Abstracts of Iberoamerican Pharmacometrics Network Congress Guadalajara, México. November 7th-9th 2018

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Oral Presentations

Semi-mechanistic Pharmacokinetic/Pharmacodynamic model of three pegylated rHuEPO and ior®EPOCIM in New Zealand rabbits

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Marketed formulations ior®EPOCIM, MIRCERA® and two new branched PEGylated erythropoietin formulations (32kDa-PEG_2-rHuEPO and 40kDa-PEG_2-rHuEPO) were administered a single dose by intravenous bolus in New Zealand rabbits. The aim of this work was to develop a semi-mechanistic pharmacokinetic/pharmacodynamic (PK/PD) model describing in a simultaneous and integrated form the time course of erythropoiesis stimulation after erythropoietin administration. The PK/PD dataset consisted of 266 EPO measurements in the pharmacokinetic analysis and 799 observations of reticulocyte (RET), erythrocyte (RBC) and hemoglobin (HGB) in the pharmacodynamic analysis from 19 and 20 rabbits, respectively.

The First Order Conditional Estimation Method with INTERACTION as implemented in NONMEM version 7.3 was used in PK/PD modeling. A semi-mechanistic cell transit model that included a two-compartment model with linear elimination and cell proliferation, maturation, and homeostatic regulation provided a good description of the data regardless the type of erythropoietin formulation administered. Inter-subject variability was associated with clearance (50%) and apparent volume of distribution of the central compartment (60%). Residual unexplained variability was estimated to be 20.5 %. The system- and drug-related parameters showed consistency and differed across formulations, respectively. The 32kDa-PEG_2-rHuEPO and 40kDa-PEG_2-rHuEPO formulations achieves a median change of 27% and 22% on RET levels, and of 63% and 47% on RBC and HGB levels, respectively compared to MIRCERA®.A semi-mechanistic PK/PD model of erythropoiesis provided and adequate description of the observed data of ior®EPOCIM, MIRCERA® and PEG-EPO 32 kDa and PEG-EPO 40 kDa in New Zealand rabbits. The administration of new branched PEG-chains formulations improves PK and PD properties, in terms of increasing el

imination half-lives and pharmacological response on RET, RBC and HGB compared to commercially available formulations (ior®EPOCIM and MIRCERA®).

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Population pharmacokinetic modeling of bromopride in healthy subjects

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The dopamine antagonist, Bromopride (BRO) is a prokinetic and antiemetic drug used to treat nausea and vomiting. Although its prescription is common in Brazil, there is a lack on studies of BRO pharmacokinetics. The aim of this study was to investigate the population pharmacokinetic of BRO after oral administration. This study is a retrospective analysis of data from bioequivalence studies submitted to Brazilian Health Surveillance Agency (ANVISA). The data was modeled using MONOLIX 2018R2. Assuming one-compartment disposition and linear elimination, the oral phase was evaluated for different structural models like zero- and first-order (with and without a lag time), transit compartment and mixed absorption. Anthropometric and laboratorial results were evaluated for covariate effect. The goodness-of-fit (diagnostic plots, BIC and log- likelihood) shows model of zero order with lag time (Tlag) and combined error described better the absorption process of BRO. Inter-individual variability was considered for all parameters, although the parameter clearance (Cl) was fixed in 0.768 L/h/kg [1]. Typical parameters estimates were bioavailability (F) of 87%, duration of the zero-order absorption (Tk0) of 0.862 h with Tlag of 0.481 h and a volume of distribution of 4.39 L/kg. The dosage form was the covariate found to significantly

affect F and Tlag, and body mass index positively affect Tk0. Zero-order models are reasonable to describe absorption process of drugs whose input is influenced by solubility. None previous information about population pharmacokinetic absorption model was described for BRO.

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Bioavailability prediction for losartan tablets by means of PBPK modeling and simulation

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The Uruguayan pharmaceutical market is composed in a large percentage of similar medicines, a situation that is common to other countries in Latin America. This factor adds variability to the PK/PD outcome in the clinical setting, both at the onset of a therapy and when products are interchanged throughout chronic treatments. In this context, development of physiologically-based pharmacokinetic models (PBPK) integrating biorelevant in vitro drug dissolution can be employed to detect possible bioinequivalence issues. Here, a PBPK model for losartan and its active metabolite, carboxylosartan, was developed to predict the performance of different multi-source products. PK-Sim® (Bayer) software was employed for modeling and simulation. The model was evaluated by comparing in silico outputs for plasma concentration-time profiles of the parent drug and the metabolite with published data for the brand-name drug Cozaar® in two stages: (i) integrating losartan and carboxylosartan physicochemical and pharmacokinetic properties to predict in vivo dispositions after an intravenous administration of them; (ii) integrating in vitro biorelevant dissolution to predict losartan bioavailability and in vivo formation of carboxylosartan from losartan. For the stage (ii) different in vitro conditions were assessed. Finally, a suitable in vitro-in silico-in vivo correlation was achieved by using data from dissolution testing in USP Apparatus II at 75 RPM in acidic (HCl/KCl pH 1.2, 37°C, 30 min) and neutral (Phosphate buffer pH 6.8, 37°C, 10 min) conditions and simulating a two- phase dissolution for the formulation input at the PBPK model. Secondary pharmacokinetic parameters for a virtual Caucasian population of healthy subjects (50:50 male:female) assessing rate and extent of absorbed drug, as well as drug disposition were simulated with acceptable mean absolute error. The validated model was finally used for extrapolation of losartan and carboxylosartan pharmacokinetics for the similar products.

Results indicate that no significant differences for losartan bioavailability are foreseen between marketed brands.

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Population pharmacokinetic analysis of PHT in epileptic patients after the oral administration of two formulations marketed in Uruguay

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Phenytoin (PHT) is a widely prescribed antiepileptic drug used to treat several types of seizures. PHT characterizes for a non-linear pharmacokinetic, narrow therapeutic range and acute dose-related side effects. Also, PHT induces efflux transporters in a dose-dependent manner.

The aim of the present investigation was to compare the oral bioavailabity of two products containing PHT marketed in Uruguay (Comitoína simple® and Antepil®). Data from a previously conducted pharmacovigilance study was modeled. A total of 57 patients (30 female, 27 male) between 18 and 76 years old with epilepsy and under chronic treatment with either one of the mentioned formulations, were enrolled in the study. Age, weight, albumin concentrations, clinical outcome and adverse effects information was collected. The protocol was approved by the Institutional Ethics Review Committee of the Faculty of Chemistry.

Morning steady state pre-dose blood and saliva samples were collected every 3 months. At least 6 extra saliva samples were withdrawn at the first 12 hours post dose.

A one-compartment pharmacokinetic model with nonlinear elimination was implemented to describe plasma PHT concentrations. A Maximum a Posterior estimation for the population parameters was employed in MONOLIX 2018. Covariates analysis was performed.

Body weight was included as a covariate in volume of distribution (V1) and maximum elimination rate (Vm). Interestingly, a correlation between Saliva/Plasma ratio and PHT plasma concentration was found. Considering albumin concentrations were within the normal range for all patients, no protein saturation may be envisaged. Then, the correlation found could not be due to a concentration-dependent PHT protein binding and would evidence the induction of efflux transporters at the salivary glands.

Lastly, no difference was found between the oral bioavailability of the studied formulations.

Population Pharmacokinetic Modeling of Tacrolimus in Pediatric and Adult Renal Transplant Patients

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Tacrolimus is a potent immunosuppressive drug widely used in adults and children for the prevention of allograft rejection after kidney transplantation [1,2]. However, because of tacrolimus narrow therapeutic index and high inter-individual pharmacokinetic (PK) variability [3,4], blood concentrations must be monitored. Population PK modeling could be a useful tool in the tacrolimus therapeutic drug monitoring (TDM). Therefore, a popPK model was developed in pediatric (n=29) and adult (n=60) kidney-transplant recipients using Phoenix NLME 8.0 version with the FOCE ELS algorithm selected as the estimation method. Some tacrolimus PK variability factors were assessed with the stepwise forward inclusion procedure. The minimum value of twice the negative log likelihood (-2LL) and the goodness of fit graphs were used to choose suitable models. The final model was internally validated. During the PK model-building procedure, different structural pharmacokinetic models were tested. The tacrolimus PK profiles were best described by a two-compartment model with first order absorption and elimination. Additionally, intra-patient variability (IPV) was modeled with an additive error. Our covariate analysis detected significant effect

of age, weight, and hematocrit, being the age, the most significant covariate tested. In conclusion, a population pharmacokinetic model of tacrolimus was developed and validated in both, pediatric and adult patients with renal transplant. The final model is expected to improve clinical outcomes during the TDM of tacrolimus. This studywas conducted according to the principles of the Declaration of Helsinki and was approved by the Institutional Review Boards and Ethics Committees.

Keywords: Tacrolimus – population pharmacokinetic – therapeutic drug monitoring

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Posters Presentations

Modeling & simulation of amikacin in pediatric cystic fibrosis for dose optimization

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Amikacin is a valid option to treat lung chronic infection in pediatric patients with cystic fibrosis (CF). The efficacy is related to the achievement of a high Cmax/MIC (maximum plasma concentration/minimum inhibitory concentration) ratio: 8 to 10. However, pharmacokinetic data in this population are very scarce. The objective of this study was to develop a population pharmacokinetic model describing amikacin disposition in pediatric CF patients. A prospective study was carried out after protocol and informed consent approval by the Institutional Review Board at Garrahan Pediatric. Patients less than 18 years old, with CF diagnosis and receiving amikacin for treatment of lung infections were eligible. Serum samples derived from therapeutic drug monitoring.

Thirty-nine patients were included (114 amikacin concentrations). A population pharmacokinetic model was developed using MONOLIX Suite-2018R1 (Lixoft). Final population estimates for the elimination rate constant (k) and the volume of distribution (V) were 0.541 h^{-1} and 0.451 L/kg, respectively. Between-subject and between-occasion variability were 53% and 16.5% for k and 31% and 22% for V, respectively. Body-weight remained as a significant covariate associated with V. Simulations allowed prediction and evaluation of C_{max} and C_{trough} distributions for different dosage regimes with clinical implications. Based on our analysis, 67% of the simulated patients receiving 30 mg/kg/day, could achieve an appropriate Cmax/MIC. Although all our patients had good clinical results and a very good adverse events profile, further studies are necessary to redefine an optimal therapeutic strategy.

Population pharmacokinetics of mycophenolic acid in patients with lupus nephritis

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Lupus nephritis (LN) is the most frequent severe complication of systemic lupus erythematosus and is associated with increased morbidity and mortality [1]. Mycophenolate mofetil (MMF) is the prodrug of mycophenolic acid (MPA) a potent immunosuppressant agent that provides effective treatment for LN patients [2-3].

The aim of this study was to analyze the pharmacokinetic behavior of MPA and estimate the dosing requirements in Mexican patients with LN using nonlinear mixed effects modelling (NONMEM®).

The study enrolled 40 patients receiving MFM with LN from HCIMP of San Luis Potosí. Samples were collected pre-dose, 0.3, 0.6, 1, 1.5, 2, 4 and 6 hours post-dose.

MPA concentrations were determined by an UPLC-MS/MS technique. Patients were genotyped for enzymes UGT1A8, 1A9, 2B7 and transporters ABCC2 and SLCO1B3.

A two-compartment model with first order absorption and elimination best described the data. The final population pharmacokinetic model obtained was: $CL(L/h)=15.4*(CrCl/80)^{0.633}*(1+0.583PDN)$; $Vc(L)=0.38*BW$, $Ka(h^{-1})=1.28$, $Q(L/h)=15.4$, $Vp(L)=755$. (CrCl: creatinine clearance; PDN: prednisone; BW: body weight). Apparent clearance of MPA decreased with reducing renal function. Patients with decreased CrCl have a reduced hepatic metabolism generated by the chronic renal failure state itself [4]. PDN comedication showed an increase in the CL of MPA, possibly through induction of UGT [1,5]. The only covariate that demonstrated influence in Vc was BW. The internal validation of the model obtained for MPA was performed by the Bootstrap and the visual predictive check techniques. Stochastic simulations were executed to propose dosing guidelines considering CrCl, BW and PDN comedication to achieve expected MPA AUC0-12 h (30-60 μg*h/L).

Ethical approval

The protocol of this study was approved by The Ethics Committee in Research of the Hospital Central "Dr. Ignacio Morones Prieto" (No.71-17) and the Research and Teaching Ethics Committee of the Faculty of Chemical Sciences of the Autonomous University of San Luis Potosí (No. CEID2017113-S). Each patient provided written informed consent prior to study enrolment.

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Determination of mycophenolic acid and pharmacokinetic application in kidney transplant patients

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Mycophenolic acid (MPA) is an antimetabolite immunosuppressant of choice in solid organ transplant regimens [1]. Mycophenolate of mofetil is a pro-drug and after oral administration, it is completely absorbed and readily hydrolyzed to its active metabolite MPA. The pharmacokinetics of MPA is characterized by large inter- and intraindividual variability[2]. A chromatographic method (UPLC-MS/MS, Waters Corporation) was standardized and validated according to national. Pharmacokinetic parameters of MPA were calculated using WinNonlin® software (v. 4.2) by non-compartmental analysis. Optimal conditions for UPLC-MS/MS method were obtained with ESI (+). Selected transitions correspond to m/z 321.07→159.0 and 321.07→207.0 for qualification and quantification of MPA. Indomethacin was used as internal standard. The method was validated according to NOM177-SSA1-2013. Calibration curves were linear at 0.2 – 30 μg/mL of MPA in plasma (r2>0.996) with recoveries between 90 and 110%. Inter and intra- assay precision were 2.98% and 3.4% of coefficient of variation (<5%). The implemented and validated technique was used to quantify MPA in 10 concentration- time profiles (0 – 12 h) from 10 kidney transplant patients. Mean AUC was 40.6±17 L/h, Cmax 11.9±5 μg/mL, CL of 15.57±9 L/h, V 104.3±48 L. This study represents an advantage on therapeutic drug monitoring of this immunosuppressant in kidney transplant patients to support pharmacological treatment.

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Pharmacokinetics and pharmacogenetics of lamotrigine in adult patients with epilepsy

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Lamotrigine (LTG) is a second-generation anti-epileptic drug (AED) that has been widely used for focal and generalized seizures in adults and children as monotherapy or in combination with other AEDs [1-3]. The aim of this study was to develop a population pharmacokinetic model for quantitative evaluation of the influence of various demographic, pathophysiological, genetic variants and adjunctive therapy on LTG pharmacokinetics.

A total of 73 adult patients on stable treatment with LTG at least two weeks as mono or adjunctive therapy attended at the Epilepsy Clinic of the Hospital Central "Dr. Ignacio Morones Prieto" were included. LTG was determined by HPLC-UV technique in one plasma sample per patient. Population pharmacokinetics analysis was performed by non-linear mixed effects modelling approach using NONMEM® software. The covariables tested were: age, sex, height, weight, serum albumin, creatinine, alanine transaminase, and aspartate aminotransferase levels, creatinine clearance, body mass index, body surface, tobacco consumption, UGT2B7 genetic variants, comorbidities and adjunctive therapy.

Absorption rate constant, bioavailability and distribution volume were fixed at 1.4 h^{-1}, 1.00 and 1.8 L/kg, respectively, to stabilize the model. LTG clearance was estimated at 1.82 Lh^{-1} and was associated with co-treatment with valproic acid (VPA) and carbamazepine (CBZ). The final population pharmacokinetic model for LTG was CL (L/h) = 1.82 x (1 - 0.465 VPA) x (1 + 0.841 CBZ) and it explains 23% of the interindividual variability associated with LTG clearance. This model was internally validated by

bootstrap and visual predictive check techniques. Stochastic simulations were performed to propose dosage regimens considering comedication with VPA and CBZ to achieve reference interval (2.5 – 15 mg/L).

This is the first population pharmacokinetic study of LTG in Mexican patients and indicates that co-treatment with VPA and CBZ should be considered to individualize epilepsy treatment with this drug.

Ethical approval

The study was approved by Research Ethics Committee and the Research Committee of the Hospital Central "Dr. Ignacio Morones Prieto" (registration number 70-17) and under the knowledge of the Committee of Ethics in Research and Teaching of the Faculty of Chemical Sciences (code of registration: CEID2017112-S).

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Bioanalytical method validation for the simultaneous determination of paracetamol, amantadine and chlorpheniramine in human plasma by high performance liquid chromatography-tandem mass spectrometry

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Paracetamol, amandatine and chlorpheniramine are used as a combination in the treatment of common cold. "This combination is one of the most popular over the counter analgesic and antipyretic drugs which is available in different dosage forms" [1]. A rapid, sensitive and specific high performance liquid chromatography with positive electrospray ionization tandem mass spectrometry method was developed and validated to simultaneously determine paracetamol, amantadine and chlorpheniramine, using diphenhydramine and memantine as internal standards. Following a liquid-liquid extraction with ether:dichloromethane:hexane:isopropanol, the analytes where separated using a ZORBAX ECLIPSE XDB-CN 4.6X75 mm, 3.5 µm column, with a composition of formic acid 1% in acetonitrile: Ammonium acetate 10 mM in formic acid 1% (80:20 v/v) used as mobile phase, and analyzed by positive electrospray ionization tandem mass spectrometry (Agilent HPLC- MS/MS Triple Quadrupole). Multiple Reaction Monitoring (MRM) was used with the precursor to product ion transitions of m/z 152.1→110.0 (Paracetamol), 152.1→135.1 (Amandatine), 275.1→230.0 (Chlorpheniramine), 180.1→107.05 (Memantine) and 256.1→167.05 (Diphenhydramine). The method was linear in the range of 50.0-10000.0 ng/mL for paracetamol, 2.0-700.0 ng/mL for amantadine and 0.1-10.0 ng/mL for chlorpheniramine (r^2>0.99). Precision was less than 15% (%CV) and accuracy was less than 15% (%RE) for the three analytes. The method was full validated according to the Mexican guidance NOM-177-SSA1-2013 [2] and applied in a bioequivalence study of Paracetamol/Amantadine/Chlorpheniramine following a single oral dose of (300 mg/50 mg/3 mg) capsules in 20 healthy volunteers (COFEPRIS approved, 163300410B0447/2016).

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Therapeutic drug monitoring of levetiracetam in patients with epilepsy

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Therapeutic Drug Monitoring (TDM) of levetiracetam (LEV) allows to evaluate therapeutic adherence and determine the impact of interchangeability of innovative LEV by generic products, as it may result in loss of seizure control or pharmacological toxicity. This is achieved through the plasma LEV quantification in patients with epilepsy (PWE). The study was approved by the Hospital's Research Ethics Committee (No. 86-16) and participants signed informed consent. Patients ≥18years were required to be on stable dose treatment with immediate-release LEV for at least 1week, in monotherapy or polytherapy with another antiepileptics. From each patient, 1 to 4 samples of blood were obtained at different times in the range from 0 to 12h post- dose. Samples were analyzed by a validated HPLC-UV method. Innovative and generic products of LEV available in the market were identified. LEV plasma concentrations of 110 PWE were determined. Pharmacokinetic parameters Cmax=26.16μg/mL (500mg dose-normalized) and Tmax=1.37h were calculated using non-compartmental analysis (NCA) with WinNonlin® Professional Version 4.1. Median elimination half-time (t1/2) was 5.81h (5.1 to 6.7h) for patients ≤60years and 8.97h (7.74 to 10.92h) for elderly patients, which is greater due to age-associated decreased renal function. Results are in accordance with previous reports [1]. Only 48.48% of the patients had plasma concentrations within the therapeutic range (6 to 46μg/mL), and 34.55% of patients may require dose reduction, while 17.27% may need dose increase. We identified 18 generic products and only 10% of the patients acquire the innovative product. No correlation was found between reached Cmax and innovative or generic products administration. TDM of LEV in PWE has been successfully implemented as a clinically useful tool to protect patient's quality of life.

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Therapeutic drug monitoring of isoniazid and rifampicin and genotyping analysis in patients with tuberculosis

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Strictly supervised shortened treatment (DOTs) for tuberculosis includes isoniazid (INH), rifampicin (RIF), pyrazinamide and ethambutol. One strategy to improve the response to treatment is the individualization of doses through the plasma monitoring of antimicrobial concentrations. Prospective, analytical, observational and cross-sectional study was approved by ethics committee, number 77-15. 43 patients with TB under DOTs scheme were included. Samples of venous blood were taken at 2 and 4 hours post-dose. Genotyping analysis was carried out for *NAT2* and *MDR1* genes; anthropometric, clinical and medication data recorded. The quantification of RIF and INH was made using a validated UPLC-MS/MS method. Genotyping of *NAT2* showed 51.16% slow acetylators, 34.88% intermediate and 13.95% fast. The *NAT2* rapid phenotype showed significant differences ($p<0.05$) with $t_{1/2}$ (2.72h), Cmax (3.25μg/mL), $ABC_{0-\infty}$ (11.45h*/g/mL), λ ($0.28h^{-1}$) and CL/F(26.23L/h) compared to the slow acetylator, with $t_{1/2}$ (4.7h), Cmax (5.16 μg/mL), $AUC_{0-\infty}$ (22.35h*/g/mL), λ ($0.16h^{-1}$) and CL/F (13.8L/h). The therapeutic interval reported for INH is 3-5μg/mL, therefore, 32.56% of patients were identified below and 32.56% above it.

The homozygous polymorphic TT patients of *MDR1* registered increased values of Ka, Cmax and $ABC_{0-\infty}$, and lower $t_{1/2}$ and Tmax compared to other genotypes. Among wild subjects CC and heterozygous CT, significant differences were recorded in Ka, $t_{1/2}$, Cmax, Tmax and $ABC_{0-\infty}$, respectively. Therapeutic range of rifampicin ranges from 8-24μg/mL: 18.18% of patients were below and 81.81% had bactericidal concentrations.

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Application of method by UPLC-MS/MS for quantification of methotrexate polyglutamates in patients with rheumatoid arthritis

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Methotrexate (MTX) is one of the most commonly prescribed drugs for the treatment of rheumatoid arthritis (RA). The therapeutic effects are due to intracellular transport and its transformation to polyglutamates (MTX-PGs) [1]. The products of glutammation can be 2- 6 molecules of PGs; the prevalent type of PG species is PG3 associated with the efficacy and PG5 is associated with the presence of side effects.

Red blood samples were analyzed by UPLC-MS/MS using a HSS T3 column with a mobile phase 10 mM ammonium bicarbonate (pH 7.5) and a flow rate of 0.3 mL/min. The analysis consisted of simple sample preparation and run time of 8min. Detection was done using a Waters Acquity UPLC with a Waters Quattro Premmier XE with electrospray ionization operating in the positive ionization mode.

The method was linear from 1.9-500nM for PG3 and 3.9-500nM for PG5 (R^2 >0.99). It is accurate, selective and precise (reproducibility and repeatability with a CV<15%) complying with the provisions of NOM-177-SSA1-2013. Samples were stable for at least 1 month at -80°C. Fifty-nine patient samples were analyzed obtaining average concentrations of 20.53nM and 1.8nM of PG3 and PG5, respectively.

The developed of this method allows the quantification of MTX-PGs in red blood cells, which can be applied in clinical studies such as pharmacokinetic evaluations or therapeutic drug monitoring in patients with RA.

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Quantification of loperamide in human plasma by ultra-performance liquid chromatography–mass spectrometry

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Loperamide is a potent μ-opioid receptor agonist with antidiarrheal action [1]. Reported analytical methods for plasma determination of loperamide are complex or have poor sensitivity [2,3]. A method based on Liquid Chromatography-Mass Spectrometry (LC- MS/MS) has been developed and validated for the quantitative determination of loperamide in human plasma. Ethyl acetate-hexane (80:20 v/v) was used to extract loperamide and eletriptan (internal standard) from an alkalized plasma sample. The LC separation was performed on an ACQUITY UPLC BEH HILIC (3.0 x 75 mm, 1.7 μm) column using formic acid 0.1% in methanol: formic acid 0.1 % in water (60:40 v/v) as mobile phase, with a run time of 1.5 min at a constant flow rate of 0.5 mL/min. The retention time of loperamide and eletriptan were 0.73 and 0.74 minutes, respectively. The MS/MS ion transition monitored (MRM) were m/z 477.34→266.10 for loperamide and 383.22→84.30 for eletriptan. The calibration curve was linear through the range of 20 – 5 000 pg/mL (r= 0.999492). The within- and between-day precisions were all below 8.9% (CV) and accuracies below 8.8% (RE). The short term (24 h at room temperature) and long-term stability (15 days at freezing) were demonstrated. The method also showed acceptable specificity, sensibility, recovery (loperamida 83.8% and eletriptan 87.5%) and did not showed carry over or matrix effect. A simple, fast, and sensitive LC-MS/MS method for the quantification of loperamide in human plasma was validated according to Mexican regulation and was succesfully used in a clinical study of pharmacokinetic bioequivalence [4].

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Correspondence between the CYP2C19 and CYP3A4 genotypes with the inferred metabolizer phenotype by omeprazole administration in Mexican healthy children

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CYP2C19 genotypes presumably allow predicting the metabolizer phenotypes: poor (PMs), extensive (EMs) and ultra-rapid (UMs). However, evidence from previous studies regarding this predictive power is unclear, which is important because the benefits expected by health care institutions and patients are supported on this premise [1-10]. Therefore, we aimed to complete a formal evaluation of the diagnostic value of the *CYP2C19* and *CYP3A4* genes to predict metabolizer phenotypes established by omeprazole administration in 118 healthy children from Jalisco (West, Mexico). The genotypes for *CYP3A4*1B* and *CYP2C19*2, *3, *4, *5* and **17* alleles were determined. The CYP2C19 and CYP3A4 phenotypes were obtained after 20 mg omeprazole administration and HPLC quantification in plasma to estimate the Hydroxylation index (HI= OME/HOME) and Sulfonation index (SI= OME/SOME), respectively. The *CYP2C19* and *CYP3A4* genotype and phenotype distribution was similar to previous studies in Mexico and Latin America. Although differences in the HI distribution were observed between *CYP2C19* genotypes, they showed a poor diagnostic ability for predicting the CYP2C19 metabolizer phenotype. Similarly, the number of *CYP2C19* and *CYP3A4* functional alleles was correlated to the HI distribution, but also their diagnostic ability was poor to predict the CYP2C19 phenotype. In conclusion the CYP2C19 phenotype is not predicted by the number of functional alleles of the *CYP2C19* and *CYP3A4* genes. Phenotyping is still the most valuable alternative to dose individualization for CYP2C19 substrate drugs.

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Nonlinear pharmacokinetics in rats of a galloylquinic acid isolated from *Copaifera langsdorffii*

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Copaifera langsdorffii is a large tree popularly known as "copaiba" and distributed in many Brazilian states [1]. This plant species leaf extracts and isolated compounds display gastroprotective and antilithiatic activities. In previous works, *C. langsdorffii* extract demonstrated to be potent on the treatment and prevention of kidney stones in rats [2,3]. In order to investigate the influence of this species against urolithiasis, it was observed that polar fractions were more active and 5',5''-di- O-methyl-3,4-di-O-galloylquinic acid was isolated and studied pharmacokineticaly. Therefore, the aims of this study were to determine plasmatic and kidney concentrations of this galloylquinic acid and modeling the results obtained. Three groups of five healthy male Wistar rats (Ethics Comittee of Federal University of Rio Grande do Sul number 29547) were anesthetized and blood samples were collected at 5, 10, 15, 20, 30, 45, 60, 90 and 120 min. after i.v. administration of 1.0 mg/kg, 1.5 mg/kg and 2.0 mg/kg of galloylquinic acid. A tissue distribution assay was also performed, in which three animal per time had blood and kidney

collected at 5, 15, 45, 60, 90, 120 and 180 min. after i.v. administration of 1.0 mg/kg of galloylquinic acid. The pharmacokinetic parameters were analyzed using Phoenix® for non-compartmental analysis and Scientist® for two-compartmental analysis with Michaelis-Menten elimination. The $AUC_{0\text{-}inf}$ values were 113.1±26.0 vs 103.8±23.9; 289.7±81.7 vs 386.1±151.0; 386.1±151.0 vs 363.6±142.3 (ng*h/mL), respectively for non- compartmental and compartmental analyses of 1.0; 1.5 and 2.0 mg/mL. With regard to the kidney parameters, it was found an $AUC_{0\text{-}t}$ of 1.24 μg*h/mL, resulting in a tissue/plasma ratio of 12.4. In conclusion, it was demonstrated that this galloylquinic acid has a nonlinear profile, being described better with Michaelis-Menten elimination. It has also affinity to kidneys, where a high concentration was found.

Keywords: *Copaifera langsdorffii*, urolithiasis, galloylquinic acid, pharmacokinetic, modeling.

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Betacyanins from *Opuntia robusta* and *Opuntia streptacantha* fruits against acetaminophen-induced oxidative liver damage

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Acetaminophen (APAP) represent a worldwide health problem due to the risk of morbidity and mortality by its misuse [1,2]. Overdoses of acetaminophen induce acute liver injury caused by an electrophilic metabolite [3]. Plant-based medicine has been used for centuries against human diseases due to presence of biocomponents with pharmacological activities [4]. The aim of this study was to identify the main component and to evaluate the therapeutic effect of two purple cactus fruits against acetaminophen-induced hepatotoxicity. Juices were obtained by peeling and squeezing each type of cactus fruit, then lyophilized, stored, and characterized. Male Wistar rats were used to evaluate the effect of the treatments (800 mg/kg, *p.o.*) used 0.5 h after acetaminophen-induced acute liver injury (500 mg/kg, *i.p.*). Biochemical and molecular (qPCR) tests were analyzed after 6 h, and histological tests after 24 h of APAP intoxication. Results showed that betacyanin pigments are the main components in the analyzed *Opuntia* fruits. Treatments were effective by modulating the main biochemical (ALT, AST, LDH, ALP, GSH, and MDA) and molecular (Mn-SOD, HO- 1, GCL, and Gadd45β) markers of liver damage, both *in vivo* and *in vitro*. The histological and cell culture tests showed a reduction of cell death and swelling of the hepatocytes exposed to acetaminophen and treated with *Opuntia* fruit juices. The presence of betalains, specifically betacyanins, in *Opuntia robusta* and *Opuntia streptacantha* might be the cause of the improvement of the liver function due to their capacity to inactivate free radicals [5] and modulate molecular responses of detoxification [6] and survival [7] after the acetaminophen intoxication. Results suggest that betacyanins in *Opuntia robusta* and *Opuntia streptacantha* fruits might be used as an alternative treatment against APAP-induced acute liver damage although further studies to determine their bioavailability and therapeutic dosage of the isolated compound are needed to confirm this.

Abbreviations: APAP: acetaminophen; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; GSH: glutathione; MDA: malondialdehyde; Mn-SOD: manganese-superoxide dismutase; HO-1: heme-oxygenase 1; GCL: glutamate-cysteine ligase; Gadd45β: growth arrest and DNA damage-inducible beta.

Ethical approval: experiments were approved by and performed following the guidelines of the local Committee for Care and Use of laboratory animals (Permission No. 6415A of the Committee for Care and Use of laboratory animals of the University of Groningen and Mexican governmental guideline NOM-033-ZOO-1995).

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Pharmacokinetic model of lamotrigine in Mexican children with epilepsy

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Epilepsy is a complex disease that requires a fast, precise and efficient treatment to avoid severe consequences in patients' life.[1] Lamotrigine is one of the main drugs used in the pharmacologic management of the disease,[2] unfortunately, great variability in the therapeutic outcomes has been demonstrated when Lamotrigine is prescribed.[4] To explain the pharmacokinetics variability of Lamotrigine we decided to approach through a pharmacokinetic model. Children were invited to the study if they had epilepsy diagnosis and used lamotrigine (from any manufacturer). Blood samples were taken at 6 different times: 0 hours, before the drug was administered, and after that at 1, 2, 4, 6 and 12 hours. We recruited a total of 16 patients and obtained 89 observations.

Using Phoenix NLME 8.0 and the first-order conditional estimation extended least squares (FOCE ELS) algorithm we were able to test several structural pharmacokinetic models, and a one- compartment, first order absorption model was selected. In regard to the structural model we obtained the following parameters: Ka 5.30 ± 0.03 (h^{-1}), V 113.17 ± 2,12 (L) and Cl 0.94 ± 0.07 (L/h). After covariate assessment was performed we found that concomitance with Valproate impacts significantly over clearance, as well as UGT2B7 polymorphisms. [6; 7]

The largest variability in the structural model was in CL which improved in the full model, Ka is now the one with the largest variability, this may be associated with pharmaceutical quality issues found by our group.

The values obtained are:

stparm(Ka = 5.60283 * exp(4.6132923))
stparm(V = 112.226 * exp(0.0028306517))
stparm(Cl = 0.94859 * exp(-0.800187*(Val==1)) * exp(-0.457226*(UGT2B7==1))) * exp(0.10728873))

This model will be enriched with extra monitoring points over time, hence, the model is still subject to refinement. The second phase will be an external validation at hospital to improve drug clinical outcomes and reduce adverse effects frequency.

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Effect of olanzapine on indicators of oxidative stress of people with schizophrenia

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Oxidative stress plays a fundamental role in the pathophysiology of schizophrenia [1-2]. The main objective of this work is to investigate the association of oxidative stress markers with plasma levels of olanzapine in Mexican patients diagnosed with schizophrenia. For this purpose, an analytical method using ultra-high pressure liquid chromatography with diode array detector (UHPLC-DAD) was developed in order to quantify plasma olanzapine. The plasma levels of oxidative stress markers (nitric oxide catabolites, protein carbonyls and catalase activity) were quantified using standard spectrophotometric methods. Blood samples were obtained from patients diagnosed with schizophrenia and healthy control subjects non-treated with olanzapine. The study was approved by the Jalisco´s Institute of Mental Health. The sensitivity of the developed system is 1.2 ng/mL of olanzapine in plasma. The precision (%CV) of the chromatographic system was ≤ 2.0%. The clinical characteristics of healthy controls and patients with schizophrenia were similar (P=0.6203). In patients with treatment, no correlation was found between plasma levels of olanzapine and pharmacological dose (R2=1.32%). Compared to non-medicated controls, an increase in nitrite-nitrate levels was found in patients after one month of olanzapine treatment and with a decrease in psychotic symptoms (P=0037). Basal levels of protein carbonyls were significantly higher and they tend to decrease after a month of treatment with olanzapine (P=0.0016). Catalase activity increased after one month of treatment with olanzapine (P=0.0005). In patients there is a direct relationship between the plasma concentration of olanzapine and the plasma levels of nitrites-nitrates. No associations were detected between catalase activity and protein carbonyls levels with plasma levels of olanzapine.

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Pharmacokinetic evaluation of lyophilized kit formulations for the radiolabeling of monoclonal antibodies as theranostic tools in nuclear medicine applications

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Antibodies directed to tumor-associated antigens allow us the development of therapies against specific molecular targets improving treatment efficacy, while systemic toxicity is reduced. N-glycosilated ganglyosides are not common in human normal tissues, they are just expressed in some tumor cells. On the other hand, EGF receptor is overexpressed in tumors of ectodermal origin, which constitutes almost 80% of all malignancies. Thus, both receptors are a very interesting targets for the immunotherapy. Monoclonal antibodies labeled with 99mTc, directed against EGF receptor and N- glycosilated ganglyosides, can be used as theranostic tools, for the selection of patients with an overexpression of such molecular targets, the follow-up, and assessment of clinical efficacy of the immunotherapy with monoclonal antibodies. In the present work, we describe the radiolabeling procedure of monoclonal antibodies 14F7h (directed to N- glycosylated ganglioside) and nimotuzumab directed againt EGF receptor as well as the development of a kit formulation. In order to compare *in vivo* behavior of Mabs in lyophilized formulation in comparison with traditional dissolution technique a pharmacokinetic study in tumor murine models were performed fallowing a sparse data experimental design solved by means of non- lineal mixed effect model approach using Monolix. In vivo images were also obtained using a planar gamma camera. Lyophilized formulation allowed the preparation of radiolabeled Mabs with a high radiochemical purity and with no modification of pharmacokinetic behavior and target tissue uptake.

Pharmacokinetics and pharmacogenetics of metformine in patients with type 2 diabetes mellitus

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Metformin is the first line pharmacological treatment for glycemic control in patients with Type 2 Diabetes Mellitus (DM2) [1]. However, it is estimated that about 30% of patients do not respond adequately to the treatment that may be related to the high inter-individual variability in the kinetic behavior of this drug [2,3]. The aim of this study was to develop a population-based mixed effects pharmacokinetic model to evaluate the influence of genetic, anthropometric, pathophysiological, clinical and comedic factors on the kinetics of metformin in DM2 patients.

The study was approved by Research Ethics Committee and the Research Committee of the Hospital Central "Dr. Ignacio Morones Prieto" (registration number 40-15) and under the knowledge of the Committee on Ethics in Research and Teaching of the Faculty of Chemical Sciences (code of registration: CEID2015055-S). A total of 70 adult patients with DM2 from the Hospital Central "Dr. Ignacio Morones Prieto" under chronic treatment with metformin were included.

The influence of anthropometric, clinical and comedication characteristics of the patients, as well as the presence of genetic polymorphisms OCT2-808 G>T(rs316019), OCT1 1260GAT>(rs72552763) and PMAT883-522 A>G(rs2685753) on the pharmacokinetic behavior of metformin was evaluated through NONMEM software (v7.3) using one- compartment open model with first-order absorption and elimination.

Plasmatic metformin concentrations at the steady state were determined by HPLC. The final population pharmacokinetic model obtained, was: Clearance (CL) =15.9+0.308*CLcr for patients with creatinine clearance (CLcr) less than 120 mL/min and CL=49.3 L/h in patients with CLcr equal to or greater than 120 mL/min. Metformin CL increases 22% in patients with the OCT1-1260 allele, while concomitant administration of clopidogrel decreases metformin CL by 43%. Volume of distribution is described by the following expression:V=4.37*Total body weight. Internal validation was performed by bootstrapping, showing the accuracy and the stability of the final model developed.

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Understanding the impact of enteric reabsorption on drug pharmacokinetics T2

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Enteric reabsorption occurs when a fraction of drug transferred from the arterial bloodstream to the gastrointestinal tract is subsequently reabsorbed back into the systemic circulation. When present as a discontinuous process, it can cause secondary or multiple peaks in the plasma-concentration-time profile. The most studied process of this kind is referred to as enterohepatic cycling (EHC), i.e. through hepatobiliary secretion. Many drugs and endogenous compounds are known to undergo EHC [1]. However, this is not an exclusive pathway: multiple-peak phenomena have been observed after intravenous administration of drugs of negligible bile secretion. Gastric secretion and enteral reabsorption has been observed for several basic drugs [2]. Drug reabsorption has always been a pharmacokinetic challenge, both in modeling as in the interpretation of its impact on drug bioavailability and disposition, which currently remains unclear. In this work, by using a semi-mechanistic pharmacokinetic model, we evaluate the impact of enteric reabsorption and assess different models through simulation and sensitivity analysis using the package mlxR (Lixoft®, France) at the R environment for statistical computing (R-project.org). Importantly, in order to fully represent the competition between hepatobiliary secretions and hepatic metabolism, the liver was represented as a peripheral compartment. Under the model stablished, equations were

deducted for systemic clearance and oral bioavailability. As expected, results showed that the reabsorbed fraction is positively correlated with the volume of distribution and drug half-life. Moreover, for EHC, we found that given the interplay between hepatobiliary secretion and hepatic drug metabolism: (i) a negative correlation is foreseen between the reabsorbed fraction and hepatic clearance, and (ii) oral bioavailability of drugs with high hepatic extraction and low gut-wall metabolism can result increased by a higher EHC magnitude. Simulations agreed with developed equations. In conclusion, drug reabsorption can have a significant impact on systemic exposition.

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Development and characterization of metformin-loaded plga nanoparticles

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Metformin is the drug of first choice in the treatment of type II diabetes. However, in order to maintain effective concentrations of metformin in plasma, the administration of repeated doses is necessary, thus increasing the incidence of its adverse effects, mainly gastrointestinal. The new drug delivery systems in nanoparticles have been shown to be able to increase the biological activity of different drugs, modulate their release and reduce their adverse effects. Therefore, applying this new technology in the administration of drugs such as metformin improve therapeutic profile. The objective of this work was the development of metformin-loaded PLGA nanoparticles loaded in order to obtain a formulation with a particle size smaller than 300 nm, in a homogeneous system for oral administration and controlled release profile.

In the present work, three metformin formulations were prepared following the desolvation method. To characterize the formulations, the following parameters were determined: size, polydispersity index, surface charge and encapsulation efficiency. Also in vitro release profile of the drug from the nanoparticles was determined.

We obtained nanoparticles sizes between 211 to 226 nm. The polydispersity index was lower than 0.3 in all prepared formulations, which indicates that there is a homogeneous

population of nanoparticles. On the other hand, the surface charge of the formulations is similar in all of them and they do not change when the drug is incorporated into the nanoparticles, preserving the stability of the system. Metformin showed a controlled release from the PLGA nanoparticles. Our results suggest that PLGA nanoparticle could be promising for the oral administration of metformin. In addition, the PLGA nanoparticles prepared by the desolvation method can be used as vehicles for other drugs with short elimination half-lives.

Key words: Metformin, PLGA nanoparticles, drug delivery systems, desolvation.

Covariates affecting phenobarbital pharmacokinetic parameters in dogs

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Phenobarbital is an effective antiepileptic drug, both for human and canine epilepsy. Due to its narrow therapeutic index, its plasma concentrations must be monitored to improve the anticonvulsant therapy with this drug. In this work we investigate the covariates that affect its pharmacokinetic parameters in dogs. Sixty-six predose plasma samples of dogs under treatment with phenobarbital were analyzed at steady state. The impact of age, sex, body weight (WT) and total daily dose (TDD) on the apparent clearance (CL/F) and apparent volume of distribution (Vd/F) were analyzed using Monolix® software (Suite 2018R1, Lixoft S.A.S). A mononcompartmental model was chosen, the absorption constant and the volume of distribution were fixed at 1.3 h-1 and 20 L respectively based on bibliographic information. Age, WT and TDD were found to significantly affect CL/F of phenobarbital, $p<0.01$, $p<0,0001$, and $p<0.0001$ respectively.

Equations that best describes clearance was:

CL = CLpop(WT/21)^(β_WT,CL)*(TDD/140)^(β_TDD)*(AGE/5)^(β_AGE).

Vd was added with the effect of WT as V=Vpop(WT/21).

Being 21 the average WT in kg, 140 the TDD administered expressed in mg, and 5 the average age in years of the studied population. Typical parameters estimates were: Clpop= 0.218 L/h, β = 0.430, β_TDD = 0.490, β_AGE = -0.169, and β_WT,V = 0.542.

Results showed an increase of clearance with body weight and the total dose administered, confirming the autoinductive capacity of phenobarbital on its elimination rate. On the other hand, there was a decrease of clearance with age, probably due to the decrease in renal function observed in this species in the elderly, since renal excretion represents about 30% of the total clearance of phenobarbital in dogs.

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Bioequivalence of ivermectin in combined formulations of Ivermectin / Fluazuron

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Ivermectin is widely used drug in the treatment of parasitic disease caused by ticks Rhipicephalus (Boophilus) microplus. However, there are numerous reports of resistant populations, so its association with Fluazuron (an acarine growth inhibitor) is a possible strategy, to increase the efficacy of treatments, and to avoid the appearance of resistance to fluazuron, the only drug that in Uruguay does not has reported cases of resistance.

A bioequivalence study was conducted to evaluate the product in pre-formulation phase containing the combination ivermectin/fluazuron, by subcutaneous route, by comparison with a reference product.

Twenty-four male calves weighting between 209 and 234 kg were selected and randomly assigned to Test or Reference group. Each group received 0.2 μg/kg of Ivermectin and 2.5 mg/kg of Fluazuron. Blood samples (10 mL) were collected from the jugular vein in heparinized tubes prior to dose and at 6, 24, 72, 96, 216, 312, 648 and 816hours post-dose. Pharmacokinetic analysis was performed for Ivermectin using Monolix® software (Suite 2018R1, Lixoft S.A.S). Structural and statistical models were evaluated with basic goodness of fit plots and metrics and visual predictive checks

The final model included two compartments with a transit compartment absorption model and first linear elimination. Typical parameter estimates were: ktr: 0.0415

h-1, Mtt: 19.1h for reference product and 30.1h for Test product, CL/F= 6.5 L/h, V1=1130L, V2= 566 L and Q=2.22 L/h

Mean transit time product was significantly higher for Test product ($p<0.001$). This model is expected to be useful for PKPD analysis on cattle populations infected with ticks

Therapeutic drug monitoring of vancomycin in patients of intensive care unit of the instituto nacional de neurología y neurocirugía

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The consensus guidelines on TDM of vancomycin suggest the use of trough concentrations to dose patients, considering that AUC/MIC ratio (area under the concentration–time curve to minimum inhibitory concentration) is related with efficacy. Specifically, AUC/MIC ratio ≥ 400 is the suggested target. In order to examine the variability and utility of serum trough concentrations of vancomycin in patients with brain injury, we collected a data set to determine the AUC/MIC ratio and to identify the influencing factors on trough vancomycin concentrations.

Data were collected retrospectively over a three years period from ICU patients of Instituto Nacional de Neurología y Neurocirugía, receiving vancomycin in a dose range from 1.5 to 3.0 g/day. Data from 23 patients with a median age of 42.75 years (range 14 to 76), a median body mass index of 25 kg/m2 (18 to 34 kg/m2). All studies were approved by the institutional review Board (56/09). Predictive performance using a Bayesian PK method to estimate the 24-h vancomycin AUC was applied.

The vancomycin trough concentration variability was significative among patient samples. Only 17.49% of ICU patients met the concentration target of 15–20 mg/l while 65.21% showed subtherapeutic concentrations and 13.0% of them showed supratherapeutic concentrations (>20 mg/l). Only 40 % of patients showed an AUC/MIC ratio above 400. In 90 % of patients with MIC of 2 mg/L or greater was observed an AUC/MIC ratio < 400.

Further prospective studies are needed to evaluate the AUC monitoring in clinical practice in patients with brain injury. The concentrations and patients data, analyzed with software programs could increase the accuracy in vancomycin dosing.

Influence of experimental chronic *Trypanosoma cruzi* infection in the benznidazole pharmacokinetics in mice

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Trypanosoma cruzi infection leads to increased circulating levels of inflammatory cytokines network (1). Expression and/or activity of drug transporters are regulated by cytokines (2). Benznidazole (BNZ), the most commonly drug for treating Chagas disease, exhibits high variability in its efficacy and toxicity, especially in the chronic phase of disease. BNZ is considered a substrate and inducer of P-glycoprotein efflux transporter (3). To date, scarce information about the mechanisms of variability in the BNZ pharmacokinetics are available (4). This study aimed to evaluate the influence of experimental chronic *Trypanosoma cruzi* infection in the BNZ pharmacokinetics in mice. Eighty female *Swiss* mice (n= 40 animals chronically infected with *Berenice-78* strain of *Trypanosoma cruzi* and 40 healthy animals) received a single oral dose of BNZ

100 mg/Kg. Serial blood samples were collected for 6h after BNZ administration (CEUA/UFOP nº 2016/58). BNZ serum concentrations were measured using HPLC- DAD. The software Phoenix® version 7.0 was used to perform pharmacokinetics analysis and software R version 3.1.2 was used for statistics. A one-compartment model with first-order absorption and linear elimination best described the BNZ pharmacokinetics in both infected and healthy mice. The chronic *Trypanosoma cruzi* infection increased the K_a (3.92 *vs* 1.82 h^{-1}), Vd/F (0.089 *vs* 0.036 L) and CL/F (0.030 *vs* 0.011 L/h), and decreased both T_{max} (0.67 *vs* 1.17 h) and $t_{1/2a}$ (0.18 *vs* 0.38 h) as compared to healthy mice ($p \leq 0.05$). This is the first scientific evidence of the murine experimental Chagas disease influence the BNZ pharmacokinetics, probably by P- glycoprotein inhibition.

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Dog model predict the benznidazole pharmacokinetics in clinical trials

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There is a translational challenge and a need for standardization of animal models in Chagas disease (CD) drug discovery. The dog has been considered a suitable model to study both CD immunopathology and treatment efficacy (1). Benznidazole (BNZ) is the model drug that the new drugs candidates should be compared in CD drug screening (2). This study aimed to compare the BNZ pharmacokinetic profile in eight healthy undefined breed dogs (CEUA/UFOP: 2016/37) with our previously published study in eight healthy adult volunteers (EudraCT 2013-003381-14) (3). After single oral dose of BNZ 100 mg administration, blood collection was performed at intervals up to 48h for dogs and 72h for humans. The dog samples were analyzed by HPLC-DAD and human samples by UPLC–MS/MS. The pharmacokinetic analysis was performed using software Phoenix® version 7.0. In both dogs and humans, the one-compartment model with first-order absorption and linear elimination best described the BNZ pharmacokinetics. Similar K_a (0.90 *vs* 1.16 h^{-1}), T_{max} (3.77 *vs* 3.50 h), Vd/F (0.50 *vs* 0.49 L/Kg), CL/F (0.04 *vs* 0.03 L/h/Kg), $t_{1/2el}$ (9.10 *vs* 12.1 h) and K_{el} (0.08 *vs* 0.06 h^{-1}) were observed in dogs and humans, respectively. Our results showed remarkable consistency in the pharmacokinetics profiles with good absorption, high distribution and moderately slow elimination between dogs and humans. Therefore, it's possible BNZ pharmacokinetic translation from dog model to clinical trials.

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Predictive performance of a vancomycin population pharmacokinetic model in Mexican patients

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Population pharmacokinetics is a useful approach that takes into account inter- and intra- individual variability to individualize the drug therapy, however in view of the complex statistical methodology involved in the use of such models, model evaluation is an important issue. The aim was to externally evaluate the predictive performance and generalizability of a previously published population model of vancomycin. Indeed, a published vancomycin population pharmacokinetic model [1] was implemented in NONMEM 7.4. The external validation cohort consisted of adult patients receiving vancomycin from a clinical, prospective, descriptive and observational study carried out during 6 months. The model was used to predict peak and trough concentration for each patient. To explain the variability of the prediction, population was divided into groups, of each one, mean prediction error (*me)*, the root mean squared prediction error (*rmse)* and *the* standardized mean prediction error (SMPEj) were calculated. Also, a VPC analysis was performed and pharmacokinetic parameters were compared. As results the *me* method show a small value with a width range of variability, but SMPEj method that takes in count the data type, showed a better predictability of the model, supported by de VPC analysis. Finally, this model could make accurately prediction of vancomycin trough concentrations of patients with non-severe infections and provides evidence to demonstrate predictive performance and generalizability of the model to be used in therapeutic monitoring of vancomycin patients.

Ethical approve: ethics and research committee of the "Hospital Central Dr. Ignacio Morones Prieto" Register: 53-12

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