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Plenary lectures

Moving from basic PK/PD towards systems models: lessons from corticosteroids

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Over the past five decades, technological advances in bioanalysis, -omics, and computation have evolved to allow for comprehensive assessments of the molecular to whole-body pharmacology of diverse corticosteroids. Such studies have led to advancements in pharmacokinetic and pharmacodynamic (PK/PD) concepts and models that often generalize across various classes of drugs. These models encompass the 'pillars' of pharmacology, namely PK and target drug exposure, the mass-law interactions of drugs with receptors/targets, and the consequent turnover and homeostatic control of genes, biomarkers, physiological responses, and disease symptoms. Pharmacokinetic theory and methodology has come to appreciate noncompartmental (NCA), compartmental, reversible, physiological (full PBPK and minimal PBPK), and target-mediated drug disposition (TMDD) models with enactments using a growing array of pharmacometric considerations and software. Several basic PK/PD models and components have emerged (simple direct, biophase, slow receptor binding, indirect response, irreversible, turnover with inactivation, and transit models) that place emphasis on parsimony, are mechanistic in nature, and serve as a catalog of highly useful 'top-down' methods of quantitating the actions of diverse drugs. These are often components of more complex quantitative systems pharmacology (QSP) models that help explain the array of therapeutic and adverse effects of various drugs including corticosteroids. A progressively deeper mechanistic appreciation of PBPK, drug-target interactions, and systems physiology from the molecular (genomic, proteomic, metabolomic) to cellular to whole body levels have laid the foundation for building enhanced PK/PD to more comprehensive QSP models. Our research based on various animal, clinical, and theoretical studies with corticosteroids have provided ideas and quantitative methods that have broadly advanced the fields of PK/PD and QSP modeling. These models demonstrate the transition towards a global system understanding of actions of many types of drugs.

Physiologically based pharmacokinetic modeling (pbpk) in drug development and regulatory science: from bench to bedside

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PBPK is an established discipline in drug development and regulatory science in the developed world. There were 253 PBPK submissions in 94 New Drug Applications to the US FDA in 2017. Enzyme-based drug-drug interactions (ddis) accounted for 60% of submissions, pediatrics for 15%, special populations for 10%, and transporter-based ddis for 7% of all submissions. PBPK models for ddis have been re-purposed for multiple uses including virtual bioequivalence (VBE). PBPK models with high impact have predicted PK in untested scenarios, supported dose selection and facilitated PK bridging studies across formulations. PBPK is an emerging discipline in the developing world but substantial progress is being made to foster greater use of PBPK by the efforts of redif across Latin America, Bill and Melinda Gates Foundation across Africa, and WHO globally to promote model-based risk assessments. We have good reason to be optimistic. Pharmaceutical companies are using PBPK models to support the "Quality by Design" pharmaceutical manufacturing processes and to perform VBE studies of mainly generic drugs. The clinical utility of PBPK models has been demonstrated for enzyme-based ddis between combination hormonal contraceptives and HIV, tuberculosis and infectious disease medications especially in developing countries. FDA recently approved a new drug (Pretomanid R) in combination with bedaquiline and linezolid for highly treating treatment-resistant tuberculosis (TB). A PBPK population model of pretomanid was available to simulate PK in pulmonary TB patients with application to pretomanid dose selection in individual patients receiving pretomanid-containing anti-TB regimens. VBE studies have been used to develop generic formulations of nifedipine and levothyroxine that minimize the *in vivo* absorption consequences of interactions between formulations and gastrointestinal tract physiology. PBPK models of VBE have been used post-approval to modify dissolution specifications for formulations used in phase 3 trials. This presentation will highlight selected case studies illustrating these advancements in PBPK modeling.

Pharmacometrics to combat antimicrobial drug resistance

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Worldwide, the prevalence of bacterial resistance to antibiotics is rapidly increasing. In spite of the urgency to identify new treatments, the interest from pharmaceutical industry for antibiotic drug development is low due to the small expected return on investment compared to other disease areas. It is also not feasible to cover all plausible bug-indication-patient status combinations in clinical trials. There is therefore a need for streamlined processes to determine antibiotic dosing strategies for new and existing antibiotics, administered in mono- or combination therapies. Through pharmacokinetic and pharmacodynamic modelling and simulation, dosing regimens can be tailored to overcome infections with resistant bacteria while minimizing the risk of developing resistance during treatment. Bacteria can rarely be quantified over time in patients and therefore knowledge on PKPD for antibiotics rely on preclinical systems. The traditional PK/PD index methodology for translation of effects from preclinical models to patients has however several limitations. For example, PK/PD indices ignore resistance dynamics, assume that the PD target is independent of the PK profile, and are not applicable for drug combinations. PKPD-models, developed based on *in vitro* data, can on the other hand describe the time-course of bacterial growth and killing. After adjusting for *in vivo* conditions, such models may provide a more predictive approach to define efficacious doses in patients. There is also a need to connect PKPD to clinical outcomes. The response to antibiotics is typically evaluated on dichotomous endpoints, such as success/failure or alive/dead, at a certain day after treatment initiation. Time-to-event analyses of survival and discharge, bounded integer models of sequential organ failure assessment (SOFA) scores, and multi-state models for microbiological status, can contribute to the pharmacometric toolbox, aiming to better understand disease progress and changes in treatment effects to efficiently slow down the accelerating antibiotic resistance.

Translational pharmacometrics and system pharmacology models in oncology

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Cancer continues to represent a major source of morbidity and mortality around the world despite significant advancements in the development of precision chemotherapy,

biologics, and cell-based therapies. Compounds designed to treat cancer continue to exhibit one of the highest rates of attrition in drug development, primarily owing to a lack of efficacy and unanticipated adverse drug effects in later phase trials. The use of clinically approved drugs is also challenged by tumor heterogeneity and known and unknown factors that result in innate and acquired resistance. Substantial innovations in the computational modeling of cancer therapeutics have been made in pharmacometrics (Pmx) and quantitative systems pharmacology (QSP). Pmx is grounded in the basic principles of pharmacokinetics (PK), statistics, and pharmacodynamics (PD), and can be readily extended to diverse data types. Traditional PK/PD models contain a minimal number of identifiable parameters to describe temporal profiles of therapeutic and adverse drug effects. Coupled with nonlinear mixed effects modeling and relatively large clinical trials, a covariate analysis can be used to identify patient-specific characteristics that explain the variability in model parameters and clinical outcomes. This approach can be limited by study designs and is rarely sufficient for recapitulating multiple, complex genotype-phenotype relationships. A major opportunity for pharmacometrics is the extension of pharmacostatistics to QSP models, which recognize that both drugs and disease processes give rise to complex and dynamic phenotypes by altering natural interconnected biochemical networks. Multi-scale QSP models that combine physiological PK/PD principles and signaling networks can serve as a platform for integrating factors that regulate drug effects and therapeutic outcomes. This presentation will discuss basic principles of translational Pmx and QSP modeling in oncology and highlight approaches to identify or qualify drug targets, design and evaluate combinatorial drug regimens, explore the impact of tumor heterogeneity, and identify factors influencing anti-cancer drug action.

Oral presentations

PBPK/PD & QSP/ Seminar session

Open-systems-pharmacology: a platform for pre-competitive research in translational medicine leveraging a qualified framework for pbpk/pd

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Over the years, there has been an ever growing demand for specialized use-scenarios in PBPK modelling and for analyses of complex mechanism-based treatment effects

through integration of systems-biology concepts within large therapeutic-area- / disease-specific models, which is getting more and more challenging and requires an extension, i.e. An increased flexibility of current simulation software. In addition, the recently issued draft guideline on PBPK modeling by the European Medicines Agency demands the qualification of the intended use related to the PBPK platform for any type of simulation scenario in regulatory submissions. While the database and many models developed within the OSP Suite have been extensively validated over the years, changes in the software platform require continuous requalification of (these) models. OSP has implemented a technical solution for automated requalification of PBPK models. This will allow convenient and quality controlled (re-)qualification of models for their intended use, which is required once changes in the software platform have been made e.g. For a new release. This development is currently extended towards PBPK/PD (QSP) models together with a technical solution for modularization of complex disease platforms built within the software. (The) OSP (Community) is well prepared to solve these two major challenges in PBPK and complex systems modeling & simulation for the OSP Suite, namely, 1) the requirement for continuous (re-)qualification of models throughout their life-cycle and 2) handling the growing complexity of the developed models. This is achieved by 1) implementation of an automated (re-) qualification routine and by 2) improving the methods and tool functionalities for model building.

Use & applications of systems pharmacology models

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The objective of this work is to encourage members of Redif to consider Systems Pharmacology (SP) models in their academic/research plans given (i) its great potential in well-established fields as basic research in pharmacology and patient management beyond therapeutic drug monitoring (TDM), and (ii) the weak presence of research and development in Latin American's pharmaceutical industry.

Different cases studies are presented covering immune-oncology, mrna-based therapeutics for the treatment of rare diseases, and dual neutralizing antibodies. The work gives examples of the application of (contrary to the general perception) not necessarily multi-scale complex models in designing combination therapies, translation approach, early dose selection, and understanding drug disposition in critically ill patients.

Efficient ways to use prior knowledge based either on (i) data published previously in literature or (ii) predefined hypothesis supported by current biological understanding are also shown and discussed.

Virtual bioequivalence / Seminar session

Determination of bioequivalence of locally applied drugs

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Determination of bioequivalence of locally applied drugs is challenging since the usual approach of comparing blood levels may not be applicable. For example, there are only few approved generic inhaled corticosteroids available on the US market. This is surprising since this indication represents a lucrative market and the patents of some of the market leaders are already expired. The reason for this situation is the lack of a regulatory guidance that will enable generic manufacturers to submit an ANDA tor approval of a bioequivalent product. The concern, as with any topical product, is that the conventional bioequivalence study based on a comparison of drug exposure in plasma may not be appropriate and not correctly reflect the relative availability at the site of action in the lungs. Hence, the only way that a generic company can get a product approved is to undergo expensive clinical trials, which defeats the purpose of the generic drug product concept. Interestingly, the approach of the EMA in Europe has been exactly the opposite. The EMA has issued a guidance document that may allow generic approval based on in-vitro equivalence alone. However, the detailed criteria are so strict that this scenario seems not very realistic. If *in-vitro* equivalence is not achieved, then a pharmacokinetic study based on drug exposure in plasma can be submitted. Interestingly, even if the pharmacokinetic studies fail to show equivalence, generic approval is still a possibility if clinical equivalence can be shown. It can be shown that of the three different measures (*in-vitro* performance, pharmacokinetics, clinical study) the pharmacokinetic approach is the most sensitive. Hence, it is proposed to harmonize the equivalence criteria world-wide and base the approval on both in-vitro studies and pharmacokinetic studies but not require any clinical studies.

PBPK modelling in the selection of the most sensitive analyte for bioequivalence studies

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The Physiological-based Pharmacokinetic models have recently emerged as a valuable tool during drug development process. The aim of this work is to explore and assess the most sensitive analyte (parent drug or any of the metabolites) to changes in drug product performance using a semi-physiological models in two different softwares and to make recommendations based on the simulations outcome. A semi-physiological one- and two-compartment pharmacokinetic model with two active metabolites (primary (PM) and secondary metabolites (SM)) with saturable and non-saturable pre-systemic efflux transporter, intestinal and hepatic metabolism have been developed. Several scenarios were generated as a factorial combination of Biopharmaceutics Classification System (BCS) drug types, KM Pgp values, intestinal and liver metabolic scenarios, dose levels and quality levels of the drug product. Monte Carlo simulations of all bioequivalence studies were performed in NONMEM 7.3 and physpk Biosimulation Software (PPK). Results showed the parent drug (PD) was the most sensitive analyte for bioequivalence trials in all the studied scenarios. PM and SM revealed less or the same sensitivity to detect differences in pharmaceutical quality as the PD. Mean point estimate of Cmax and AUC methodology from Monte Carlo simulations allows to select more accurately the most sensitive analyte compared to the criterion on the percentage of failed or successful BE studies. The adequacy of PPK as a reliable software was demonstrated based on model predictions based on post-hoc PK estimates derived from NONMEM. Parent drug has been selected as the most sensitive analyte to detect differences in dissolution performance or orally administered formulations. The recommendation of measurement of PM by the FDA guideline when PM is formed substantially through pre-systemic metabolism might not be longer supported based on the results of this study.

Virtual bioequivalence: new perspectives in drug development

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Bioequivalence is an integral part of development and regulations for both generic and new drugs, and it is based on the determination of human bioavailability. In order to reduce the high variability of this type of test as well as the cost for failure in bioequivalence trial, the virtual bioequivalence have arisen as alternative decision-making tool. Physiologically-based pharmacokinetic (PBPK) modeling provides an approach that enables the plasma concentration–time profiles to be predicted from preclinical *in vitro* and *in vivo* data and can be used to predict bioequivalence of controlled release and immediate release oral products. Here, we proposed a new modelling strategy using different machine learning algorithms implemented in KNIME Analytics Platform to predict pharmacokinetic properties and to implement PBPK models.

PK/PD modeling / Seminar session

Individual model averaging for drug effect assessments

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Model misspecifications in longitudinal data analysis may affect both the type 1 error and the estimates of drug effects. We used simulated and real data sets to compare these aspects of the standard pharmacometric approach (STD) and a new approach, Individual Model Averaging (IMA). Multiple simulated and three reals (ADAS-Cog composite score, 11-point pain score and daily counts of epileptic seizures), placebo-only, patient data sets were used. To create data sets mimicking trials where the drug would have no effect, repeated randomizations of the subjects to "drug" vs "control" were implemented. Different combinations of models describing the placebo effect and the drug effect were used. STD contrasted nested models without (base) or with (full) the drug effect. IMA assumed two sub-models, the placebo effect with

or without the drug effect. IMA compared nested models (i) equal probability for all patients for the two sub-models (base), and (ii) the probability of each sub-model estimated using the allocation arm as covariate (full). For simulated data sets Type 1 error was better controlled for IMA than STD. IMA showed better performances in type I error control than STD on all three real data sets (nominal 5%): 26.4%, 96.9% and 45.5% (STD) versus 3.5%, 5.0% and 5.0% (IMA). For all three real data sets, STD showed considerable bias in the drug effect estimates in the majority of the scenarios, but no bias was evident for IMA in any scenario. When both STD and IMA estimates were unbiased, IMA in most cases provided more precise estimates. IMA was more robust towards model misspecifications and over-parameterization with better control of the type I error and more accurate effect size estimates. IMA seems promising to evaluate the treatment effect in longitudinal data analysis.

Antimicrobial dose optimization based on microdialysis and PK/PD modeling

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The PK/PD indexes used to calculate antimicrobials dosing regimens have important limitations regarding both PK and PD measurements. It is well know that the free drug concentration in the site of action is responsible for the pharmacological effect and that MIC value does not explain fully the antimicrobial effect since it is used as a threshold. Evaluation of free levels of Fluconazole and Amphotericin B in the kidney of healthy, *Candida albicans* infected Wistar rats using microdialysis after intravenous and oral administration of both drugs in different dosages. Plasma and kidney microdialisate were collected up to 24h after the administration of drugs. Levofloxacin microdialysis was performed in tuberculosis cavitary lesions of patients after oral dosing of 750 or 1000mg. Samples were collected up to 8 hours after administration. To evaluate the effect of fluconazole against Candida spp., amb against *C. Albicans* and levofloxacin against *M. Tuberculosis*, an *in vitro* system that exposes the microorganism to the human PK profile was set. Multiple drug concentrations were administered into the system, then the CFU/ml was counted for 7 days. Data was modelled using developed Emax model. Simulations were performed to optimize the dosing of all antimicrobials tested. No statistical difference was found when comparing free serum and cavitary lesions levofloxacin concentrations. Fluconazole showed higher potency against *C. Albicans* than against *C. Parapsilosis* and *C. Tropicalis* and equivalent efficacy against these yeasts, amb showed higher potency than fluconazole against *C. Albicans*.

Regarding levofloxacin dose selection, for the resistant population an increase in the current dose is necessary to eliminate the microorganisms according to the studied IC50 values. Microdialysis is a useful technique to obtain free antimicrobial drugs concentration in the site of action. PK/PD modeling is used to simulate alternative regimens, to compare antimicrobial drugs pharmacological effect and to optimize therapy to treat infections that are a Public Health issue.

Acknowledgments: cnpq – Brazil

Enteric reabsorption of drugs: influence on pharmacokinetics and pharmacodynamics revisited

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Enteric reabsorption occurs when a fraction of drug transferred from the systemic circulation to the gastrointestinal tract is subsequently reabsorbed back into the arterial bloodstream. When present as a discontinuous process, it can be observed as 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. However, this is not an exclusive pathway: basic drugs could suffer enterogastric cycling (EGC), i.e. Through gastric secretion. These processes are currently regarded as pure distribution, with no impact neither on drug systemic clearance nor oral bioavailability. It seems settled, however, that drug half-life result increased with higher reabsorption, commonly attributed to a higher volume of distribution. In this presentation, the impact of drug enteric reabsorption on primary pharmacokinetic parameters will be discussed. With this purpose, semi-mechanistic pharmacokinetic models were developed for EHC and EGC to perform simulations and sensitivity analysis using the package mlxr (Lixoft®, France) at the R environment for statistical computing (R-project.org). Under the model established, equations were deducted for systemic clearance, volume of distribution and oral bioavailability. Results and examples will be shown. For EHC, given the interplay between hepatobiliary secretion and hepatic drug metabolism, results show that the reabsorbed fraction correlates negatively with the hepatic clearance and positively with oral bioavailability for drugs with high hepatic extraction. This could be of importance for the assessment of drug-drug interactions. For EGC these correlations are not expected. Valproic Acid and Nevirapine pharmacokinetic data will be used to show both scenarios. Moreover, a theory for the concentration and time dependent hepatobiliary secretion for phenytoin will be discussed as a mechanism for its nonlinear pharmacokinetics. Finally, the impact of drug reabsorption on the effect vs. Time profile will be discussed.

Therapeutic drug monitoring / Seminar session

Alternative dosing guidelines for childhood tuberculosis: applications of model-based approaches

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Tuberculosis (TB) kills 234,000 children each year. Malnourished and young children are especially vulnerable to severe forms of TB, poor treatment response, and death. Current WHO guidelines recommend dosing children based on weight alone, with the same mg/kg dose range applied to children of all ages. These guidelines may lead to subtherapeutic exposures and worse outcomes in young and underweight children. We aimed to evaluate the population impact of current guidelines in 20 countries with highest child TB incidence and explore how novel dosing strategies may improve the child TB epidemic. We used a novel, integrated model linking country-specific individual-level demographic data to pharmacokinetic, outcome, and epidemiological models to assess TB treatment outcomes in children under 5 years. Drug exposures and outcomes were predicted under WHO guidelines and a proposed algorithm that utilizes age, weight, and available formulations. We estimated that 57,234 (43%) of 133,302 treated under-5 TB cases would be underdosed with WHO dosing and only 47% of children would reach recommended rifampicin exposure target. Subtherapeutic exposures and unfavorable outcomes were more common in malnourished children. A proposed simple dosing approach, by age and nutritional status, might ensure adequate exposure in 62% of children. This proposed method has the potential to reduce unfavorable treatment outcomes by at least 1/3, saving 2436 children at minimum and up to 7884 children if all cases are diagnosed and treated in these countries annually. This simple change in dosing method to include age and nutritional status could be immediately implemented in clinic and greatly improve child TB treatment outcomes, especially among malnourished children who are at high risk of mortality.

Application of pharmacometrics to therapeutic drug monitoring in Uruguay: paving our way

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Pharmacometrics is a relatively new discipline in Uruguay and so is its application to therapeutic drug monitoring. The presentation focuses on the first steps we have taken

in Uruguay to apply PMX tools as way to build models for own population. The two group of drugs we have worked to date are immunosupressants (IS) and antiepileptics (aeds).

Cyclosporine (csa), an IS, was the first drug we were able to build a preliminary model for Pharmacokinetic parameter estimation was performed using nonlinear mixed effect modelling. A two-compartment model with first order disposition model including lag time was used as a structural model. The covariate analysis identified creatinine clearance (clcrea) as an individual factor influencing the Cl of csa. The model was then externally validated with another set of patients. The model developed reasonably estimates the individual csa clearance for patients. Hence it can be utilized to individualize csa doses for prompt and adequate achievement of target blood concentrations of csa.

Tacrolimus is another IS that has been approached to, however, taking into consideration the nuances with csa metabolism, its model is still under construction and should be improved by the incorporation of other parameters.

In the case of aeds, levetiracetam (LEV) and valproic acid (VPA) were of choice due to safety concern regarding efficacy and adverse drug reactions. For LEV, a preliminary model for terminal patients under palliative care was developed. Though number of patients was low, and the condition fortunately not common LEV Cl and half-life were successfully estimated for the condition and age of the patients.

Regarding VPA our aim was to develop a model for the understanding of the mechanisms behind VPA induced hyperammonemia and the assessment of the benefits related to carnitine supplementation (CS). A mechanistic QSP model describing the VPA-Ammonia pathway was built including CS to reverse this adverse drug reaction.

Methodologies / Seminar session

A brief history of nlmixr & lessons learned

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Nlmixr is a free and open source R package for fitting nonlinear pharmacokinetic (PK), pharmacodynamic (PD), joint PK/PD and quantitative systems pharmacology (QSP) mixed-effects models. Currently, nlmixr is capable of fitting both traditional compartmental PK models as well as more complex models implemented using ordinary differential equations (odes). It is under intensive development and has succeeded in attracting extensive attention and a willingness to make contributions from the

pharmaceutical modeling community. We believe that, over time, it will become a capable, credible alternative to commercial software tools, such as NONMEM, Monolix, and Phoenix NLME. The fast growth and development of nlmixr is a shining example of the power of open-source software and an inspiration to computational pharmacometrics. In this talk, the development history of nlmixr is briefly reviewed. I then use nlmixr as a case study to promote future open-source tools for pharmacometrics.

Covariate model building

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Introduction: Population pharmacokinetic (PK), pharmacodynamic (PD) or PKPD analyses aim to summarize the model parameters and its sources of variability among individuals who are the target patient population receiving the drug of interest. Covariates are used to describe predictable sources of variability in model's parameters leading to a decrease in unpredictable variability. A good understanding of the relationships between model parameters, patient characteristics and other intrinsic and extrinsic factors will facilitate dose adjustment decisions. Materials and Methods: Different methodologies could be used to screen and estimate relevant covariates: stepwise covariate modeling (SCM), full fixed effects modeling (FFEM), and full random effects modeling (FREM). Results and Discussion: The most common approach is the incorporation of covariates in a stepwise manner. With SCM p-values are difficult to interpret and difficult to adjust appropriately for multiple comparisons (selection bias), further, correlated covariates lead to difficulties in interpretation and estimation. FFEM has been presented as an alternative to stepwise regression, however, pre-defined covariates have its own limitations. Adding covariate relations to only some of the model parameters can lead to selection bias. Allowing all covariates to affect all parameters mitigates the risk of selection bias. This could be accomplished by using FREM. This methodology proposes the incorporation of covariate relations using random effects. With FREM covariates are treated as observations and all covariate-parameter relations are estimated simultaneously. Conclusions: This presentation will provide an overview of the methodologies. Predictable and robust covariate modeling is key in drug development; thus, a good understanding of the different methodologies will help selecting the appropriate approach for a better covariate characterization.

Statistical tests and model building strategy for mixed effects models

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Building and validating a mixed effects model are generally difficult and laborious tasks for the modeler. Indeed, it requires to find the "best" covariate model, i.e. To identify which covariates significantly explain the variability of some individual parameters, to identify the "best" correlation model for the random effects, and to find the "best" residual error model for continuous data. I will present an extension of the EM algorithm that allows to build a linear mixed effects model by optimizing a penalized likelihood criterion (AIC, BIC) in an iterative way. I will also present the SAMBA (Stochastic Approximation for Model Building Algorithm) algorithm, an extension of this method for non-linear mixed effects models. Once the model is built, it must be validated, i.e. Each of the hypotheses made on the model must be tested (covariate model, correlation structure of the random effects, distribution of the random effects, distribution of residual errors, etc.). I will show that it is possible to construct unbiased hypothesis tests using test statistics based on observations and random effects sampled from their conditional distributions. These methods for building and validating mixed effects models are implemented in the Rsmlx package (http://rsmlx.webpopix.org). I will illustrate them with applications in population pharmacokinetics.

Internal dosimetry in radiopharmaceutical development / Seminar session

Population approach in non-clinical models for dosimetric evaluation of new radiopharmaceuticals

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During the development of new radiopharmaceuticals is necessary to estimate the amount of energy deposited in tissues, as it is directly related with radiation damage to target and non-target tissues. That is the goal of dosimetric evaluations with relevance in the case of radiopharmaceuticals for therapy in order to maximize radiation damage

to target while minimizing it to non-target tissues. All dosimetric evaluation are based on standardized anatomical and kinetic models which make difficult to estimate accurately actual population parameters and its variability. The goal of the present work is to present the use of the population approach to obtain bio-kinetic models during non-clinical evaluation radiopharmaceuticals for therapy. We used a set of data from real pharmacokinetic evaluation of technetium labeled peptide in an animal tumor model following a sparse data design. In sake of simplicity tumor was considered a uniform sphere and accumulated dose (mgy/mbq/h) was estimated for tumor sizes from 0.1 to 4 g using Olinda (version 1, 2003, Vanderbilt University, USA). Tumor retention time, as well as other pharmacokinetic parameters, were estimated by non-linear mixed effect models using Monolix (Suite 2019, Lixoft, France). Then, actual accumulated doses (mgy/mbq/h) were calculated from individual pharmacokinetic parameters and tumor mass. Based on our results we could estimate pharmacokinetic parameters as well as radiation dose in tumor using a non-standardized kinetic model and a modeling option that allow us estimation of corresponding variability, which was 71% for TRT and 65 % for accumulated dose.

Pharmacokinetics and internal radiation dosimetry in the evaluations of new radiopharmaceuticals in humans

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The development of new radiopharmaceuticals for diagnosis and therapy demand the use of appropriate formalisms for internal radiation dose estimations. Dosimetry estimations based on good clinical practices are a mandatory requirement to introduce new radioactive compounds in the routine nuclear medicine services. The main objective of this work is to show the available methodologies and formalisms for absorbed dose estimations at organ and voxel levels and to show the available tools for dose calculations in clinical conditions. Principles and mathematical formalism for *in vivo* activity quantification and patient specific dose calculations are presented. Dosimetry formalisms such as the MIRD methodologies, Monte Carlo techniques and "local deposition" approaches are shown enhancing their main features, different steps and their general requirements for practical use; their strengths and limitations are also discussed. The available methods for *in vivo* activity quantification including the description of standardized correction methods to compensate the physical factors

affecting the quantification accuracy are shown. It involves the radiation scatter and attenuation, partial volume effect, background, organ overlapping, count lost dead time, etc. On the other hand, the principal available tools to perform internal radiation dosimetry calculation, developed by vendors independent companies and research groups (dosisoft, mirdcalc, MRT-3dslices, etc., are also evaluated. The main features of these tools, including the implemented methodologies and details of practical use, are presented as well as the scope of their clinical applications. Other requirements, such as inputs/outputs parameters are described and analysis of their strengths and weaknesses are also included. Basic elements of the quality assurance program to warranty the accuracy of dose estimations are finally presented including an integral and detailed evaluation of all its components.

Role and impact of dosimetry in radiopharmaceutical development

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Absorbed dose determination in nuclear medicine can be achieved by answering 3 questions:

How many radioactive sources are present in the tissues in space and time?

How much energy is emitted per decay?

How does the emitted energy propagate and is eventually absorbed in the tissues?

These generic steps can be applied to cell, small animal or clinical dosimetry.

The first question is usually related to pharmacometry: how the drug distributes in space and time. Depending on the type of experiment (cell, small animal, humans) the objective is to assess activity distribution, and integrate time-activity-curves to derive the number of radioactive decays that contribute to the irradiation.

The second step is usually the easiest to deal with, as the type of radioactive decay and the number, are usually well known for a given radionuclide.

The third step, which of absorbed dose calculation, may require different methodological approaches depending on the context (scale, but also the level of refinement associated to the determination of the absorbed dose: average absorbed dose, or absorbed dose gradients in a given volume, etc.).

Dosimetry in the context of radiopharmaceutical development can be performed in two different situations:

When the question to address is that of providing an estimate of the irradiation delivered to humans based on preclinical (small animal) experiments, the idea is not to perform small animal dosimetry per se, but rather to obtain pharmacokinetics in animals, to extrapolate from animal to human, and then, based on these estimates, use a human dosimetric model to derive an estimate of the absorbed doses that "could be" delivered to the human.

The only situation where dosimetry is performed in animals is that of experimental molecular radiotherapy, when the objective is to relate the effect (efficacy or toxicity) with an objective index (the absorbed dose or derivate). In that situation, the first steps (assessment of pharmacokinetics and determination of the energy emitted per decay) are the same as in the previous case, but the calculation of the absorbed dose must be performing on the animal itself. There are dosimetric models of small animal that can be used to get a rough estimate of the irradiation delivered. However, specific dosimetry, based on the animal geometry may be needed is some situations, namely when the dimensions of organs and tissues of interest are close to that of radiation range. Dosimetry is an integral part of radiopharmaceutical development. Methodologies have been proposed to allow addressing most of the situations encountered in preclinical experiments. Standardization is needed and guidelines should be written to improve the dissemination of the dosimetric methodology in the world of radiopharmaceutical development.

Posters presentations

Estimation of the cyp2c19 phenotype through the genotype cyp2c19 and cyp3a4

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The CYP2C19 genotypes presumably allow predicting the metabolizer phenotypes: poor (pms), extensive (ems) and ultra-rapid (ums). This is important because of the expected benefits by health care institutions and patients are supported on this premise. However, evidence from previous studies regarding this predictive power combining CYP2C19 and CYP3A4 genotypes Chas been ruled out in Mexican children. Because of the reported metabolism differences between children and adults, we evaluated the association of CYP2C19 and CYP3A4 genotypes and metabolizer phenotypes

established by omeprazole administration in 74 adults 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. Differences in the HI and SI distribution were observed between CYP2C19 and CYP3A4 genotypes ($p<0.05$), respectively. The CYP2C19 and CYP3A4 genotypes and IH and IS distribution (phenotypes) were different to previous studies in Mexico and Latin America ($p<0.05$), respectively. High correspondence was observed between CYP3A4 phenotype and genotype (91.94 %), but for CYP2C19 was less (70.27%) and showed weak concordance ($k=0.0355$). The CYP2C19 phenotype showed high sensitivity (98.077%) with 70.27% of accuracy to predict the phenotype from the genotype. These results are contrary to the previously null diagnostic ability reported in Mexican healthy children (Favela-Mendoza et al., 2018). We demonstrated a poor -but significant- genotype-phenotype association in Mexican adults between CYP2C19 and CYP3A4 genotypes for CYP2C19 phenotyping, which is a valuable alternative to dose individualization for CYP2C19 substrate drugs.

Quantification of polyglutamates of methotrexate in patients with rheumatoid arthritis to evaluate two dosing regimens

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Methotrexate (MTX) is the first-line drug to treat rheumatoid arthritis (RA) due to its sustained effect. Intracellularly, the drug is converted to polyglutamates of MTX (MTX-pgn). MTX-PG3 has been associated with the efficacy of treatment, while MTX-PG5 is associated with adverse events. The suggested initial dose of MTX is 12.5 mg/week; however, although it is common to divide the total dose in daily doses, there is no information of the effectiveness of this dosing schedule. Ninety-two MTX-naïve patients with RA were enrolled in this cross-sectional, observational and analytical study approved by local ethics committee (register 70-18). Each patient was randomly assigned into two groups: 1) Daily dose (n=45) and 2) Weekly dose (n=47) of MTX.

Patients were evaluated by a rheumatologist at baseline and after 6, 12, 24 weeks; one blood sample was taken 24 h post-dose of MTX. Red blood cells MTX-PG concentrations were analyzed by UPLC-MS/MS. Most of patients included were female (97%); the mean age was 45 years and total body weight was 68.51 kg. No significant differences in baseline clinical and anthropometric characteristics were observed between groups ($p>0.05$). Twenty-eight patients receiving daily dose and eighteen patients with weekly dose of MTX were able to complete this study; there were no significant differences in MTX-PG3 concentrations between groups ($p>0.05$). There was a significant difference between the time in treatment and the intragroup MTX-PG3 levels ($p<0.05$); in the steady state the geometric mean concentration of MTX-PG3 was 159.9 (95%CI of 109, 233) nm. Patients with BMI less than 25 kg/m^2 had higher levels of MTX-PG3. The MTX-PG5 levels was not detected throughout this study. This study shows that there are not differences in red blood cells levels of MTX-PG3 between the weekly and daily dosing schedule; the last one may adequate to ensure adherence to treatment in patients with RA.

Pharmacometric approach to support dosing strategy of nimotuzumab in patients with autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) is a genetic disease characterized by an overexpression and mislocalization of epidermal growth factor receptor (EGFR) to the apical membranes of cystic epithelial cells. Nimotuzumab is a humanized monoclonal antibody targeted to the extracellular domain of human EGFR. To develop a population pharmacokinetic (poppk) model for nimotuzumab as well as to identify demographic, biochemical and clinical predictive factors of the pharmacokinetic variability. A Phase I, single center, and non-controlled open clinical study was carried out in patients with ADPKD. Five patients were enrolled at each of the following fixed dose levels: 50, 100, 200 and 400 mg. Blood samples were drawn during 28 days for pharmacokinetic assessments. Poppk analysis of 409 concentration-time data from 20 patients was performed using the nonlinear mixed-effect model approach with

NONMEM 7.3. The first-order conditional estimation method with interaction was used throughout the modeling process. The unexplained residual variability was best described with an additive residual error model. Impact of patient demographics and clinical indices on pharmacokinetic parameters were explored using automated stepwise covariate model-building technique in psn. Quasi Steady State approximation of the full TMDD model with constant target concentration best described the concentration-time profiles. The final model estimates (res%) were 0.0102 L/h (5%) for linear clearance, 2.32 L (8%) for central volume (Vc), 0.0126 L/h (21%) for inter-compartimental clearance (Q), 4.27 L (21%) for peripheral volume (Vp), 7.27 mg/L (15%) for steady-state constant, 0.299 h-1 (4%) for internalization rate, and 0.432 mg/L (6%) for total target concentration. Interindividual variability was associated with Vc, Q, Vp. In addition, serum creatinine was identified as significant covariate for Vp. This is the first poppk study of nimotuzumab in non-oncological disease. The model was able to describe the effect of the mab–target binding, and target and mab–target complex turnovers on nimotuzumab pharmacokinetics.

Population pharmacokinetics of levetiracetam in Mexican adult patients with epilepsy

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Levetiracetam (LEV) is an antiepileptic drug (AED) used to treat all types of seizures in patients from all ages. Objective: The aim of this study was to develop and validate a population pharmacokinetics (poppk) model of LEV in Mexican adults with epilepsy to design individualized dosage regimens. The study was approved by the Hospital's Research Ethics Committee (No. 86-16). A total of 109 adult patients under treatment with oral LEV in monotherapy or polytherapy with other aeds were enrolled, 375 plasma samples between 15 minutes and 12 hours post-dose were obtained, and covariate information as sex, age, bodyweight, height, body surface area (BSA), serum creatinine, creatinine clearance (crcl), concomitant diseases, polypharmacy and the administered innovative or generic product of LEV were collected. Samples

were analyzed by a validated HPLC-UV method. Poppk modelling was executed with NONMEM v.7.4.1. Software. Pharmacokinetics of LEV was best described by a one-compartment open model with first order absorption and linear elimination. The final model equations were: Ka(h-1)=3.64, V/F(L)=29.9*(BSA/1.7)2.44 and CL/F(L/h)=2.79*(crcl/99.4)0.59. Interindividual variability (IIV) of V/F and CL/F decreased from 44.7% and 51.6% in the base model to 33.2% and 43%, respectively in the final model. Results are in accordance with other published poppk models of LEV. Significant influence of the LEV products over bioavailability (F) was noticed but didn't remain in the final model. Internal validation was performed by bootstrap and Visual Predictive Check. A priori estimation allowed proposing dosing recommendations to reach target trough concentrations (12–46 μg/ml) and maximum a posteriori estimation showed the developed poppk model is useful to optimize dosage regimens using Bayesian approach. In this model, LEV CL/F was related to crcl and V/F to BSA. The developed model will allow optimizing dosage regimens to achieve better control of epilepsy, avoiding risks of under or over dosage.

Circadian variation of the urinary 6β-hydroxycortisol to cortisol ratio in HIV-infected women during third trimester of pregnancy and postpartum

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Chronopharmacological studies have demonstrated the impact of the time of day on pharmacokinetics and pharmacodynamics. Even though the evidence that pregnancy alters the CYP3A activity, little is known about the impact of HIV, antiretroviral treatment and biological rhythms. The aim of this study was to evaluate the circadian variation of the 6β-hydroxycortisol to cortisol ratio (6β:C), a known endogenous biomarker for CYP3A phenotyping, in HIV-infected women during third trimester of pregnancy (3T) and postpartum (PP). After ethics committee approval, HIV-infected pregnant women taking oral raltegravir in combination with tenofovir/lamivudine during 3T (n = 9) and 4-5 weeks PP (n = 7) were enrolled in this study. The 6β:C ratios evaluated each 2 h for 24 h were compared intra (among the urine collection times; Kruskal-Wallis, $p < 0.05$) and inter period (3T and PP; Wilcoxon test,

p < 0.05). There was no significant difference in 6β:C ratios between 3T and PP periods or among urine collection times. In the 3T period, the 6β:C ratios ranged from 2.57 to 51.69 with median of 12.73. Similar values were obtained in the PP period, ranging from 3.48 to 44.54, with median of 10.66. The data show that CYP3A activity was not upregulated in the 3T period when compared to PP in HIV-infected pregnant women taking raltegravir and tenofovir/lamivudine. However, the observed high variability in the 6β:C ratios and the small sample size remain as a study limitation. Additionally, the lack of difference between 6β:C ratios during the urine collection times in both periods demonstrate that this biomarker can be sampled in any time, with no circadian variation. Urine collection for CYP3A phenotyping using 6β:C ratios can be sampled at any time due no circadian variation in HIV-infected women during third trimester of pregnancy and postpartum.

Population PK of nimotuzumab in patients with colorectal metastatic cancer

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Nimotuzumab is a humanized monoclonal antibody targeted to the extracellular domain of human epidermal growth factor receptor.

To develop a population pharmacokinetic (poppk) model for nimotuzumab as well as to identify demographic, biochemical and clinical predictive factors of the pharmacokinetic (PK) variability.

A Phase I, single center, and non-controlled open clinical study was carried out in patients with colorectal metastatic cancer. Five patients were enrolled at each of the following fixed dose levels: 200, 400, 800 and 1200 mg. Blood samples were drawn during 14 days for PK assessments. Poppk analysis of 179 concentration-time data from 19 patients was performed using the nonlinear mixed-effect model approach with NONMEM 7.3. The first-order conditional estimation method with interaction was used throughout the modeling process. Interindividual variability (IIV) was modeled assuming a lognormal distribution and was associated with clearance (CL), central

volume of distribution (Vc), volume of tissue distribution (Vt) and steady-state rate constant (Kss). The unexplained residual variability was best described with an additive residual error model.

Quasi Steady State approximation of the full Target Mediated Drug Disposition model best described the concentration-time profiles. The model was able to describe the effect of the mab–target binding, and target and mab–target complex turnovers on nimotuzumab PK. The final model parameters (IIV) were CL 0.0304 L/h (49.5%), Vc 6.36 L (44.9%), Q 0.057 L/h, Vt 2.52 L (138.9%), Kss 0.0717 mg/L (1.2%), Kint 0.0089 h^{-1}, Ksyn 17.3 (mg/L)/h, Kdeg 703 h^{-1}. Exploratory covariate analysis indicated dose and weight as potential covariates on Vt and Kss. Therefore, as a final step, correlation between several covariates and model parameters will be examined using the automated stepwise covariate model-building technique in psn.

The developed poppk model can be used to guide the dose selection for nimotuzumab during routine clinical practice in patients with colorectal metastatic cancer.

Development and validation of a bioanalytical method for simultaneous quantification of four antimalaric drugs using dried blood spot by LC-MS/MS for surveillance of antimalarial drug efficacy

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Malaria is still a neglected disease and a major public health concern worldwide. Objectives: The aim of this work was to develop and validate a bioanalytical method for the simultaneous determination of four antimalarial drugs (chloroquine, mefloquine, primaquine and lumefantrine) in dried blood spot (DBS) using carbamazepine as an internal standard (IS) by LC-MS/MS to evaluate safety and efficacy of the schizonticidal drugs with concomitant use of primaquine in a clinical trial in Brazil. The method was based on the liquid-liquid extraction (LLE) using tert-butyl methyl ether (TBME). The chromatography separation was achieved on ACE® C8 column (100mm×4.6mm×3.0μm) using a mixture (25:75, v/v) of 40mm ammonium acetate buffer ph 3.5 and methanol/ acetonitrile (80:20, v/v), using a flow gradient. The chromatographic run time was 5.5min. The ion transitions monitored were m/z 320.0<247.0 for chloroquine, m/z 379.0<321.0 for mefloquine, m/z 260.0<86.0 for

primaquine, m/z 530.2<512.1 for lumefantrine and m/z 237.0<194.1 for IS. In this study, the blood samples patients were collected on days 3, 7, 14, 21, 28, 42 and 63. The parameters pharmacokinetics Area Under the Curve (AUC) and the terminal elimination half-life (t1/2β) were determined. The assay exhibited a linear dynamic range of 5-500ng/ml for chloroquine, 10-2500ng/ml for mefloquine, 1-50ng/ml for primaquine, and 1-500ng/ml for lumefantrine in DBS. The values for inter- and intra-day precision and accuracy were within the generally accepted criteria for analytical methods (<15%). Selectivity, linearity (correlation coefficients were >0.99 for all four analytes), lower limit of quantification (LLOQ), precision, accuracy, stability, matrix effect and carry-over effect were evaluated for all four analytes. The overall AUC (μg/ml.h) for mefloquine, chloroquine and lumefantrine were 338.6, 103.8 and 6.7, respectively. The t1/2β (days) for mefloquine was 17.8 and chloroquine was 18.7. The developed and validated method was successfully applied for surveillance of antimalarial drug efficacy in accordance with WHO guidelines.

Simultaneous quantification of sofosbuvir and its major metabolite gs-331007 in three different biological matrices by lc-ms/ms and its application to a pharmacokinetic study

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Sofosbuvir, an approved drug against Hepatitis C virus, has demonstrated activity against Zika virus (ZIKV). This pathogen causes severe neurological disorders such as microcephaly and Guillain-Barré Syndrome. Moreover, it may be transmitted through sexual contact. Objectives: The aim of this survey was to develop and validate bioanalytical methods to quantify sofosbuvir and its metabolite GS-331007 in plasma, cerebrospinal fluid (CSF) and semen by LC-MS/MS. The methods were applied in a pharmacokinetic study in healthy research participants. They took a 400 mg tablet (Sovaldi®) and samples of CSF, semen and blood were collected at 0.00h, 1.50 h (Cmax) and 5.00h and analyzed. The validation showed that the methods had selectivity, linearity, precision and accuracy. The LOQ for sofosbuvir in the three matrices was 0.50 ng/ml, for the metabolite it was 2.0, 5.0 and 10.0 ng/ml for plasma, CSF and semen respectively. The results of the research participants are in the tables below. Table 1. Concentrations in plasma and CSF Time (h) [Sofosbuvir] ng/ml [GS-331007] ng/ml

Plasma CSF Plasma CSF 1.50 88.45±78.12 Undetected 575.68±348.88 2.04±3.78 5.00 3.27±4.38 Undetected 809.95±233.66, 36.80±26.83, Table 2. Concentrations in plasma and semen Time(h) [SFB] ng/ml [GS-331007] ng/ml Plasma Semen Plasma Semen 1.50 48.29±32.0, 983.46±111.00, 435.95±204.09 78.71±115.76, 5.00, 4.92±8.26, 10.57±4.51, 830.38±536.46, 1285.63±1218.42 Sofosbuvir was undetected in CSF, while low concentrations of GS-331007 were found in this matrix. However, an infected person may have a higher permeability to sofosbuvir due to an inflammatory process that occurs in the case of meningitis. In semen, the penetration rate of sofosbuvir were (127.5±92.6) % and (145.6±97.4) % at 1.50h and 5.00h, respectively and the penetration of GS-331007 were (18.5±21.4) % and (158.5±201.5) %. As sofosbuvir was found in semen, the data suggested that the drug may have a clinical relevance such as preventing sexual transmission of ZIKV. This work demonstrates that the methods were adequate to the objective and provide new opportunities in the clinical area.

Assessment of the impact of S2 results (on pharmacopeial dissolution tests) on multisource pharmaceutical products on the list of medications of the social insurance of Costa Rica priority drugs and which must demonstrate therapeutic equivalence in vitro

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An evaluation of the variability of the results of the pharmacopoeia dissolution test for Irbesartan, developed by Laboratory C and distributed by the Social Security of Costa Rica, was carried out. To evaluate its possible impact on the similarity of the comparative dissolution profiles of Irbesartan, a USP II dissolution assay was developed at 75 rpm, using a dissolution medium at ph 6.8 and 900 ml of the dissolution volume. In addition, a criterion was established to select the best available drug, together with a protocol for the implementation of the comparative dissolution profile, its respective validation of the system and method, as well as the statistical correlations established between the results of the pharmacopoeia (Q: 87.7, 83.5 and 90.9 %) tests and the

values obtained from f 1 (3.63, 7.48 and 4.53) and f 2 (74.2, 64.6 and 72.7) respectively. It was concluded that the higher the Q value obtained when evaluating a production batch for the dissolution test, the lower its difference factor (f 1) and the higher its similarity factor (f 2) in a comparative dissolution profile. However, with the data obtained for the production batches it cannot be demonstrated that this product is or is not an *in vitro* therapeutic equivalent compared to the reference product.

Development and application of a workflow to process high-throughput combinatorial data using the general pharmacodynamic interaction model

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Antimicrobial resistance is one of the key challenges in the current healthcare system. As new antibiotics are lacking, combinations of existing drugs can help to treat multi-drug-resistant (MDR) infections. These combinations can be investigated using high-throughput methods. Here, a dataset of ~3000 compounds in Gram-negative species was analysed using a robust workflow based on the General pharmacodynamic Interaction (GPDI) model. Using this approach, the magnitude and directionality of an interaction can be quantitatively elucidated. A model selection & evaluation workflow was developed using R (v.3.4.4) and rstudio (v.1.1.447). First, linear, power and EMAX-type models were fitted to single compound concentration-effect data, after which their parameters were fixed and all combinations of interactions and model structures were estimated by ELS regression and precision was assessed using the Fisher Information Matrix. Model selection was based on precision and the Akaike Information Criterion. The parameters of the best GPDI model were then used to assess the magnitude and direction of each interaction. A validation dataset consisting of extended-dose data was first analysed using the developed workflow. The selected models described the experimental data well and identified similar interactions as conventional response-surface analyses suggested. As opposed to convention, using the estimated interaction parameters, the nature and directionality of the interactions could be identified. The workflow was then applied to the entire dataset of ~3000 combinations leading to quantification of synergistic combinations such as vanillin and

spectinomycin, and colistin and macrolide antibiotics. A GPDI-based robust workflow was set up and applied to high-throughput data. Promising combination candidates could be identified, and their interaction quantified. These combinations can now be further investigated and pushed towards pre-clinical and clinical testing. Furthermore, clustering approaches will be applied to the model repository to group interactions according to their intensity and directionality to inform mechanistic hypotheses.

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

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Directly observed treatment, short-course (DOTS) for tuberculosis (TB) includes isoniazid (INH), rifampicin (RMP), pyrazinamide and ethambutol. One strategy to improve the response to treatment is the individualization of doses with Bayesian estimation of individual pharmacokinetic parameters using the monitoring of INH and RMP plasma concentrations (Cp). A prospective, analytical, observational and cross-sectional study was approved by ethics committee (register 66.18). Venous blood samples were taken at 2- and 4-hours post-dose. Genotyping analysis was carried out for NAT2 gen (codes for the enzyme NAT2 involved in the metabolism of INH) and MDR1gene (codes for the P-Gp efflux protein, which participates in the absorption process of RMP). Anthropometric and clinical data were collected from medical records. The RMP and INH Cp quantification was made using an UPLC-MS/MS validated method. NONMEM® software was used to estimate the individual pharmacokinetics parameters on each patient; a posteriori dose adjustment was proposed to reach therapeutic Cp of INH (38 mg/L) and RMP (8-24 mg/L). A total of 77 TB patients from 18 to 80 years old and 29 to 117 kg of total body weight were included; 57% presented CT genotype for the MDR1gene and 60% were slow acetylators for the NAT2 enzyme. Subtherapeutic Cp for both drugs were found in 16 patients, while 3 patients only for INH. For example, a male patient with meningeal TB (37 years old and 75 kg of total body weight; slow acetylator and CC genotype of MDR1gene) was receiving a standard dose of 600 mg (RMP) and 300 mg (INH). He remained with symptoms and drug monitoring was performed; Cp was subtherapeutic for both drugs. After Bayesian estimation of the pharmacokinetic parameters, it was required

an increase to 750 mg of RMP and 375 mg of INH. Dose adjustment resulted in clinical improvement and therapeutic concentrations of both drugs.

Analysis of substrates and metabolites of NAT's enzymes by HPLC from cell culture for pharmacometrics and toxicology studies

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Acute Lymphoblastic Leukemia (ALL) is an oncology disease very frequent in children. The decrease of the efficiency of the detoxification process by enzymes N-acetyltransferases (NAT's) can be associated with the probability of presenting neoplasms. The objective was implement and validate two methods by High Performance Liquid Chromatography (HPLC) for quantify substrates and metabolites of NAT's enzymes, from peripheral blood mononuclear cell (PMBC) culture as base for study its enzymatic activity in drugs metabolism and ALL research. The PMBC were obtained from blood samples and were cultured RPMI® medium with the corresponding substrate and metabolite. We used one equipment HPLC Waters System, mixtures of INH (substrate) y Ac-INH (metabolite) (NAT2); and PABA (substrate) y Ac-PABA (metabolite) (NAT1). The column and pre-column used were X-Terra RP18. The mobile phase was formed by acetic acid and acetonitrile for NAT1 activity; sodium 1-heptanesulfonate combined with phosphates buffer and acetonitrile for NAT2 activity. Detection was at 270 and 266 nm in UV, respectively. The retention times for substrate and metabolite of NAT1 activity were 4.5 and 5.5 minutes for PABA and Ac-PABA; for NAT2 were of 6.6 and 8 minutes for Ac-INH and INH, respectively. Each method was validated according NOM-177-SSA1-2013. The linear interval of each method was established: 0.56–18 μg/ml (NAT1, r=0.999) and 1.35–18 μg/ml (NAT2, r=0.998). Both methods were precise and accurate in terms of intra- and inter-day (CV<15%). The analytes were stable up to 30 days at -80°C. The limit of quantification was 0.56 μg/ml for NAT1 and 1.35 μg/ml for NAT2. The limit of detection was 0.082 μg/ml for NAT1 and 0.366 μg/ml for NAT2. These methods will be applied for evaluate the activity of NAT's enzymes in PMBC and their mechanism of participation in pharmacometrics and toxicology studies such as ALL, other hematological neoplasm, and the pharmacokinetics of drugs substrates of the NAT's.

Model-based characterization of neutrophil dynamics in children receiving busulfan or treosulfan for haematopoietic stem cell transplant conditioning P

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Busulfan and treosulfan are used in the conditioning prior to paediatric haematopoietic stem cell transplantation (HSCT). To establish: (i) a PKPD model for the treatment effects on neutrophil counts, (ii) optimised dosing schedules, and (iii) optimised PK sampling for Bu TDM. Records from 72 children receiving Bu (7 m-18 y, 5.1–47.0 kg) and 54 Treo (4 m–17 y, 3.8–35.8 kg), were collected. 8,935 neutrophil counts were recorded for 3 months. The Friberg model was extended to account for HSCT effects. The model was used to evaluate dosing schedules through simulations. The optimal Bu PK sampling collection times were determined using the R package poped. A 2-compartment model best described Bu and Treo profiles. A maturation function was included affecting clearance - PM50 was 45.7 and 42.2 weeks for Bu and Treo, and Hill was 2.3 for both drugs. The final model included separate steady-state neutrophil count (CIRC0) before and after transplant ($p<0.01$). The HSCT enhanced cell proliferation and maturation increasing by 2-fold the parameters ($p<0.01$). HSCT increased proliferation and γ in a 5%. System parameters were consistent across drugs (CIRC0, MTT and γ), estimated as 0.79·109 cells/L, 8.02 days and 0.10. The neutrophil decline was modelled with a linear model for Bu (KKILL=0.7) and an EMAX model for Treo (EMAX=1.2). The presence of alemtuzumab enhanced the HSCT effect, with a 2.9-fold increase in proliferation. A 2-day delay in Treo administration would leave the patient less time immunocompromised without damaging the HSCT. The optimal design exercise suggested a reduced sampling schedule (5 vs 6 samples), obtaining similar parameter precision (maximum bias <10%) The semi-mechanistic PKPD model developed predicts neutrophil reconstitution trajectories from children after HSCT, being a useful tool to improve their clinical management. New dosing and sampling schedules are proposed.

A quantitative systems pharmacology model characterizing the main immune components involved in Crohn's disease to test new therapeutic scenarios

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Crohn's disease (CD) is a complex inflammatory bowel disease, which causes a functional impairment of the gut wall. The reported lack of effectiveness in the standard of care require the application of techniques aiming to find new targets and therapeutic strategies. We aimed to develop a quantitative SP (QSP) model in humans characterizing the dynamics of the main immune system components involved in CD. We followed a workflow for robust application of SP model: (i) identify main project goals; (ii) selection of species and literature search for blood levels in healthy subjects (HS) and CD patients; (iii) representation of model topology and parametrization of the interactions using data extraction and curation. Model components kinetics were characterized by zero or first-order synthesis and first-order degradation constants. Constant levels for ils and cells at the steady state (SS) of HS and CD were assumed for synthesis rate constant derivation. To parametrize the IL interactions, different sub-models were tested using nonlinear regression in Rv3.5.0. Ordinary differential equations (odes) were implemented in simbiology® (MATLAB®vr2018b). Afterwards, (iv) deterministic simulations for CD were run and model evaluation was performed. A total of 21 species representative of the innate and adaptive immune response in CD were included. Graphical representations were generated providing a big picture of model structure. The developed QSP model included 21 odes. A quantitative reproduction of CD was obtained. We present a QSP model for the main ils and cells involved in CD. Not only is supported by a comprehensive repository summarizing the most relevant literature in the field, but also by a standardized methodology for QSP model building. This model proved to be promising for the in silico evaluation of potential therapeutic targets and the search for specific biomarkers. Finally, it can be expanded or reduced as demanded, leading to different quantitative model/s to address research gaps regarding CD.

Population pharmacokinetics of variants of Cuban pegilated recombinant human erythropoietins

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Recombinant human erythropoietin stimulates the formation of erythrocytes in the bone marrow. This therapeutic glycoprotein has a short half-life (4-11h), so it is rapidly eliminated from the body. One of the technological strategies used to solve this problem is pegylation. The aim of this study was to develop a population pharmacokinetic of two newly pegylated-EPO analogues (PEG-EPO 32 and 40 kda) formulations compared with the reference products ior®EPOCIM and MIRCERA®. For each product, a single dose of 10 μg/kg was administered via intravenous bolus in 19 New Zealand rabbits and serum concentrations were determined at different times. Initial population pharmacokinetic modeling was conducted using NONMEM version 7.3., via FOCEI method. Standard goodness-of-fit plots, individual predicted/experimental versus time profiles, eta histograms and normalized prediction distribution error plots were generated to evaluate the model performance. The final model obtained was translated into rxode and executed using nlmixr, with SAEM method, in order to allow for performance comparison between NONMEM and the open-source R based software nlmixr. A two-compartment population pharmacokinetic model with linear elimination was obtained. The interindividual variability was associated with CL and V1. The PEG-EPO 32 and 40 kda had lower clearance than with ior®EPOCIM and MIRCERA® ($CL_{EPO-\ PEG-32}$: 5.77×10^{-3} L/h, $CL_{EPO-PEG\ 40}$: 4.34×10^{-3} L/h, $cl_{ior®EPOCIM}$: 1.02×10^{-1} L/h, $CL_{MIRCERA®}$: 1.06×10^{-2} L/h); which allowed a decrease in the frequency of administrations. Model output comparison between NONMEM and nlmixr resulted in very similar results when comparing the final parameter estimates and goodness-of-fit plots of model performance. The results of this investigation contributed to establish the potential of PEG-EPO 32 and 40 kda formulations obtained in Cuba as promising candidates for the use in the clinic. Additionally, this work demonstrated the availability of nlmixr as a reliable tool for the use of pharmacometric analyses.

Antiretroviral blood monitoring and effectiveness analyses of Cuban HIV-AIDS patients treated with generics AZT3TC-NVP

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Quantification of the blood concentration of antiretroviral drugs (BCAD) allows individuals evaluation to guarantee an appropriate suppression of the viral load. This monitoring activity in HIV-aids patients don't include in clinical practice in Cuba. It was carried out a cross sectional and analytic study including 100 Cuban patients assisted at IPK Hospital and treated with AZT/3TC/NVP combination. For the evaluation of the BCAD (AZT, 3TC, NVP) was used chromatographic conditions of previous analytical validated methods in a liquid chromatograph Knauer. It was evaluated the number of T lymphocytes CD4+, the viral load and the behavior of hematological and hemochemistry indexes previous and two months after of the determinations. The age median was 40 ± 10 years, with prevalence of the masculine sex (81/100) and white skin color (92/100). Most of the BCAD for the studied group were in the effective therapeutic interval (NVP: 3.94 ± 2.99, AZT: 0.39 ± 0.46, 3TC:0.27 ± 0.28 x 10^{-3} μg/ml). The progression markers (number of lymphocytes TCD4+ and the viral load) evidenced a simultaneous modification with effectiveness of 23% for the group, as well as alterations of some hematologic and hemochemistry indexes without pathological or toxic significance. Different number of patients with drug concentrations in effective therapeutic range were detected through the individual analysis (NVP: 49/100, AZT:88/100, 3TC:61/100). Analysis allowed to the identification of sub optimal concentrations in 75% of the evaluated patients. The effectiveness analysis of patients considering BCAD in the therapeutic range for the three drugs was 86.3%. The findings corroborate relationship between the BCAD and the drug effectiveness. Similar analysis can contribute to prolong the useful period of each combination, to prevent both the resistance and the associate toxicity and to consider the treatment accomplishment objectively.

Systematic review of the most reliable analytical methods for monitoring fluconazole, itraconazole and amphotericin b, in routine clinical practice

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To identify the most reliable analytical methods for the therapeutic monitoring of fluconazole, itraconazole and amphotericin B in routine clinical practice. A literature search was conducted in the databases of electronic data LILACS, pubmed, Medline, Cochrane and scielo. The search was conducted from January 2018 to June 10, 2019. "Analytical methods", "Antifungals", "Fluconazole", "Itraconazole" and "Amphotericin B" and their equivalents in English and Portuguese. Studies that describe the methodology of antifungal therapeutic monitoring and study that evaluates the different analytical methods for the quantification of antifungal agents were established as inclusion criteria. Review studies of pharmacokinetic and pharmacodynamics properties of antifungals and studies on antifungal resistance. Of 132 records identified, only 5 were included. In the selected articles, it is recommended to monitor high resolution liquid chromatography according to the pharmacokinetic properties of fluconazole and itraconazole in clinical practice. For amphotericin B there are still no studies to support its monitoring. This procedure allows adjusting the dose of treatments for each patient and minimizing the risks associated with their use. The most reliable methods for the therapeutic monitoring of antifungals in clinical practice are liquid chromatography with high efficacy, ultraviolet-visible and coupled to mass spectrometry, which is a high specificity and rapidity of response.

Characterization of the pharmacokinetics and pharmacodynamics of three Cuban recombinant interferon alpha formulations

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Pharmacokinetics (PK) and pharmacodynamics (PD) are critical for the evaluation of biopharmaceutical products. The aim of the entire work was to characterize these

properties in the Cuban recombinant interferon (IFN) alpha present in its different formulations, establishing in each case comparisons with similar reference products. Three clinical studies were carried out in healthy male volunteers, to evaluate PK, PD, and biological safety of three respective formulations containing IFN alpha, developed at the Center for Genetic Engineering and Biotechnology (CIGB) in Havana. These were a liquid formulation without albumin, a second formulation with the molecule conjugated to polyethylene glycol ("pegylated") and another combined with IFN gamma in synergistic proportions. Clinical studies were randomized, double-blind and crossover, with a 3-week washout period between the administration of test and reference formulations. Serum IFN concentrations and serum classic IFN-inducible markers were measured by commercial enzyme immunoassays. Non-compartmental and compartmental methods were applied. An integrated PK/PD model was written using the build-in MLXTRAN code in MONOLIX, based on the best-fit PK model and a classical indirect response model with response stimulation. PK and PD parameters, as well as the observed adverse events, demonstrated the similarity between Cuban IFN alpha formulations and their commercial referents. Pegylated IFN demonstrated slow absorption and elimination. The combination of IFN alpha and gamma produced pharmacodynamic potentiation. Neopterin levels were nine-fold higher than initial, 48 hours post-injection, beta2-microglobulin was approximately the double, while 2'-5' oligoadenylate synthetase concentrations were four-fold higher than baseline on the eighth day and the moment to return to normality could not be predicted. Formulations were safe; flu-like symptoms and hematological count reductions were the most common adverse events. The formulations of the Cuban recombinant IFN alpha have favorable pharmacological properties, being the same comparable to their respective commercial similar.

Genotype-driven pharmacokinetic simulations of warfarin levels in Puerto Ricans

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The variability in response to warfarin among individuals has been linked to genetic polymorphisms. This study was aimed at performing genotype-driven pharmacokinetic

(PK) simulations to predict warfarin level differences among Puerto Rican subjects with CYP2C9 genetic polymorphisms. A PK simulation analysis of each individual dataset was performed by one-compartmental analysis using winnonlin® software (v6.4, Certara, USA). The elimination rate constants (Ke) of warfarin given a CYP2C9 genotype were: *1/*1=0.0189 hr^{-1} (wild-type); *1/*2=0.0158 hr^{-1}; *1/*n=0.0132 hr^{-1}; *2/*2=0.0130 hr^{-1}; *2/*n=0.009 hr^{-1}; *n/*n=0.0075 hr^{-1}, being n=*3, *5, *6 or *8. Data from 128 male subjects, mostly elderly of Caribbean Hispanic origin, were used to perform secondary analyses in this study. Subjects were divided into wild-types and carriers and statistical analysis by two-sample unpaired t-tests were performed to compare their corresponding PK parameters. In the carrier group (n=64), 53 subjects were single carriers (i.e., 30 with *1/*2 and 23 with *1/*3, *1/*5 or *1/*8 genotypes) and 11 double carriers of CYP2C9 polymorphisms (i.e., two *2/*2, seven *2/*3 or *2/*5 and the other two with *3/*5 and *3/*8 genotypes, respectively). The mean peak concentration (Cmax) was higher for wild-types (0.36 ±0.12 mg/L vs. 0.32 ±0.14 mg/L). Likewise, the average clearance (CL) was faster among non-carriers (0.22 ±0.03 L/h vs. 0.17 ±0.05 L/h; p=0.0001), with lower area under the curve (AUC) when compared to carriers (20.43 ±6.97 h·mg/L vs. 24.78 ±11.26 h·mg/L; p=0.025). Statistical analysis revealed a significant difference between carriers and wild-types with regard to AUC and CL, but not for Cmax and Vd. The latter parameter being on average higher in carriers, due probably to larger body weights in this group versus non-carriers. These pharmacogenomic-driven PK simulations provided useful information for further development of warfarin dosing prediction models that account for individual pharmacokinetics and genotyping. Further assessments are needed to validate our findings.

Cyclosporine pharmacokinetic model for kidney transplant hosts and autoimmune disease patients

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Calcineurin inhibitor, Cyclosporine (CYA) is widely used in the hospital setting, either to prevent graft rejection or to control autoimmune diseases. CYA nephrotoxic effects has led to a reduction in its use in kidney transplantation, whereas it has grown considerably in autoimmune diseases. TDM of CYA is a common practice to avoid adverse drug effects or inefficacy. For many years now, predose (C0) and concentration 2 hours post administration (C2) have been adopted as the most common samples in practice, though it is known that a complete profile of concentration (C0, C1, C2, C3, C4) is

the most accurate way to follow treatments due to CYA high interindividual variability. As a consequence, model building is a useful tool to take into consideration population characteristics and formulations available in the country to optimize dose regimen. For model building we analyzed curves of concentration vs time and we also included C0 and C2 when possible. Blood samples were analyzed using an immunoassay chemiluminescent microparticle immunoassay (CMIA, Architect® analyzer, Abbott Laboratories). To validate our pharmacokinetic model new patients' blood samples were analyzed and their results compared with the predicted concentrations using root mean square error. Data modeling were performed using Monolix® 2019R1, meanwhile the R package mlxr developed by Lixoft. A bicompartimental model with lag time is the one that best fits CYA pharmacokinetic model. Only Creatinine CL is a significant covariable in the model. During the validation of the model, C2 concentrations were the ones that were predicted with less error, and C0 predictions highly improved from one occasion to another. Creatinine Clearance proved to be the most important parameter to explain CYA CL changes in patients. In case only one sample could be drawn, C2 determination appears to be the one that is best predicted by our model.

Pharmacokinetics of xylazine in horses

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Xylazine is widely used drug in veterinary practice for its potent sedative, analgesic and myorelaxant properties. Nevertheless, despite its extensive use, no pharmacokinetics population models have been published for this drug in horses. In this prospective study, six horses (three males and three females) were selected and randomly assigned in two groups according to two periods, crossover compensated design, comparing two doses, 0.5 and 1 mg/kg of Xylazine via iv bolus. Two jugular catheters were implanted for injection (right) and blood sample collection (left). Blood samples were collected at 2, 5, minutes and 0.25, 0.5, 0.75, 1.0, 1.5, 2- and 3 hours post dose. Pharmacokinetic analysis was performed for Xylazine using Monolix® software (Monolix Suite 2019R1, 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 described Xylazine disposition in horse appropriately, consisting in a two-compartment structure with first order elimination kinetics. Typical parameter estimates were: CL = 2268 L/h,

V1=984 L, Q=2454 L/h and V2=450 L. Interoccasion variability was included for CL and V1, with estimates of 5.36% and 14.2% respectively. A combined residual model was implemented. Weight was included as covariate in all disposition parameters according to an allometric model with an exponent of 0.75 and 1.0 for clearance and volume terms respectively. Reported estimates are the typical parameters for a 400 kg bodyweight animal.

Pharmacokinetics of methadone in horses

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Methadone is a synthetic μ-opioid agonist with potent analgesic properties useful in the treatment of both, acute and chronic pain. This work describes the pharmacokinetic of methadone in horses. In this prospective study, six female horses were selected and randomly assigned in four groups according to four periods, crossover compensated design, comparing three doses, 0.1 and 0.2 mg/kg via iv bolus and 0.5 mg/kg via iv bolus or intramuscular of Methadone. Two jugular catheters were implanted for injection (right) and blood sample collection (left). Blood samples were collected at 2, 5, 10 minutes and 0.25, 0.33, 0.75, 1.0, 1.33, 1.67, 2.0, 2.33, 2.66- and 3.0 hours post dose. Pharmacokinetic analysis was performed for Xylazine using Monolix® software (Suite 2019R1, 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 described Methadone disposition in horse appropriately, consisting in a two-compartment structure with first order elimination kinetics. Typical parameter estimates were: CL = 208.8 L/h, V1=66.7 L, Q=774 L/h and V2=59.3 L. Absorption parameters for intramuscular administration were F= 0.82 and ka=20.76 h-1. Interindividual variability was included for CL with an estimate of 27.0% and interoccasion variability was included for CL and V1, with estimates of 25.8% and 29.0% respectively. A combined residual model was implemented. Weight and administered dose were included as covariate for V1.

Naïve-pooled pharmacokinetic analysis of betulinic acid in mice plasma after oral administration as nano-emulsion type formulations

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Betulinic Acid (abet) arouse special interest in the scientific community as substances with beneficial health effects, and is evidenced by studies involving effects, actions and risk prevention in certain diseases. Information related to bioavailability and pharmacokinetics process is required to development of abet as a functional food alternative. A murine model was applied to describe the pharmacokinetics of a single oral dose of abet (50 mg/kg) as a conventional emulsion (EMC) and nano-emulsions with original phosphatidylcholine (NEM-PC1) and enzyme-modified phosphatidylcholine (NEM-PC2), under fasting conditions. Pharmacokinetics profiles were obtained by chromatographic analysis of plasma samples. Pooled naïve and NCA analysis was performed by Monolix-Lixotf (v2019r1) to obtain pharmacokinetics parameters and evaluate bioavailability between formulations. The plasma sampling times from experimental animals were as follows: 0.5, 1.0, 2.0, 3.0, 4.0, 8.0 and 12.0 h. 3 experimental animals were used for each sampling time, giving a total of 21 mice per formulation. Data from all formulations were adjusted to a monocompartmental pharmacokinetic model with a first order process of absorption and elimination. Population parameters values and random standard error (%) obtained as follows: ka=0.185 h^{-1} (17.5), V/F= 0.850 L (38.0), CL=1.1 L/h (7.02). Inclusion of formulation as covariate increased the performance of the model. Non compartmental analysis between formulations demonstrated the average and standard deviation of ABC0-inf (mcg.h/L) and Cmax (mcg/L) of EMC, NEM-PC1 and NEM-PC2 (1059.14±105.61 / 195.104±56.93), (3059.28±601.4 / 515.05±115.24), (4308.10±875.27 / 536.66±69.06) respectively, indicated significant differences (P<0.0001) between EMC and nanoemulsions. Half-life between formulations reveal an important increase of permanence of abet in NEM-PC2. The bioavailability of nano-emulsions is superior compared to EMC as reported in previous studies, where the enzymatic modification of phosphatidylcholine is a starting point for the control of bioavailability.

Effect of ^{177}Lu-ipsma on viability and dna damage of human glioblastoma cells under hypoxia-mimetic conditions

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Glioblastoma is a human neoplasm characterized by a high degree of hypoxia. Hypoxic condition improves therapy resistance of cancer cells. Lutetium-177 has been used in targeted radiotherapy, due to its physical properties allow beta particles to deposit their energy in small volumes and deliver high doses to targeted cells. PSMA is a transmembrane protease that is considered a target for different therapeutic strategies because of its overexpression in the neovasculature of several solid tumors, including glioblastoma. The aim of this work was to evaluate the effect of ^{177}Lu-ipsma on cell viability and DNA damage in U87MG human glioma cells under hypoxia mimetic conditions.U87MG cells treated with ^{177}Lu-ipsma were incubated with $cocl_2$ in order to induce hypoxia-mimetic conditions. The cytotoxic and genotoxic effect was evaluated with an *in vitro* viability test and a neutral comet assay. ^{177}Lu-ipsma exposure time significantly reduced the percentage of viable cells both with and without $cocl_2$ (72 and 78%, respectively). Percentage of DNA in U87MG cell comet tails indicate that 177Lu-ipsma treatment had a genotoxic effect after 4 h. Even though $cocl_2$ exposed cells acquired important radioresistance, the continuous emissions from Lu-177 produced an increase in DNA damage at 24 and induced irreparable DNA double strand breaks in U87MG human glioma cells under hypoxia-mimetic conditions. ^{177}Lu-ipsma produced the maximum effect at 48 h, suggesting that this radiopharmaceutical could be used as a strategy for the treatment of human glioma hypoxic cells.

Pharmacokinetics and pharmacogenetics of valproic acid in Chilean patients with epilepsy

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The use of valproic acid (VPA) is licensed for the monotherapy or the adjunctive treatment of any form of epilepsy in patients of any age, however, it is estimated that

approximately 30% of patients are refractory. There are many factors that could affect drug response, such as drug-drug interactions and the presence of some allelic variants, which result in large differences between individuals in the dose-to-plasma concentration relationship. The aim of this study was analyzing the effect of the associations of allelic variants CYP2C9*2, *3 and UGT2B7*2 plus coadministration of inducers drugs on pharmacokinetic of valproic in patients with epilepsy. A total of 52 adult patients on stable treatment with VPA as mono or adjunctive therapy attended at "Complejo Asistencial Dr. Sótero del Río" and "Centro de Referencia de Salud Dr. Salvador Allende Gossens" were included. The Cl/F were calculated by non-compartmental analysis using one plasma sample per patient and the genotype of epileptic patients was obtained by PCR-RFLP technique. The allelic frequencies of UGT2B7*2, CYP2C9*2 and CYP2C9*3 were 0.302, 0.080 and 0.058, respectively. The presence of one or more copies of the T allele for the UGT2B7(T<C) polymorphism results in an increase in valproic acid clearance, particularly, significant differences were observed when the drug is administered together with an antiepileptic drug that induce its metabolism and when the patients are extensive metabolizers for the CYP2C9 genotype classification.

Population pharmacokinetic modeling of clozapine-loaded nanocapsules in male Wistar rats

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Clozapine is an atypical antipsychotic of first choice in refractory schizophrenia. Its therapeutic use is limited due to agranulocytosis and cardiotoxicity. Our research group developed polysorbate 80 (NC1), PEG (NC2) or chitosan (NC3) coated clozapine-nanocapsules and published data from non-compartmental and compartmental pharmacokinetic analysis, demonstrating the relevance of nanoencapsulation. In this context, our aim was to develop the populational approach (poppk) of nanoencapsulated Clozapine. 384 observations from 25 individuals (male Wistar rats, IV administration, 25 mg/kg clozapine dose) were used to poppk via Monolix (Lixoft®, 2018R2). We consider the formulations as covariate. Visual predictive assessment (VPC), relative standard deviation (R.S.E. %), *P* value, Akaike Information Criteria (AIC) and -2xlog likelihood were considered for model selection. A 3-compartment open model with intravenous bolus administration and linear elimination process was selected as the best model, corroborating previously published data. Clearance population was 1.89 L/h, NC1 and NC2 showed negative beta. V1 was reduced with NC3 acted as covariate, while V2 decreased by NC2. V3 was significantly altered by NC2

(beta = 3.81). Important changes in pharmacokinetic parameters were observed from nanoencapsulation, suggesting Clozapine-loaded nanocapsules are promising in the treatment of schizophrenia.

Therapeutic peptides quantitation in human plasma using mass spectrometry: our experience applied to pharmacokinetic studies during clinical trials

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Mass Spectrometry (MS) has impressive capabilities in terms of sensitivity, resolving power, mass accuracy and different scan-modes versatility. Either alone or in combination with liquid chromatography it is the analytical tool of choice for synthetic therapeutic peptide characterization. Nevertheless, for peptide quantitation in human plasma or other biological sample, the design of the Internal Standard (IS) and the optimization of the sample processing and LC-MS analysis are also key elements for a successful outcome. In consequence, all strategies involving the peptide quantitation in biological fluids are still a challenge and need to be tailored. We present here our recent experiences in the development and validation of customized bioanalytical methods applied to pharmacokinetic studies included in phase I clinical trials. For the absolute quantitation of these three therapeutic peptides, alternatives to the AQUA® methodology were used. However, the design of the IS, sample processing and mass spectrometry techniques were optimized case by case for CIGB-500, CIGB-300 and CIGB-814 candidates. IS for CIGB-500 and CIGB-814 were synthetic peptides labeled with stable isotopes (^{13}C and/or ^{15}N) in specific residues within the amino acids sequence, instead of IS for CIGB-300 that was a N-terminus acetylated peptide. Sample processing mainly based on plasma proteins organic or acid precipitation was adapted according to the peptide recovery. In the particular case of CIGB-300, no liquid chromatography separation was needed before MS analysis by MALDI-TOF MS. For CIGB-500 it was applied LC-MS analysis with Simultaneous Ion Monitoring (SIM) in full scan mode. For CIGB-814 it was used LC-MS analysis in Single Reaction Monitoring Mode (SRM). The three bioanalytical methods were fully validated and applied to Pharmacokinetic (PK) analysis in a phase I clinical trials. It was possible to obtain PK profiles and main PK parameters for all of the assessed candidates.

Pharmacokinetics characterization of cyclosporine A after oral administration of nanoparticles Gantrez® and using nonlinear mixed effects models (nlme)

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Cyclosporine A (csa) has been used as a potent immunosuppressive agent despite its low oral bioavailability and formulation problems. In our work we develop 4 new formulations of PVM/MA nanoparticles loading Cyclosporine including cyclodextrin derivatives or poly (ethylene glycol) 2000 (PEG2000) in order to increase their bioavailability. The content of Cyclosporine A in the nanoparticles was quantified by HPLC in order to determine stability, encapsulation efficiency and *in vitro* release; we also determine the particle size and surface charge of nanoparticles. The bioavailability of nanoparticles loaded Cyclosporine was evaluated in rats, compared to the currently available cya microemulsion (Neoral®) and csa pharmacokinetic was characterized using nonlinear mixed effect models. Formulations A, C and D showed the best results in the characterization of nanoparticles and were evaluated in order to describe their *in vivo* behavior. When Formulation A is administered orally in rats, the bioavailability of the drug has been found to increase in magnitude by 21.43% than when administered in sandimmunneoral® oral. The results of pharmacokinetic characterization suggest that the type of formulation that is administered to rats has influence on the pharmacokinetic parameters obtained and two-compartment model fits to our data. Our results suggest that new formulations A, C and D may be an alternative to commercial csa formulations and formulation A increases the bioavailability of the drug.

Population pharmacokinetic approach of 400 mg ibuprofen oral dose soft gelatin capsules in healthy volunteers. Covariates matters

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Ibuprofen (ibpf) has largely been administered as an anti-inflammatory non-steroidal drug by oral administration. Usually noncompartmental analysis (NCA) has been considered to describe pharmacokinetics, however, the inclusion of covariates as age, weight, gender, Body Mass Index (BMI), has not been clearly explored. This type of analysis requires the development of mixed effects models to incorporate covariates to the analysis. Data were obtained from previous 2x2x2 crossover bioequivalence study where 24 healthy volunteers (9F/15M) participated. All received an oral administration of reference and test soft gelatin capsule containing 400 mg ibpf solubilized in a polymeric semi-liquid matrix after a wash period of 7 days. 17 sampling times (basal included) of plasma were analyzed by UPLC-Mass assay. Five covariates were recorded: age, gender, BMI, type of formulation (Reference or Test) and occasion (OCC). We focused our study to the estimation of the parameters and the selection of the covariate model. A maximum likelihood expectation maximization approach was used to fit the data. Ibuprofen pharmacokinetics was best described by one-compartment (volume V) and a linear elimination clearance (Cl). Type of administration was extravascular with a first order absorption (rate constant k_a) and a lag time (T_{lag}). Typical values and SD for ibpft$_{lag}$, k_a, V/F, Cl/F were 0.314 ± 0.017 h, 2.26 ± 0.645 h^{-1}, 7.4 ± 0.293 L/kg, 0.802 ± 0.376 L/h respectively. Type of formulation was found to be a statistically significant covariate of T_{lag} and k_a, meanwhile BMI was found to be a covariate of Cl. Our results support the need to evaluate in this study covariates to develop pharmacokinetics models to enhance predictions of plasmatic concentrations of drugs. This evidence is relevant to development of new pharmaceutical formulations and the design of clinical studies taking in to account such information.

Pharmacometric study of ^{125}I-neuroepo after intranasal and intravenous administration in Sprague Dawley rats

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Neuroepo is a nasal formulation of recombinant Human Eritropoietin (rhuepo) whit low content of sialic acid and proved neuroprotector effect in non-clinical and clinical

assays. Its distribution in the central nervous system is rapid but the pharmacokinetics of the product have not been previously characterized. A pharmacokinetic study of sparse data in Sprague Dawley rats was designed for intranasal and intravenous administration of 50 μg of [125I]-neuroepo. The amount of [125I]-neuroepo in blood and tissue of different organs of interest was determined at different times for 24 hours. The population pharmacokinetic parameters were modeled using MONOLIX (Suite 2018, Lixoft S.A.S, Francia). The formulation is weakly captured in the central nervous system, approximately 0.1% of the dose administered per gram of tissue according to a previous study in Mongolian gerbils and macaques. The preliminary analysis of the data showed a better adequacy of the plasma concentration profile to the model represented by the tri-exponential equation. Population pharmacokinetic parameters were determined. For the estimation of the areas under the curve, together with the rest of the non-parameterized parameters, an enriched data set was simulated using the resampling bootstraping. The adjustment to a tri-exponential model implies a very rapid plasma elimination of the molecule at an initial stage after administration. Part of the dose administered intranasally passes into the digestive and respiratory system influencing the variability observed. The uptake of 125 I-neuroepo in the central nervous system is quantitatively very low and has a high dispersion, which makes mathematical modeling difficult following a sparse data design. The exploration of other statistical methods should be continued to achieve a model that adequately describes the process studied.

Labelling and pharmacological study of ^{188}Re-nimotuzumab

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The aim of the present work was to label monoclonal antibody nimotuzumab with ^{188}Re, to assess its biodistribution in an animal model and to evaluate its internal dosimetry and toxicity in patients with grade III-IV gliomas through a phase I clinical trial. Labelling efficiency of ^{188}Re-nimotuzumab was 98.0±0.4%. Animal biodistribution was assessed at 3 and 24 h after IV administration of ^{188}Re-nimotuzumab through tale vein of male Wistar rats, showing a similar pattern as ^{99m}tc-nimotuzumab (control). A phase I clinical trial was performed by administering into the post-surgery

cavity through an indwelling catheter a single dose of 3 mg of ^{188}Re-nimotuzumab (370 mbq - group I and 555 mbq - group II). Biodistribution and dosimetric studies were performed. ^{188}Re-nimotuzumab showed a high retention in the tumoral cavity with an effective $T_{1/2}$=9.4±1.6 h. The mean absorbed doses in the tumor was 24.1±2.9 Gy for group I and 31.1±6.4 Gyfor group II. Highest doses were received by kidneys, liver, and urinary bladder: 0.754, 0.223 and 0.604 mgy/mbq, respectively. The maximal tolerated dose was considered 3 mg of the antibody labelled with 370 mbq of ^{188}Re. One patient with has a partial response for more than 1 year and 2 patients showed complete response after 3 years of treatment. No patient developed a HAMA response. Proposed procedure allowed the stable efficient labelling of nimotuzumab with ^{188}Re. Preliminary results of this study strongly suggest that loco-regional radioimmunotherapy of high-grade glioma using ^{188}Re-nimotuzumab may be safe and constitute a promising therapeutic approach for these patients.

Development and preclinical assessment of ^{18}F-Amylovis as a potential PET radiopharmaceutical for b-amyloid plaque

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Alzheimer's disease (AD) is the most common form of dementia. Neuroimaging methods have widened the horizons for the AD diagnosis and therapy. Herein, the synthesis of 2(3-fluoropropyl)-6-methoxynaphthalene and its ^{18}F-radiolabeled analogue (^{18}F-Amylovis) were described. ^{18}F-Amylovis was obtained with satisfactory yield, high radiochemical purity and specific activity. A comparative *in silico* studies with Amylovis and PIB and the Aβ peptide were carried out. All studies predict that Amylovis should have affinity to the peptide and the ligand-Aβ peptide complexes is stable. Determinate log P value point out its potential ability of crossing the blood brain barrier (BBB). *In vitro* stability (ethanol, HAS, PBS and plasma protein binding) were assayed and it was found stable for 12 h and had low plasma protein binding.

Higher affinity to Aβ plaques were found for Amylovis than PIB. Biodistribution and PET imaging studies in healthy and transgenic appswe/PS1dE9 mice, showed that ^{18}F-Amylovis crosses BBB, and has different behaviour in healthy animals and transgenic mice, the plasma half-life was 37±10 min. Radiopharmaceutical was *in vivo* metabolised in 60 min. Preclinical assessment of ^{18}F-Amylovis showed that it could be a new potential radiopharmaceutical for the imaging of β-amyloid plaque.