacokinetic properties of AM and, with it, its safety profile[3]. However, the absorption properties of AM are uncertain with a low and variable bioavailability after oral administration.

Objectives: The aim of this study is to quantitatively characterize the pharmacokinetics of AM in rats following different dose levels and routes of administration in order to better understand the mechanisms involved in its absorption and distribution.

Methods: The study design included three different routes of AM administration: intravenous (IV), oral (OR) and intraperitoneal (IP); with single (IV, OR and IP) and multiple dosing regimens (IVIV, IVOR, IVIP). Male Wistar rats were randomly allocated into different groups. The dose levels selected were 12.5 mg (IV and IP), 10 mg (OR), and 25 mg (OR). AM plasma concentrations were described with compartmental models assuming linear and non-linear PK processes. Inter-individual variability (IIV) associated to the PK parameters was modeled exponentially and residual unexplained variability (RUV) was described with an additive model on the logarithmic scale. The population PK

parameters were estimated using SAEM+IMP. Model selection was based on the statistically decrease of the objective function value (OFV) and the goodness of fit (GOF) plots. Model evaluation was performed through pc-VPC and bootstrap analysis (n=1000). Experimental data were logarithmically transformed. All data analyses were performed based on the population approach with the software NONMEM v7.4.

Results: A total number of 88 rats with 899 AM observations were included in the PK analysis. The structural PK model selected assumes a central compartment and a peripheral compartment where the drug is distributed. A non-instantaneous saturable and dynamic plasma protein binding (Amax, Qu and Qb) and linear depot dynamic binding (Qtu and Qtb) were incorporated to account for the AM binding in plasma and in the peripheral compartment, respectively. The maximal amount bounded in plasma was 5.98 mg and the clearance was 0.0437L/h. Two depot compartments were considered to account for the different absorption process after OR (CMT=1) or IP (CMT=3) administration. Different bioavailability was considered for each extravasal administration (F_{OR}= 58.3% and F_{IP}= 52%). The structural model assumes a rapid distribution into the peripheral compartment (Q4 = 0.131 L/h and V4 =1.09 L), acting as depots and causing a sustained decay in AM plasma levels after dosing.

Conclusions: The pharmacokinetics of AM were successfully described using a two-compartment model with linear absorption after oral and intraperitoneal administration in rats. The intravenous administration allowed to characterize the oral and intraperitoneal absolute bioavailability of AM in rats. A saturable and non-saturable protein-binding mechanism in plasma and peripheral compartment, respectively, statistically improved the description of the data.

References:

[1] Mujović, N., et al. (2020). "The role of amiodarone in contemporary management of complex cardiac arrhythmias." Pharmacological Research, 151, 104521.
[2] Campos-Moreno E., et al. (2007) Population modelling to describe pharmacokinetics of amiodarone in rats: relevance of plasma protein and tissue depot binding. European Journal of Pharmaceutical Sciences, 30, 190-197.
[3] Ahmed MS., et al. (2019) A Supramolecular Nanocarrier for Delivery of Amiodarone Anti-Arrhythmic Therapy to the Heart. Bioconjug Chem, 30(3), 733-744.

***KEYWORDS**: Amiodarone, pharmacokinetic, bioavailability.*

3 IMPLEMENTING A PHARMACOKINETIC MODEL FOR THE EVALUATION OF DRUG RELEASE FROM COATED MATRIX TABLETS

PONENTE: Roberto Arévalo Pérez

Es graduado en 2013 en Farmacia por la Universidad de Salamanca. Realizó el máster de Biología y Clínica del Cáncer ofertado por la Universidad de Salamanca y el Centro de Investigación del Cáncer. Desde que acabó sus estudios en 2014 ha trabajado prácticamente de manera ininterrumpida como técnico de laboratorio, primero en el Complejo Asistencial Universitario de Salamanca en el Área de Anatomía Patológica/Biología Molecular y posteriormente en el departamento de Ciencias Farmacéuticas/Área de Farmacia y Tecnología Farmacéutica. Actualmente está matriculado en el programa de doctorado de Farmacia y Salud de la Universidad de Salamanca, y su trabajo se centra en el desarrollo de comprimidos de liberación controlada en el colon siguiendo una estrategia de Calidad por Diseño (QbD), bajo la dirección de los profesores José M. Lanao y Cristina Maderuelo. Cuenta con una publicación en el Journal of Controlled Release, revista con un factor de impacto en 2020 de 7.6.

3 IMPLEMENTING A PHARMACOKINETIC MODEL FOR THE EVALUATION OF DRUG RELEASE FROM COATED MATRIX TABLETS

Arévalo-Pérez, Roberto[1]*; Maderuelo, Cristina[1]; M. Lanao, José[1,2]

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2: Instituto de Investigación Biomédica de Salamanca (IBSAL), Paseo de San Vicente, 58-182, 37007 Salamanca, Spain

ABSTRACT

Introduction.

Colon drug delivery systems have become a growing interest search field in the past few years due to the advantages they provide to treat several diseases locally at the colonic region while avoiding drug absorption in the upper parts of the gastrointestinal tract, reducing potential undesirable side effects. Either time- or pH-dependent coating polymers can be used to target the colon, leading to different drug release profiles. Simulation tools such as SimCYP® can help predicting *in vivo* drug release and drug absorption behaviours from physicochemical results obtained *in vitro*.

Objectives.

The present work tries to predict drug release and absorption rates using SimCYP® software in an attempt to explain the behaviour of matrix tablets with the same composition coated with two different polymers.

Methods.

Simulations were carried out using SimCYP® software (Certara, Sheffield, UK) implementing the Advanced Dissolution Absorption Metabolism (ADAM) model. A total of 100 trials with 10 subjects per trial were performed using SimCYP® Sim-Healthy Volunteers aged between 18-65 years. Substrate was one single oral dose of 500 mg of metronidazole, administered in a fasted state with 250 mL of water intake. Drug release profiles obtained *in vitro* from matrix tablets coated with Eudragit® FS 30D (pH-dependent polymer) and Eudragit® RL 30D (time-dependent polymer) were introduced to run the simulation.

Results.

Matrix tablets coated with a pH-dependent polymer achieve a delayed drug release with a Tmax = 9.90 h, Cmax = 0.19 mg/L and AUC = 2.48 mg/L*h; luminal concentration of total drug at 24h = 9.20 g/L. Matrix tablets coated with a time-dependent polymer achieved earlier drug release with a Tmax = 6.50 h, Cmax = 1.26 mg/L and AUC = 16.1 mg/L*h; Luminal concentration of total drug at 24h = 8.82 g/L.

Conclusions.

Time-dependent coating agents allow drug release as soon as water gets in contact with the matrix core, which could lead to early drug release and absorption before the tablet reaches the colon. pH-dependent polymers however will only dissolve at the higher pH levels of the colon, delaying drug release and thus reducing the maximum drug concentration in plasma, which potentially reduces the risks of adverse effects associated with the drug. Nevertheless, both polymers achieve an effective drug release in the colonic region, showing similar luminal concentration at 24h, making them both effective against colonic infections of diverticulitis disease

***KEYWORDS**: Release profiles, ADAM model, SimCYP®, colon drug delivery systems, coated matrix tablets.*

4 PHARMACODYNAMIC MODELLING AND SIMULATION OF AMPHOTERICIN B TIME-KILL CURVES AGAINST *CANDIDA AURIS*

PONENTE: Unai Caballero Cuenca

Unai Caballero Cuenca es licenciado en Farmacia (2014) y Máster en Farmacología (2015) por la Universidad del País Vasco/Euskal Herriko Unibertsitatea (UPV/EHU). Actualmente realiza su tesis doctoral en el Departamento de Farmacología de la UPV/EHU bajo la supervisión de la Dra. Nerea Jauregizar Albonigamayor. Su labor de investigación se centra en el estudio de la actividad in vitro de fármacos antifúngicos y su modelización farmacocinética/farmacodinámica. Colabora en la docencia práctica de asignaturas del Departamento de Farmacología. Como parte de su aprendizaje predoctoral ha asistido a varios cursos sobre el campo de la Farmacometría, asistido y presentado sus resultados en congresos nacionales e internacionales y recientemente, ha completado una estancia de 6 meses en La Universidad de Florida (Orlando, Estados Unidos) en el "Center for Pharmacometrics and Systems Pharmacology" liderado por el Dr. Stephan Schmidt.

4 PHARMACODYNAMIC MODELLING AND SIMULATION OF AMPHOTERICIN B TIME-KILL CURVES AGAINST *CANDIDA AURIS*

Caballero, Unai[1]*; Eraso, Elena[2]; Pemán, Javier[3]; Quindós, Guillermo[2]; Vozmediano, Valvanera[4]; Schmidt, Stephan[4]; Jauregizar, Nerea[1]

1: Department of Pharmacology, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), Leioa, Spain.
2: Department of Immunology, Parasitology and Microbiology, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), Leioa, Spain.
3: Servicio de Microbiología, Hospital Universitario y Politécnico de La Fe, Valencia, Spain.
4: Center for Pharmacometrics and Systems Pharmacology,Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA

ABSTRACT

Introduction. *Candida auris* is an emerging fungal pathogen that exhibits remarkable resistance to first-line antifungal agents. The reported resistance to Amphotericin B (AmB), a highly effective drug, is variable (between 0-30%) but the minimum inhibitory concentration (MIC) value of 1 mg/L used as cut-off is not based on specific preclinical or clinical data. Pharmacometric analysis of in vitro time-kill curves is a useful tool to better characterize the antimicrobial activity of drugs against pathogens and their susceptibility profile and can help to design better strategies to optimize therapy.

Objectives. To develop a model that characterizes the in vitro activity of AmB against *C. auris* and perform simulations of standard dosing regimens to evaluate the efficacy of AmB to treat *C. auris* infections

Methods. In vitro static time-kill curve assays were performed with six *C. auris* clinical isolates (MIC=1 mg/L) from an outbreak in Hospital La Fe (Valencia, Spain). Tested concentrations of AmB ranged from 0.25 to 4 mg/L and samples for viable counts were taken at 0, 2, 4, 6, 8, 24 and 48 h. Experiments were conducted in duplicate on different days. Logarithm of colony forming units (log CFU/mL) for each isolate and drug concentration were simultaneously analysed in NONMEM v.7.4. Different semi-mechanistic models that accounted for reduced drug susceptibility were tested. Precision of parameter estimates, goodness of fit plots and internal validation techniques (VPC and bootstrap) were evaluated for model performance. Once the final model was chosen, standard regimens of Amphotericin B deoxycholate (DAmB) were simulated using in vivo

pharmacokinetic parameters. Additional simulations were performed testing MICs lower than 1 mg/L.

Results. A two-subpopulation model that included a drug susceptible subpopulation (S) and a slower growing resistant subpopulation (R) best described the data. An Emax sigmoidal function described the concentration-dependent activity of AmB, the typical values and relative standard errors being Emax: 0.784 h^{-1}(12%), EC50: 1.88 mg/L (3%), Hill factor: 4 (fixed). Simulations of dosing regimens of 0.6, 1 and 1.5 mg/kg/day showed that the studied *C. auris* strains would be resistant to treatment. The simulations for *C. auris* with lower MIC (0.06 to 0.50 mg/L) showed that strains with a MIC=0.06 mg/L would be susceptible to doses of 1 and 1.5 mg/kg/day whereas those with a MIC=0.125 mg/L would only be susceptible to doses of 1.5 mg/kg/day. Strains with MIC higher than 0.125 mg/L were resistant to treatment.

Conclusions. The developed model successfully described the in vitro activity of AmB. Standard treatment of DAmB would not be effective against certain strains of *C. auris*. Accordingly, simulations based on different MIC scenarios suggest that the resistance rate to AmB may be higher than previously reported and support the clinical guidelines that point AmB as a second-line treatment option.

***KEYWORDS**: PK/PD; simulation; amphotericin B; Candida auris*

5 PHYSIOLOGICALLY-BASED PHARMACOKINETIC/PHARMACODYNAMIC MODEL OF MBQ-167 TO PREDICT TUMOR GROWTH INHIBITION IN MICE

PONENTE: Javier Reig López

Javier Reig López, Graduado en Farmacia por la Universitat de València en 2014 con Premio Extraordinario de Grado. Realicé mi formación de tercer ciclo en el Máster Oficial Interuniversitario en Química Orgánica Experimental e Industrial de la Universitat de València en 2015 y actualmente soy estudiante de tercer año del programa de doctorado en Biomedicina y Farmacia de la Facultad de Farmacia de la Universitat de València bajo la dirección de los profesores Matilde Merino Sanjuan y Victor Mangas Sanjuan. El objeto de la tesis es el modelado PBPK de atorvastatina para su evaluación en ensayos de bioequivalencia.

5 PHYSIOLOGICALLY-BASED PHARMACOKINETIC/PHARMACODYNAMIC MODEL OF MBQ-167 TO PREDICT TUMOR GROWTH INHIBITION IN MICE

Reig-López, Javier[1*]; Maldonado, María del Mar[2]; Merino-Sanjuan, Matilde[1,3]; Cruz-Collazo, Ailed M.[2]; Ruiz-Calderón, Jean F.[2]; Mangas-Sanjuán, Víctor[1,3]; Dharmawardhane, Suranganie[2]; Duconge, Jorge[4]

[1]Department of Pharmacy and Pharmaceutical Technology and Parasitology, University of Valencia. Valencia, Spain.
[2]Department of Biochemistry, University of Puerto Rico Medical Sciences Campus. San Juan, Puerto Rico.
[3]Interuniversity Research Institute for Molecular Recognition and Technological Development. Valencia, Spain.
[4]School of Pharmacy, University of Puerto Rico Medical Sciences Campus. San Juan, Puerto Rico.

ABSTRACT

Introduction. MBQ-167 is a dual inhibitor of the Rho GTPases Rac and Cdc42 that has shown promising results as an anticancer therapeutic at the preclinical stage. This drug has been tested *in vitro* and *in vivo* in metastatic breast cancer mouse models. Physiologically-based pharmacokinetic (PBPK) modelling represents a mathematical framework that integrates physicochemical, physiological, and biochemical information to predict the concentration-time course at target tissues for a wide range of exposure conditions in animals or humans. The tumor growth inhibition (TGI) model constitutes a highly valuable preclinical methodology in oncology for the selection of therapeutic candidates and the design of optimal clinical evaluation strategies for the *in vivo* evaluation of anti-tumor effect.

Objectives. The aims of this work are i) to develop a PBPK model of MBQ-167 after intraperitoneal (IP) administration in mice and ii) to characterize tumor growth dynamics in two human breast cancer cell lines (Her2+ and Triple Negative).

Methods. PBPK and Simeoni TGI models were developed using the Simcyp V19 Animal Simulator. An experimental dataset of plasma and different tissue concentrations of MBQ-167 were used to evaluate the model both graphically (fitting of the simulated individual to the 95% Confidence Interval of the observations at each time) and numerically (computing the fold error in the prediction of the exposition parameters AUC_{0-t} and C_{max}). *In vivo* monitoring of tumor dynamics served as an external validation of the PBPK-PD model developed. In this sense, Relative Error (RE) in the prediction of the

final tumor volume was calculated and the simulated tumor volume profile was superimposed to the observed individual behaviour at different dose levels. Both graphical and numerical analyses were performed in RStudio version 1.2.5019 with R version 3.5.1.

Results. The developed PBPK model is capable to describe the pharmacokinetics (PK) of MBQ-167 in each of the mouse tissues (e.g., lungs, heart, liver, kidneys, spleen and tumor) and plasma, with RE in AUC_{0-t} and C_{max} prediction being less than 20%. The predicted plasma exposition PK parameters AUC_{0-t} and C_{max} are remarkably close to that observed, with fold errors of 1.09 and 0.99, respectively. The predicted volume of distribution at steady state, V_{ss}, (20.21 L/kg) reveals high distribution into peripheral tissues, with little amount of MBQ-167 remaining in the bloodstream.
The TGI model successfully predicts tumor shrinkage in both breast cancer cell lines after the IP administration of 1 and 10 mg/kg of body weight three times a week, with predicted (observed) final tumor volumes (mL) for the HER2+ cell line of 0.8 (0.95) and 0.23 (0.22), respectively, and of 0.35 (0.36) and 0.23 (0.36) for the Triple Negative cell line, respectively.

Conclusions. The PBPK-PD model here presented is able to properly describe the time course of MBQ-167 in plasma, tumor and different mice tissues, and to predict tumor growth inhibition in two breast cancer cell lines. Additionally, the findings from this study suggest that MBQ-167 has a higher net effect and potency inhibiting Triple Negative growth compared to HER2+ breast cancer cell lines.

***KEYWORDS**: breast cancer; physiologically based pharmacokinetic modelling; tumor growth inhibition model; Rac inhibitor; MBQ-167.*

6 MECHANISM-BASED CHARACTERIZATION OF COMBINATION TREATMENTS IN IMMUNONCOLOGY

PONENTE: Aymara Sancho Araiz

Graduada en Farmacia por la Universidad de Valencia. Actualmente se encuentra realizando su segundo año del Programa de Doctorado en Medicamentos y Salud en la Universidad de Navarra bajo la dirección de los profesores Iñaki Fernández de Trocóniz y Victor Mangas SanJuan. Su proyecto de tesis se basa en la aplicación de la farmacometría en el desarrollo de fármacos oncológicos.

6 MECHANISM-BASED CHARACTERIZATION OF COMBINATION TREATMENTS IN IMMUNONCOLOGY

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ABSTRACT

Introduction: Immunotherapy promoting the stimulation of innate and adaptive immune systems to induce tumor cells death is a growing therapeutic strategy in oncology [1]. Immunological treatment of cold-tumor is a great challenge as no adaptive immune response has been set up or maintained. Consequently, different approaches such as vaccination, chemotherapy, or adaptive cellular therapy need to be combined in order to obtain a clinical response [2]. Cancer vaccines are able to activate antigen-presenting cells as dendritic cells, but the success of this strategy relies on the choice of and adjuvant, like polyinosinic-polycytidylic acid (PIC), a toll-like receptor, to ensure proper stimulation. Blockade of the PD1-PD-L1 immune-checkpoint (IC) with an anti-PD1 monoclonal antibody has demonstrated clinical benefit enhancing patients' outcomes [3].

Objectives: To develop a semi-mechanistic pharmacodynamic model to predict tumor growth inhibition in mice through the interactions between the tumor and immune system, including dendritic cells and cytotoxic CD8+ T cells, upon different treatment combinations.

Methods: A total of 105 mice were included in the analysis and treated with different immunotherapy combinations. Mice were divided into 8 groups: control (n=27); monotherapies with E7 long peptide (n=6), PIC, and anti-PD1 (n=12); biotherapies, E7 long peptide/PIC (n=12), E7 long peptide/anti-PD1 (n=12), and PIC/anti-PD1 (n=12); and tritherapy (E7 long peptide/PIC/anti-PD1) (n=18). Control and treated mice groups were modelled sequentially. Due to the lack of pharmacokinetic data, a K-PD approach was implemented, where the kinetics is inferred from the dynamics of the observed response [4]). Different structural tumor growth models were applied to describe the control group.

Non-linear mixed effects modelling using NONMEM 7.4 was applied for parameter estimation.

Results: Tumor growth in the absence of any therapeutic agent was characterised with an exponential model based on the parameters of the tumour size at baseline (Ts_0) and the proliferation constant (ʎ). Then, tumor growth parameters were fixed and the effect of the different treatments was estimated. Vaccine and PIC concentrations at the target site stimulate the proliferation of dendritic cells, which lead to the appearance of cytotoxic CD8+ T cells at tumor site. A resistance mechanism triggered by the tumor diminishes the number of cytotoxic CD8+ T cells. The administration of anti-PD1 inhibits the resistance mechanism. Lack of treatment effect was observed for the monotherapy groups while an improvement in efficacy (tumor reduction and responder rate) was found for certain drug combinations, although with high variability among the individuals.

Conclusions: A semi-mechanistic pharmacodynamic model describing the effect of immunological combination treatments on tumor growth was successfully developed. This model can maximize the information obtained from preclinical cancer immunotherapy experiments and therefore, could be useful for the design of better clinical trials of immunomodulation drugs.

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***KEYWORDS**: Immunotherapy, mathematical modelling, tumor growth, vaccine, antiPD-1, PIC.*

7 DEVELOPMENT OF A PHARMACOKINETIC MODEL TO ADJUST INTRADUODENAL ADMINISTRATION IN HUMANS.

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7 DEVELOPMENT OF A PHARMACOKINETIC MODEL TO ADJUST INTRADUODENAL ADMINISTRATION IN HUMANS

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ABSTRACT:

Introduction. This work is based on explaining the dissolution of small and large particles of a drug in the different physiological sections, that is, in their interaction with the different physiological buffers (phosphate buffer, acetate and bicarbonate). Mooney and RNE models were used to estimate surface pH and calculate equivalent buffer concentrations. Ibuprofen was selected as the drug to be tested and ibuprofen suspensions were administered intraduodenally by a modification of the Bioperm method for the local administration of drugs in the human intestine (Bioperm AB, Lund, Sweden).

Objectives. The objective of this work is to develop a biopredictive method to explain the dissolution of Class II drugs according to the Biopharmaceutical Classification System

Methods. Ibuprofen plasma concentrations are available from 7 healthy volunteers after drug administration at two different infusion rates. The Berkeley Madonna software was used, implementing two models using differential equations

Model 1: Consists of 4 compartments, reservoir, intestinal, central and peripheral compartment. The following rate constants were used; Kinf (infusion rate), Ka (absorption rate), k12 and k21 (peripheral delivery rates) and k0 (elimination rate).

This first model was used to determine the values of ka, k12, k21 and the volumes of distribution of each individual. These data were used as input in the second model.

Model 2: In this model the intestinal compartment was divided into four compartments, representing two sections of the intestine and differentiating the state of the drug between solid and dissolved.

Both models used the Runge-Kutta 4 (RK4) integration method, a start time of 0 hours, an end time of 10 hours, and a default interval of 0.02.

Results.

The pharmacokinetic parameters calculated by the model indicate that ibuprofen is a rapidly absorbed drug, (ka 9.75h-1). The volumes of distribution calculated coincide with those reported in the literature, after intravenous administration.

Conclusions.

The proposed model predicts the in vivo intestinal dissolution of ibuprofen reasonably well. This type of model reveals the great potential of modeling and would be a useful tool to extend bio-exemptions to BCS class IIa compounds.

***KEYWORDS**: Class II BCS; intraduodenal administration; human data*

8 APPLICATION OF A DUAL PBPK-POPPK MODEL BASED APPROACH ACROSS THE AGE-POPULATION OF ADULTS USING BILASTINE AS A PROBE DRUG

PONENTES:

Valentina Lo Re

Valentina Lo Re (MSc) attended a double degree program receiving a Master's degree in Biomedical Sciences from the University of Applied Sciences, Rheinbach (Germany) and a Master's degree in Biologia della Salute (Health Biology) from the University of Palermo (Italy). She started her full-time PhD studies in Pharmacology on 2017/2018 at the University of Basque Country with a project titled "Optimizing pharmacotherapy in the elderly using modelling and simulation methods".

The PhD Project is supervised by two thesis directors: Dr Monica Rodriguez, (BSc, PhD) from the Company Dynakin (Derio, Bizkaia) and the Professor M Elena Suárez from the University of Basque Country (UPV-EHU). This co-supervised PhD thesis project between the University of Basque Country (UPV/EHU) and the company Dynakin.SL is carried out as part of an international project ("Desarrollo de una plataforma para optimizar la dosificacion de los regimens farmacologicos en adulto mayores ") started on 2017 as a collaboration with the CENTER FOR PHARMACOMETRICS AND SYSTEMS PHARMACOLOGY-UNIVERSITY OF FLORIDA (USA) and DYNAKIN, S.L. (Derio, Basque Country).

Chaejin Kim

Chaejin Kim is a third year PhD student in pharmaceutics at the University of Florida, under supervision of Dr. Valvanera Vozmediano. She received her Pharm.D. (2015) at Ewha Womans [sic] University, Seoul, South Korea, and MPH in Biostatistics (2018) at Emory University. She is a registered pharmacist in South Korea and a member of Delta Omega honorary society in public health. Her research interest is in quantitative approaches to answer questions raised during drug development process. She is currently working on several projects including development of physiologically based absorption model for nasal spray and intramuscular administration, development of mathematical declining function of striatum binding ratio in Parkinson's disease patients, and investigation of the food effect on the in-vitro-in-vivo correlation of extended release formulation using a case example.

8 APPLICATION OF A DUAL PBPK-POPPK MODEL BASED APPROACH ACROSS THE AGE-POPULATION OF ADULTS USING BILASTINE AS A PROBE DRUG

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ABSTRACT

Introduction

Despite the increasing size of the geriatric population and specific guidance on the elderly regarding medicinal products, this patient population is clinically understudied. Gathering an in-depth understanding of physiological changes in a special population, such as geriatric patients would allow a better understanding of age PK and PD relating factors in order to optimize drug therapy in the elderly

Objective

Use of a dual physiologically-based pharmacokinetic model- population pharmacokinetic (PBPK-popPK) model-based approach to integrate bilastine physicochemical, *in vitro* and *in vivo* data in young adults to: 1) enhance the mechanistic understanding of intestinal transporters on drug PK, and 2) predict the PK in elderlies of different biological age (*i.e.*, young old, middle old and oldest old).

Methods

1) PBPK model: Using GastroPlus 9.6® a PBPK model for young adults was developed considering apical efflux and apical and basolateral influx transporters in the enterocyte, using PK data from young adults after IV (10mg SD) and PO (20mg SOD). The model was qualified using an external dataset containing data from 12 Phase-I studies with 13 different SOD and MOD. The model was then used to extrapolate the PK to young olds, which also served to verify the predictive capacity of the model. 2*) PopPK model:* A semi-mechanistic predictive popPK model for elderlies was develop in NONMEM version 7.2 using a previously developed young adult popPK model incorporating declining functions on different physiological systems (glomerular filtration, unbound fraction) and differences in body

composition. Model predictive capacity was evaluated using observations from young olds. Both models were qualified by comparing the predicted *vs* observed PK parameters in elderlies, and by comparing the predicted concentration-time profiles to the clinical data.

Results

Final PBPK model predictions showed AUC_{pred}/AUC_{obs} ratios within 0.5 and 2 for all the doses (5mg - 220mg). The final PBPK adequately predicted plasma concentrations in geriatrics. Similar results were also obtained for the semi-mechanistic popPK model where more than 90% of observations were within the 5~95% of simulated confidence intervals.

Conclusions

This study suggests that the developed models can be successfully used to scale the pharmacokinetics of Bilastine from adults to geriatrics.

Moreover, this complementary approach allowed to enhance the accuracy of the predictions and to fine tune them by applying additional physiological based factors and pharmacokinetic based knowledge. The application of both models indicate that 20 mg QD dose is appropriate for geriatrics of any age. Current work is ongoing to establish the influence of pathophysiological conditions that are common in this patient population.

***KEYWORDS**: elderly; modelling; pharmacokinetics; semi-physiological model; PBPK model*

9 EVALUATION OF THE PREDICTIVE PERFORMANCE OF TWO POPULATION PHARMACOKINETIC MODELS OF VEDOLIZUMAB IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

PONENTE: Silvia Márquez Megías

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9 EVALUATION OF THE PREDICTIVE PERFORMANCE OF TWO POPULATION PHARMACOKINETIC MODELS OF VEDOLIZUMAB IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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ABSTRACT

Introduction. Vedolizumab is a recombinant humanized IgG1 monoclonal antibody directed against the human lymphocyte α4β7 integrin, that has been approved as a therapeutic agent for the inflammatory bowel disease. The treatment with biological drugs can be benefited by the therapeutic drug monitoring (TDM), by calculating the Empirical Bayesian Estimates (EBEs) of the PK parameters. However, there are several population pharmacokinetic models (popPKm) in literature. A proper evaluation of these models in the target population should be performed before implanted in a clinical routine.

Objectives. To evaluate the predictive performance of two popPKm of vedolizumab in adult patients diagnosed with inflammatory bowel disease.

Methods. A retrospective observational study was performed in the General University Hospital of Alicante, with the following inclusion criteria: Adult patients with ulcerative colitis or Crohn's disease treated with vedolizumab, with at least three trough plasma concentration (PCT) between 2017 and 2020.
Two different popPKm were evaluated: Rosario et al, 2015 (Mod-A) and Okamoto et al, 2020 (Mod-B). The models were implemented in NONMEM® v7.4.
The individual and population predictions of vedolizumab concentrations were estimated from the two popPKm, by calculating the EBEs of the individual pharmacokinetic parameters. Three different scenarios were considered from the dataset to evaluate the predictive performance using only the first two, three or four PCT of each patient, respectively, to estimate the EBEs. The PCT that were left out were evaluated with the

individual prediction calculated by the EBEs.

To validate the two popPKm, the bias and precision of the PCT predictions were estimated by calculating the mean predictive error (MPE) and the mean square predictive error (MSPE), respectively. In both cases, the model closer to zero, will be the most accurate and precise, respectively. Bland-Altman analysis were also performed to calculate the 95% agreement limits between individual predictions and observations.

Results. The dataset comprised 32 patients and 287 PCT. The mean values (95% CI) of weight, basal albumin and TC were: 72 kg (48 - 118), 3.64 g/dL (2.66 - 4.76) and 13.67 mg/L (0 - 47), respectively. 40.6% of patients developed antibodies anti-vedolizumab.

The bias (95% CI) of the predictions for the predictive performance in Scenario 1, 2 and 3 were: Mod-A: -2.34 (-5.22 : 0.55), 0.48 (-1.55 : 2.52) and -2.76 (-5.56 : 0.048); Mod-B: -2.27 (-4.78 : 0.24); 0.86 (-1.14 : 2.86) and -3.07 (-5.71 : 0.44), respectively.

The precision (95% CI) of the predictions for the predictive performance in Scenario 1, 2 and 3 were: Mod-A: 8.53 (1.08 : 15.98), 5.51 (4.00 : 7.02) and 7.81 (3.05 : 12.56); Mod-B: 7.50 (1.64 : 13.36); 5.48 (4.04 : 6.92) and 7.51 (3.24 : 11.78), respectively.

Conclusions. The evaluation of the predictive performance of the two popPKm found in literature showed that both models performed similar. Mod-A performed slightly better in term of bias in Scenario 2 and 3 and Mod-B performed slightly better in term of precision in all scenarios. However, the results are not conclusive to choose one model to use in the clinical routine for the dose individualization of vedolizumab for patients with inflammatory disease, in the General University Hospital of Alicante.

***KEYWORDS**: Inflammatory bowel diseases, Vedolizumab, Pharmacokinetics, Therapeutic Drug Monitoring*

10 POPULATION PHARMACOKINETIC MODEL OF CEFTRIAXONE IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK AND CONTINUOUS VENO-VENOUS HEMODIAFILTRATION

PONENTE: Carla Bastida Fernández

Carla Bastida Fernández es farmacéutica especialista en Farmacia Hospitalaria y Doctora en Medicina por la Universidad de Barcelona. Actualmente es adjunta responsable del área de Farmacocinética clínica y del área de Cuidados Intensivos del Hospital Clínic de Barcelona. Sus intereses en investigación se centran en el modelado farmacocinético/farmacodinámico poblacional para optimizar pautas de dosificación de tratamientos farmacológicos, entre ellos, anticuerpos monoclonales y antibióticos.

10 POPULATION PHARMACOKINETIC MODEL OF CEFTRIAXONE IN CRITICALLY ILL PATIENTS WITH SEPTIC SHOCK AND CONTINUOUS VENO-VENOUS HEMODIAFILTRATION

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11 POPULATION PHARMACOKINETIC MODEL OF LEVETIRACETAM IN CRITICALLY ILL PATIENTS: ARE WE UNDERDOSING OUR PATIENTS?

PONENTE: Idoia Bilbao Meseguer

Es Licenciada en Farmacia por la Universidad del País Vasco (UPV/EHU) desde el año 2010. Entre los años 2011 y 2015 realizó la residencia de Especialista en Farmacia Hospitalaria en el Hospital Universitario Cruces, donde trabaja actualmente como adjunta.

Está realizando los estudios de doctorado en el "Programa de doctorado en Investigación y Evaluación de Medicamentos. Aplicación de la Tecnología Farmacéutica al Desarrollo de Terapias Avanzadas" de la UPV/EHU. El proyecto de investigación trata sobre el aumento del aclaramiento renal en pacientes críticos y su influencia en la farmacocinética de antimicrobianos y anticonvulsivantes."

11 POPULATION PHARMACOKINETIC MODEL OF LEVETIRACETAM IN CRITICALLY ILL PATIENTS: ARE WE UNDERDOSING OUR PATIENTS?

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ABSTRACT

Introduction. Levetiracetam is a broad-spectrum antiepileptic drug commonly used in seizure treatment and prophylaxis in the intensive care units (ICUs).

Objectives.The objective of this study is to evaluate the adequacy of levetiracetam dosing for the achievement of therapeutic levels in patients with high renal clearance admitted to the ICU by the characterization of the levetiracetam pharmacokinetics in ICU patients by population modeling and simulation.

Methods. A prospective study was performed in the ICU of Araba University Hospital and 12 de Octubre University Hospital. Patients with creatinine clearance (CrCl) > 50 mL/min and treated with levetiracetam were included. The protocol was approved by the Basque Clinical Research Ethics Committee. Each patient received 500, 1000 or 1500 mg of levetiracetam as multiple dose every 12 h, by 30 minute intravenous infusion. Six blood samples were drawn at previously defined times and drug concentration was quantified using a previously validated HPLC-UV technique. Nonlinear mixed-effects modelling was implemented by NONMEM 7.4, using first-order conditional estimation method with interaction (FOCE+I). The model selection was based on the decrease in objective function value (OFV), the relative standard errors (RSE) of the parameters, and the goodness-of-fit (GOF) plots. Demographic and clinical variables were studied as potential covariates. Parameter precision was evaluated by performing a 2000-dataset bootstrap (PsN 5.0). Simulation-based model diagnostic were used for final model evaluation.

Results. A total of 23 critically ill patients (134 plasma samples) were included in the study and considered for pharmacokinetic model development. Levetiracetam plasma

concentrations were best described by a two-compartment model. Inter-individual variability (IIV) on the total body clearance (CL) and the central compartment volume of distribution (V1) was also estimated. Variability was modeled by using an exponential model for IIV, and a proportional error model for the residual variability. Parameter estimates (%RSE) were as follows: CL 4.47 L/h (9%), V1 18.5 L (24%), Q 35.6 L/h (30%), V2 33.8 L (14%), IIV estimates were, for the CL, 37.4% (21%) and, for V1, 57.2% (39%). None of the covariates studied (sex, diagnostic, presence of augmented renal clearance, age, creatinine clearance, weight, body surface area and blood glucose) resulted in a relevant reduction in the OFV. Interestingly, more than a half of the plasma levels were below 12 mg/L, which is the lower limit of the therapeutic interval proposed by the International League Against Epilepsy (ILAE). In all of the patients treated with 500mg/12h (n=17), at least one sample had concentration below 12 mg/L, and in 9 patients (53%) in samples obtained within the first 4 hours after dose. Conversely, 2 out of the 3 patients treated with 1500 mg/12 h achieved levels within the therapeutic range during all the dosing interval.

Conclusions.

The pharmacokinetics of levetiracetam was best described by a two-compartment model. Model performance was confirmed by bootstrap and visual predictive check. Unfortunately, the study is underpowered to detect relevant covariates. Regarding dosing adequacy, patients treated with levetiracetam 500mg/12h are clearly under-dosed according to the therapeutic interval proposed by the ILAE. Recommendations for dosing protocol improvement are needed.

***KEYWORDS**: Population pharmacokinetic model; Intensive Care Unit; Levetiracetam.*

12 MODELING CARDIAC EFFECTS OF INVESTIGATIONAL COVID-19 TREATMENTS

PONENTE: Itziar Irurzun-Arana

Itziar Irurzun-Arana, PhD, studied Biomedical Engineering as an undergraduate in the University of Navarra (Spain) and she also graduated from the Bioinformatics Master program from the Autonomous University of Barcelona. She obtained her PhD in Pharmacometrics and Systems Pharmacology in the University of Navarra too under the supervision of Prof. Iñaki Trocóniz. Her research was focused on the development and implementation of different methodologies and tools that could benefit standard Pharmacometrics and Systems Pharmacology modeling, which includes the evaluation of different type of models belonging to qualitative (e.g. Boolean networks) and quantitative approaches (e.g. NLME models) and nonstandard optimization techniques (e.g optimal control). She served as an international exchange PhD student intern for the Center of Cancer Evolution in the Department of Data Sciences at the Dana-Farber Cancer Institute (Boston, US) under the supervision of Prof. Franziska Michor and she also served as a postdoctoral research fellow in Eric Sobie's lab at the Department of Pharmaceutical Sciences in the Icahn School of Medicine at Mount Sinai (New York, US), where she worked in the evaluation of the cardiotoxic effects of anticancer drugs using cardiac QSP models. Nowadays, she is a Clinical Pharmacometrician in AstraZeneca (Cambridge, UK).

12 MODELING CARDIAC EFFECTS OF INVESTIGATIONAL COVID-19 TREATMENTS

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ABSTRACT

Introduction.

Many drugs that have been proposed for treatment of COVID-19 are reported to cause cardiac adverse events, including ventricular arrhythmias. In order to properly weigh risks against potential benefits, particularly when decisions must be made quickly, mathematical modeling or both drug disposition and drug action can be useful for predicting patient response and making informed decisions.

Objectives.

To explore the potential effects on cardiac electrophysiology of 4 drugs proposed to treat COVID-19: lopinavir, ritonavir, chloroquine, and azithromycin, as well as combination therapy involving these drugs.

Methods.

Our study combined simulations of population pharmacokinetic models (popPK) with quantitative systems pharmacology (QSP) modeling of ventricular myocytes to predict potential cardiac adverse events caused by investigational COVID-19 treatments: lopinavir+ ritonavir and chloroquine + azithromycin. These 4 drugs were initially selected because their effects on cardiac ionic currents have been assessed under standardized conditions[1]. The O'Hara et al mathematical model of the human endocardial ventricular myocyte was used to simulate the effects of drugs on ventricular action potentials[2]. Block of ionic currents by particular drugs was simulated with a pore block model, which consists on scaling the conductance of each ionic current based on drug concentrations and IC_{50} values. Then, differences between male and female and between healthy and failing myocytes were simulated by scaling the ionic current maximal conductances based on measured differences in ion transport pathways found in the literature[3,4].

Results.

Simulation results predicted that drug combinations can lead to greater cellular action potential prolongation, analogous to QT prolongation, compared with drugs given in isolation. The combination effect can result from both pharmacokinetic and pharmacodynamic drug interactions. Importantly, simulations of different patient groups predict that females with pre-existing heart disease are especially susceptible to drug-induced arrhythmias, compared males with disease or healthy individuals of either sex.

Conclusions.

Overall, the results illustrate how popPK and QSP modeling may be combined to more precisely predict risks of COVID-19 therapies, thereby helping to guide treatment decisions during this rapidly-evolving pandemic.

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***KEYWORDS**: Quantitative System Pharmacology; Adverse events; Electrophysiology; Ion Channels; COVID-19.*

13 ASSOCIATION BETWEEN HETEROGENEITY OF INDIVIDUAL TUMOR LESIONS AND OVERALL SURVIVAL ASSESSED BY MACHINE LEARNING IN FOUR METASTATIC COLORECTAL CANCER CLINICAL STUDIES

PONENTE: Diego Vera Yunca

Graduado en Bioquímica por la Universidad de Navarra y obtuvo el máster en Investigación, Desarrollo e Innovación de medicamentos en dicha Universidad. Actualmente se encuentra realizando el tercer año de la tesis doctoral en el programa de doctorado de "Medicamentos y Salud" de la Universidad de Navarra, titutlado "Development of disease and drug models for rare diseases and cancer", dirigida por el catedrático Iñaki Fernández de Trocóniz y la doctora Zinnia Parra. En 2019 le fue concedida una ayuda para la formación del profesorado universitario (FPU) por el Gobierno de España. Realizó una estancia doctoral de 8 meses en el "Merck Institute for Pharmacometrics" (parte de la empresa Merck KgaA) en Lausanne (Suiza), supervisado por Nadia Terranova, en la que llevó a cabo estudios farmacométricos con datos oncológicos.

13 ASSOCIATION BETWEEN HETEROGENEITY OF INDIVIDUAL TUMOR LESIONS AND OVERALL SURVIVAL ASSESSED BY MACHINE LEARNING IN FOUR METASTATIC COLORECTAL CANCER CLINICAL STUDIES

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ABSTRACT

Introduction.

Total tumor size (TS) metrics have been extensively used in oncology disease modeling but remain oversimplified measures of cancer progression. Indeed, these may lead to loss of information on tumor heterogeneity, which could be used to improve the prediction of disease progression, drug efficacy and patient overall survival (OS). In a previous work [1], a methodology called ClassIfication Clustering of Individual Lesions (CICIL), which integrates knowledge from signal processing and machine learning (ML), was developed and used to assess differences in dynamics of individual target lesions (iTLs). In this work [2], we analyzed iTLs of patients with metastatic colorectal carcinoma (mCRC) receiving cetuximab, an epidermal growth factor receptor inhibitor.

Objectives.

The objectives of this work were (i) to assess tumor heterogeneity in iTLs dynamics, (ii) to compare results with respect to different factors (KRAS mutation, tumor metrics); and (iii) to apply these results in survival analyses of several clinical trials.

Methods.

Data from mCRC patients receiving cetuximab in four clinical studies were analyzed (1781 patients, 6369 iTLs) and combined in a pooled analysis. The CICIL methodology was used to explore differences in lesion TS dynamics within a tissue (intra-class analysis) or across different tissues (inter-class analysis).

- Step 1: iTLs were automatically classified based on the recorded tumor location and anatomical and physiological features according to methods described in [1].
- Step 2: the comparison of paired lesions was performed by estimating the Cross-

Correlation coefficients (CCs). CCs were computed at zero lag, i.e. without considering any time delay between the dynamics of paired lesions as well as at lags maximizing the CCs by shifting one of the lesions over the other (therefore adding a delay).

- Step 3: CCs were grouped by using the K-means clustering method, an unsupervised ML technique.

Survival analyses were performed to assess the relationship between CICIL-derived metrics and OS.

Results.

Tumor heterogeneity was lower within a tissue than across different tissues for those patients receiving cetuximab. KRAS wild-type (KRASwt) patients in the cetuximab arm showed fewer differences in lesion dynamics than KRAS mutated patients. Slightly less tumor heterogeneity was indicated when the TS was measured bi-dimensionally as the product of diameters vs. unidimensional as the longest diameter.

Tumor heterogeneity quantified as the median CC for each patient was found to be a predictor of OS, both in a univariate analysis and in a multivariate analysis along with other clinically relevant risk predictors. This predictor was especially significant in KRASwt patients with a relevant decrease of risk with decreased heterogeneity, whereas a small decrease was observed in KRAS mutated patients.

Conclusions.

CICIL allowed us to assess heterogeneity of iTLs TS dynamics within a tissue and between different tissues in a large dataset of tumor measurements. Comparisons between groups based on KRAS mutation or tumor size metrics were performed. A CICIL-derived metric was found to be a significant predictor of OS. Models in the oncology area would benefit from considering the heterogeneity between lesions to better predict OS.

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***KEYWORDS**: individual tumor lesion dynamics; machine-learning; metastatic colorectal cancer; survival analysis; tumor size modeling.*

14 PHARMACODYNAMIC MODELLING OF MOVEMENT RESPONSE AFTER NOXIOUS STIMULUS IN PATIENTS UNDERGOING SURGERY

PONENTE: Nicolás Marco Ariño

Nicolás Marco Ariño es graduado en Ciencias Biomédicas por la Universidad de Barcelona y máster en Investigación Clínica y traslacional por el Imperial College London. Tras finalizar sus estudios estuvo trabajando para la empresa farmacéutica AstraZeneca en Gotemburgo (Suecia) antes de empezar la tesis doctoral en la Universidad de Navarra bajo la dirección del profesor Iñaki Fernández de Trocóniz. Su proyecto de tesis se basa en la aplicación de la farmacometría para mejorar el desarrollo de fármacos para el dolor.

14 PHARMACODYNAMIC MODELLING OF MOVEMENT RESPONSE AFTER NOXIOUS STIMULUS IN PATIENTS UNDERGOING SURGERY

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15 QUANTITATIVE ASSESSMENT OF THE EXPOSURE-EFFICACY RELATIONSHIP USING MARKOVIAN ELEMENTS IN GAUCHER PATIENTS

PONENTE: Victor Mangas-Sanjuán

Victor Mangas Sanjuán es Licenciado en Farmacia por la Universidad Miguel Hernández de Elche en 2009. Continuó sus estudios de postgrado en la Universidad de Valencia, donde en 2010 obtuvo el título de Máster en Investigación y Uso Racional del Medicamento por la Universidad de Valencia. En 2014, obtuvo el título de Doctor en Farmacia por la Universidad de Valencia, bajo la dirección del Dr. Vicente Germán Casabó, la Dra. Maria del Val Bermejo y la Dra. Maria Isabel González. Ha sido Premio Extraordinario de Master en 2011 y Premio Extraordinario de Doctorado en 2015. Durante 2016, realizó su actividad post-doctoral en la Universidad de Navarra, bajo la dirección del Dr. Iñaki Trocóniz. Ha realizado estancias en la University of Leiden, Universidad de Navarra y University College of London. Desde 2017 es profesor Ayudante Doctor en la Universidad de Valencia. Su investigación se centra en el área de la farmacometría, mediante el desarrollo de modelos PK/PD poblacionales, modelos PBPK y metodologías para la comparación de perfiles de disolución. Es asesor externo de la EMA y AEMPS y miembro de MSWP de la EMA.

15 QUANTITATIVE ASSESSMENT OF THE EXPOSURE-EFFICACY RELATIONSHIP USING MARKOVIAN ELEMENTS IN GAUCHER PATIENTS

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ABSTRACT

Introduction: Gaucher disease (GD) is a rare, recessively inherited lysosomal storage disorder caused by deficiency of a lysosomal enzyme, glucocerebrosidase (GBA1), which leads to insufficient elimination of cellular glucosylceramide[1] and its subsequent storage in cell lysosomes from the monocyte-macrophage system [2]. Pathologic accumulation of glucosylceramide (or other substrates, such as glucosylsphingosine) in the lysosomes of tissue macrophages (Gaucher cells), results in splenomegaly, hepatomegaly and multiple forms of skeletal disease[3].

Objectives: The aims of this study are (i) to quantitatively characterize the relationship between efficacy markers and treatment exposure and, (ii) to determine the conditions for the optimal selection of the dosage regimen.

Methods: A prospective follow-up, observational multicentre study was conducted in four public hospitals from June 2010 to December 2017. Continuous glucocerebrosidase activity (GBA1) observations were collected 10 and 75 minutes pre- and post-administration, respectively, during therapeutic drug monitoring (TDM) up to one year after the patient's enrolment. GBA1 observations in leukocyte and monocyte were available for the analysis. Two different analytical procedures (Fluorescence and ultraviolet) were used, which measured GBA1,2,3 and GBA1, respectively. The efficacy dataset consisted of categorical data of infiltration of Gaucher cells in the bone marrow collected every 12 months during seven years of treatment based on the number of infiltrated Gaucher cells, where several different indexes were evaluated (SMRI, Zimran and GausSI scales). Logistic regression models using a discrete-time Markov model (DTMM) was performed. The efficacy data were treated as ordered categorical data, and

through a fist-order Markov element. Several exposure metrics were evaluated (Cmin, Css, and AUC), which were predicted based on the population PK model, coinciding with the days on which the PD samples were obtained. A simulation-based analysis was carried out to assess how different experimental conditions may affect parameter estimation, and subsequently dose selection.

Results: A population PK model developed in 25 individuals with 266 GBA1 in leucocytes and monocytes observations was used to derived the exposure metrics. Briefly, a two concatenated compartments to describe GBA1 observations in leucocytes and monocytes, respectively, assuming zero-order endogenous production of GBA1 to describe a constant synthesis of the endogenous enzyme. A first-order distribution of GBA1 from leucocytes into monocytes and a first-order elimination process of GBA1 from monocytes properly modelled GBA1 profiles. An exponential time-dependency effect on CL1 statistically improved the description of the data ($p<0.01$). A total of 14 individuals with 68 observations of efficacy after ERT administration were included for the analysis during 7 cycles of treatment. The final exposure-efficacy model was a longitudinal logistic regression model with a first-order Markov element[4]. An Emax function (EC50=15.73 mU/mL and Emax=2.33) linked the relationship between the steady-state concentrations of GBA1 in monocytes to the probability of transition across the different stages. The inclusion of baseline GBA1 activity was statistically significant and allowed to partially explain the inter-individual random effects on EC50.

Conclusions: A dose-efficacy relationship, measured as infiltrated Gaucher cells in bone marrow scale adequately predicts the pharmacodynamic outcome along treatment cycles using a first-order Markov dependency.

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***KEYWORDS**: Gaucher disease, Enzyme-replacement therapy, GBA1, discrete-time Markov model.*