GMP

Groupe de Métabolisme et Pharmacocinétique

Group of Metabolism and Pharmacokinetics

When DMPK is out of sight but not out of mind

2020 First GMP Virtual Symposium

From 18th of September to 23rd of October 2020

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PROGRAM AND SPEAKERS

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PROGRAM

When DMPK is out of sight but not out of mind

Day 1: 18th September 2020

11:00 - 12:00 **OPENING SPEAKER**

Drug Impact of antibiotic therapy on the bacterial diversity of the intestinal microbiota
Charles Burdet, IAME Inserm, Paris, France
Chairs: N Gregoire (Poitiers Univ.), J Henri (Anses)

Day 2: 25th September 2020

10:30 - 12:00 **SESSION 1**

10:30 – 11:15 **S1.1 IN VITRO TESTING**
An in vivo like 3D hepatic liver spheroid system for studies of aetiology and treatment of chronic drug hepatotoxicity and hepatic fibrosis
Magnus Ingelman-Sundberg, Karolinska Institute, Stockholm, Sweden
Chairs: M Rachid (Genoscience Pharma), Y Courbebaisse (Adocia)

11:15 – 12:00 **S1.2 ARTIFICIAL INTELLIGENCE**
Machine Learning Approach to Forecast Chemotherapy-Induced Haematological Toxicities in Patients with Rhabdomyosarcoma
Vesna Cuplov, SmartC, Marseille, France
Chairs: C Serdjebi (Biocellvia), Y Parmentier (Servier), Q Nguyen (Ipsen)

Day 3: 2nd October 2020

10:30 - 12:00 **SESSION 2**

10:30 – 11:15 **S2.1 IN VITRO TESTING**
A fluid-dynamic Multi-In Vitro Organ- MIVO device as alternative approach for in vitro drug testing
Silvia Scaglione, React4life, Genoa, Italy
Chairs: M Rachid (Genoscience Pharma), M Fonsi (Charles River)

11:15 – 12:00 **S2.2 INNOVATIVE THERAPIES**
Car-T cell development and registration – Opportunities for the application of Pharmacometrics
Rik De Greef, Certara, Oss, The Netherlands
Chairs: V Duval (Certara), F Gattacceca (Aix-Marseille Univ.)

Day 4: 9th October 2020

10:30 - 12:00 **SESSION 3**

PK challenges in pediatric drug development

Chairs: R Barcham (Oroxcell), L Del Frari (Pierre Fabre), F Hurbin (Sanofi), A Coquerel (Caen Univ.)

10:30 – 11:00 **S3.1**

Prediction of midazolam pediatric plasma profiles for multiple routes of administration using physiologically based pharmacokinetic model

Maxime Le Merdy, SimulationsPlus, Basel, Switzerland

11:00 – 11:30 **S3.2**

PopPK/PD scaling from adults to children using priors: A case example with Alirocumab

Elisa Calvier, Sanofi, Montpellier, France

11:30 – 12:00 **S3.3**

Use of model informed extrapolation in regulatory submissions - Examples

Flora Musuamba Tshinanu, EMA, Brussels, Belgium

Day 5: 16th October 2020

15:00 – 16:30 **SESSION 4**

DDI risk assessment and evaluation in pharmaceutical development

Chairs: O Barberan (Elsevier), O Nicolas (Sanofi), Y Parmentier (Servier), A Sharma (Senzagen)

15:00 – 15:30 **S4.1**

PBBM application to support formulation changes, prediction of pH related DDI and impact of beverages on exposure to acalabrutinib

Xavier Pepin, AstraZeneca, Macclesfield, UK

15:30 – 16:00 **S4.2**

Drug-drug interactions of therapeutic proteins

Antoine Deslandes, Sanofi, Alfortville, France

16:00 – 16:30 **S4.3**

Ivabradine metabolite PBPK modelling: CYP3A4 mediated DDI risk evaluation in adults and children

Jennifer Lang, Manchester Univ., Manchester, UK

Day 6: 23rd October 2020

10:30 - 12:00 **GMP 2020 CLOSURE**

10:30 – 11:00 **Students' presentations**  **AWARDS**

11:00 – 12:00 **ASSEMBLEE GENERALE DU GMP**

J'adhère, je participe, je vote !!!

SPEAKERS

Opening Speaker

Impact of antibiotic therapy on the bacterial diversity of the intestinal microbiota

Charles Burdet[a,b], Thu Thuy Nguyen[a], Xavier Duval[a,b], Stéphanie Ferreira[c], Antoine Andremont[a], Jérémie Guedj[a], France Mentré[a,b]

a *IAME, INSERM, Université de Paris, Paris, France*
b *AP-HP, Bichat Hospital, Département d'Epidémiologie, Biostatistique et Recherche Clinique, Paris, France*
c *Genoscreen, Lille, France*

The development of next generation sequencing broadened our knowledge on the role of commensal bacterial communities on their host's health, and the negative impact of their disruption. Antibiotics are the main disrupting factor, but their impact has not been precisely quantified.
We first quantified, in an animal model of antibiotic-induced Clostridium difficile infection, the relationship between antibiotic fecal concentrations and the loss of bacterial diversity in the intestinal microbiota, and modelled the link between the loss of diversity and mortality. We showed that the Shannon diversity index and the number of bacterial taxonomic units are good predictors of mortality in this model.
In human healthy volunteers, we then developed a semi-mechanistic model of the evolution over time of bacterial diversity following an antibiotic perturbation, and quantified the relationship between antibiotic concentrations in plasma and feces and the loss of bacterial diversity in the intestinal microbiota. We showed that the intestinal microbiota is highly susceptible to antibiotics, and that the perturbation of the intestinal microbiota persists several weeks after the end of the antibiotic treatment.

Charles Burdet, MD, PhD, is Associate Professor in Epidemiology at Université de Paris and Hopital Bichat – Claude Bernard, Paris.
His research interests focus on the optimization of antibiotic treatments using modeling approaches. He is in particular interested in their individualization in the context of growing bacterial resistance and the identification of strategies allowing the reduction of antibiotics' impact on the intestinal microbiota.
He conducts his research activity at the Inserm UMR1137 IAME research unit, BIPID team, directed by Prof France Mentré, which designs, performs and analyses clinical trials and cohorts in order to better understand variability in response to antimicrobial agents and for epidemiological description and prognosis assessment of infectious diseases.

S1-1

An in vivo like 3D hepatic liver system for studies of aetiology and treatment of chronic drug hepatotoxicity and hepatic fibrosis

Magnus Ingelman-Sundberg

Department of Physiology and Pharmacology, Section of Pharmacogenetics, Karolinska Institutet, Stockholm, Sweden

Much effort is devoted to the generation of phenotypically appropriate in vitro systems for studying hepatic drug metabolism and clearance, drug hepatotoxicity and liver disease. Of specific importance among liver diseases is NASH which is becoming the leading hepatic disease in the world. The lecture will be focused on a 3D spheroid liver system based on monocultures or co-cultures of PHH and NPCs, where toxicity, clearance and metabolism of drugs can be predicted. Furthermore, in this system it is possible to elucidate mechanisms behind chronic drug hepatotoxicity, to mimic liver disease like steatosis and fibrosis and to study genetic, mechanistic and environmental factors of importance for the disease and pharmacological treatment. By choice of different donors and siRNA- based gene silencing the contribution of different polymorphic genes and gene products of importance for developing the diseases can be studied.

Magnus Ingelman-Sundberg, PhD; BSc.Med is Professor of Molecular Toxicology and research group leader in Pharmacogenetics at the Department of Physiology and Pharmacology, Karolinska Institutet, Biomedicum since 2006. He has more than 460 original papers (http://www.ncbi.nlm.nih.gov/pubmed/?term=ingelman-sundberg+m31,618 citations (ISI), 47,000 in Google Scholar and an h-factor of 90 (ISI) or 115 (Google Scholar) and assigned "Highly Cited Researcher" for 2014, 2015, 2016 and 2017 by Thomson & Reuters/Clarivate. He holds an ERC Advanced Grant (AdG) for 2017-2022). He was a member of The Nobel Assembly at Karolinska Institutet 2008-2018 and a member of Editorial Advisory Boards of e.g. Trends in Pharmacological Sciences (Edit Board),Pharmacogenetics and Genomics, Pharmacogenomics, Drug Metabolism Reviews, Drug Metabolism and Disposition, Human Genomics. He has received numerous Awards, most recently the 2018 BCPT Nordic Prize in Basic and Clinical Pharmacology and Toxicology. His research focuses on genetics, polymorphism, regulation, function and toxicology of the hepatic ADME system with aims at understanding interindividual differences in drug response. Furthermore he develops novel hepatic in vitro systems for studying liver function, liver diseases and validation of hepatic drug targets. Further info from an Interview with Magnus Ingelman-Sundberg See: Trends Pharmacol Sci. 2015; 36:65-7.

S1-2

Machine Learning Approach to Forecast Chemotherapy-Induced Haematological Toxicities in Patients with Rhabdomyosarcoma

Vesna Cuplov, Ph.D

SMARTc, Marseille Cancer Research Center (CRCM), UMR Inserm 1068, CNRS UMR 7258, Aix Marseille Université U105, Institut Paoli Calmettes & APHM, 13385 Marseille, France

Developing precision medicine is a major trend in clinical oncology. The main adverse effects of ifosfamide, actinomycin D and vincristine (IVA) treatment for rhabdomyosarcoma are haematological toxicities such as neutropenia or thrombocytopenia. The severity of these effects vary among patients but their dynamic profiles are similar. A non-empirical adjustment of the chemotherapy dose to avoid severe toxicities could help secure the treatment administration. Twenty-four patients with rhabdomyosarcoma treated with IVA chemotherapy courses were selected. Before and during each cycle, routine multiple blood cell counts were performed allowing for a dynamic study of the haematological toxicities. We developed a machine learning analysis using a gradient boosting regression technique to forecast the ifosfamide induced haematological toxicities as a function of neutrophils and platelets initial levels and the initial ifosfamide dose. To validate models' accuracy, predicted and observed neutrophils and platelets levels were compared. The model was able to reproduce the dynamic profiles of the haematological toxicities. Among all cycles, the mean absolute errors between predicted and observed neutrophils and platelets levels were 1.0 and 72.8 G/L, respectively. Adjusting a patient's ifosfamide dose based upon the predicted haematological toxicity levels at the end of a treatment cycle could enable tailored treatment.

Accomplished scientist with a PhD in Theoretical Physics, Vesna has more than 15 years of experience in the fields of high energy physics, medical physics and data science. Highlights of her experience include working on experiments at the most powerful particle accelerators ever built: the Tevatron at Fermilab near Chicago and the Large Hardon Collider at CERN in Geneva, Switzerland. Since 2011, she has been involved in scientific projects in the field of medical physics and oncology. She has worked for the Commissariat à l'Energie Atomique in Orsay on the GATE simulation tool by developing the code that performs nanoparticle-mediated hyper-thermal cancer therapy. She has a strong expertise in medical imaging through her work at the Institute for Nuclear Medicine of the University College London Hospitals. These experiences have helped her cultivate an analytical mind with strong abilities in mathematical modelling, data analysis and artificial intelligence. She has recently developed computing tools designed to assist decision making for medical professionals, such as a web-based application that predicts chemotherapy induced toxicity in patients with rhabdomyosarcoma.

S2-1
A fluid-dynamic Multi-In Vitro Organ-MIVO device as alternative approach for in vitro drug testing

Silvia Scaglione, CSO[1,2], Ilaria Pulsoni, PhD[1], Maurizio Aiello, CEO[1]
1 React4life, Genoa, Italy 2 National Research Council, Genoa, Italy

Background and Objectives: In vitro reproducible and quantitative studies of molecules absorption through biological interfacing tissues are quite limited due to the lack of reliable experimental models able to resemble the in vivo responses. Recently, 3D in vitro tissue models (e.g. organoids, 3D reconstructed tissues) are becoming important alternatives to animal models and traditional 2D assays. Moreover, the integration of these tissue models with macro-fluidic culture chambers allows to mimic the in vivo organ-organ fluidic connections and the systemic administration of bioactive molecules/drugs, finally offering a more reliable and fast approach for toxicity and efficacy testing.
Material and Methods: We have developed a fluid-dynamic multi-chamber device resembling the in vivo systemic circulation and the organ-organ fluidic connections. The MIVO® -Multi In Vitro Organ - device has been validated in different applications1,2, such as: (i) the intestinal permeability of molecules, (ii) the anti-cancer drug efficacy assay against ovarian and breast tumors, (iii) the medical device absorption through skin tissues. 3D human tissues cultured within MIVO® chamber were analysed in terms of cells viability and proliferation, while the bioactive molecule passage through the tissues was measured via HPLC analysis.
Results: Intestinal permeation assays, which is crucial in regulating the bioavailability and consecutively the biological effects of drugs, showed trans-cellular and paracellular mechanisms within MIVO in line with clinical data. Interestingly, in the oncological filed, MIVO allows to resemble the circulating tumor cell migration and survival under shear stress induced fluid flow, opening new scenarios towards alternative therapeutics treatment.
Discussion and Conclusion: Biochemical and biological results confirmed that the MIVO platform combined with human 3D tissues can represent a novel, highly reliable and easy-to-use in vitro model of interfacing phenomena for studying the passage of bioactive molecules of drugs and their effect on cellular behavior.

1. Cavo M., Caria, M., Pulsoni I. et al. (2018) Sci Rep 8:5333 | DOI:10.1038/s41598-018-23250-4
2. Marrella A, Buratti P, Markus J, et al. (2019) ALTEX. 2019 Dec 30. doi: 10.14573/altex.1908311.

Dr Silvia Scaglione is researcher, founder and chief scientist of React4life S.r.l. She received in 2005 the Ph.D. in Bioengineering at the University of Genoa, Italy. In 2004 she was Visiting Scientist at the University Hospital of Basel, Switzerland. Since 2010 Silvia Scaglione is permanent Researcher at National council of Research and head of the Laboratory of Tissue Engineering in Genoa. Since 2017 she is responsible of the R&D team of React4life, involved in 3D tumor models, fluidic dynamic platforms for in vitro testing. She is author of more than 80 international peer-reviewed papers, book chapters, author of 7 patents. She is responsible of some national and international research projects, and coordinator of a Future Emerging Technology (FET-OPEN) H2020 project, pillar excellent science, entitled "Modeling spontaneous Breast cancer metastasis TO the Bone with a first-of-its-kind 3D device that recapitulates physiological tissue-level complexity -B2B".

S2-2
CAR T cell development and registration – Opportunities for the application of pharmacometrics

Rik de Greef, MSc
Certara, Oss, The Netherlands,

Over the past decades, pharmacometrics, or pharmacokinetic and pharmacodynamic modeling and simulation, has become an increasingly important tool in optimizing decision making during clinical development and regulatory assessment of new drugs and biologics. With the advent of cell based therapies, opportunities are sought to apply similar methods and approaches in the development of these modalities.
This presentation will summarize key differences and similarities in the application of pharmacometric approaches in the development and registration of Chimeric Antigen Receptor (CAR) T cells, as compared to other modalities. The discussion will be illustrated with a number of examples of such applications and also describe future opportunities of the application of quantitative methods within this context.

Rik de Greef, SVP Quantitative Science Services at Certara, has more than 20 years of expertise in applying quantitative clinical pharmacology and pharmacometric methods in support of drug development decisions. Trained as PK-PD scientist at Leiden University, The Netherlands, during his tenure within pharma industry at Organon, Schering-Plough and Merck/MSD, he supported key decisions on programs around dose regimen, population choice and trial design across all phases of development from preclinical development through life cycle management. In addition, Rik has been leading the early clinical components of numerous regulatory filings in areas such as thrombosis, women's health, psychiatry and immuno oncology. Since 2014, Rik is a senior consultant at Certara, providing strategic and scientific oversight to a wide range of client projects, and currently is leading the team of pharmacometrics consultants.

S3-1

Prediction of midazolam pediatric plasma profiles for multiple routes of administration using physiologically based pharmacokinetic model

Maxime Le Merdy, PhD, PharmD
SimulationsPlus, Basel, Switzerland

The aim of the study presented was to predict midazolam absorption and pharmacokinetics (PK) after intranasal (i.n.) administration in young children using a physiologically based pharmacokinetic (PBPK) model. The PBPK model combined with in silico or in vitro parameters describing the drug's physicochemical and biopharmaceutical properties along with in vitro parameters describing the drug's metabolic stability correctly described PK after i.v. administration in both adults and children. The ACAT model, which incorporates enzyme distributions in the liver and the gastrointestinal tract, correctly described the drug's absorption and intestinal metabolism in adults and children. The intranasal-pulmonary model calibrated using in vivo data from adults correctly predicted exposure after i.n. administration in children. The approach of utilizing PBPK modeling and in vivo data in adults to predict PK in pediatric populations can be successfully applied to variety of dosage forms if relevant physiological information is available.

Dr. Le Merdy is now a Senior Scientist at Simulations Plus, the world leader company in innovative modeling and simulation software applied to the pharmaceutical research and development. Before joining Simulations Plus, Dr. Le Merdy received a Pharm.D. from University Paris-Descartes in 2015. In 2014, he received his master's degree in Pharmacometrics from the same university. He joined the FDA in 2017 as a Post-doctoral fellow in the Division of Quantitative Method and Modeling within the Office of Generic Drugs, where he developed his expertise in PBPK models for locally acting drug products and published multiple paper on ocular delivery models. Prior to this experience, he published on Ethyl-glucuronide, a biomarker of alcohol consumption as well as the physiological modification affecting children's pharmacokinetics.

S3-2
PopPK/PD scaling from adults to children using priors: A case example with Alirocumab

Elisa Calvier, PhD, PharmD, Pharmacometrician
Sanofi R&D, Montpellier, France

Paediatric popPK/PD analyses are typically underpowered due to the small number of enrolled patients and the sparsity of data. In order to increase the power of these analyses, adult data can be used. This however requires the scaling of some model parameters using covariate models based on, for instance, bodyweight and/or age, so that to account for ontogeny processes. Whereas these parameters can be fixed a priori (e.g., allometerisation of the model on adult data for a maximum a posteriori analysis), such method can lead to important prediction bias when ontogeny profiles in model parameters are unknown or uncertain. To circumvent this problem, scaling parameters can be estimated either by analysing the pool of paediatric and adult data together or by using the prior method in NONMEM, the latter being much faster and less bias prone. Using the prior method in NONMEM, the parameters of the adult model implemented as priors are re-estimated with a penalty function that informs the paediatric estimates based on previous adult estimated values, and covariate models that scale adult data to paediatric patients can be quickly estimated solely on the paediatric dataset without priors. An example of application of this method will be presented for a semi-mechanistic popPK/PD paediatric analysis using a quasi-steady-state target mediated drug disposition model for alirocumab in Heterozygous and Homozygous familial hypercholesterolemia patients.

Dr. Elisa CALVIER is a pharmacometrician at Sanofi since 2018, where she has worked on the pharmacokinetics and pharmacodynamics of biologics and small molecules using both population and physiologically-based pharmacokinetic approaches. She has expertise in paediatrics and semi-mechanistic methods which allow for extrapolations and enrichment of data analysis of underpowered studies.
Prior to joining Sanofi, she did her PhD at Leiden Academic Center for Drug Research (LACDR) in the Netherlands. The aim of her research was to expedite and ensure the systematic accuracy of clearance scaling from adults to paediatric patients, with a special focus on drugs undergoing hepatic metabolism.
Elisa has mostly published articles about pharmacometrics in the field of paediatrics and has recently co-authored a review on the use of priors in NONMEM.

S3-3
Use of model informed extrapolation in regulatory submissions – Examples

Flora Musuamba Tshinanu
Federal Agency for Medicines and Health Products, Brussels, Belgium,

The objective of the presentation is to provide an update on use of model informed extrapolation in the EU regulatory procedures and to present examples of procedures where model-based extrapolation approaches were essential for decision making.
The presentation will provide some examples of applications of principles included in the EMA within are Extrapolation Reflection Paper[1], the Modelling and Simulation Working Party Paediatric Q&A[2], and Guideline on the reporting of physiologically based pharmacokinetic modelling and simulation[3] that have been recently published. Furthermore, there is ongoing work within various aspects of paediatric drug development, and the strategy document EMA Regulatory Science to 2025.
The presentation will focus on examples from regulatory submissions. EU regulatory examples where model-based approaches played a vital role in the development and authorization of medicinal products. There are numerous examples of where model-based approaches have proven to be pivotal for the benefit/risk assessment in a market authorization application. Regulatory interactions with increasing visibility of model-based drug development are central scientific advices (through the Scientific Advice Working Party) and paediatric investigation plans (through the Paediatric Committee) will be highlighted.

1. https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf
2. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers
3. https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-2025

Flora Musuamba holds a Ph.D. in Pharmacy and biomedical sciences from Université Catholique de Louvain, in Belgium.
She is currently the vice-chair of the modelling and simulation working Party (MSWP) at the European medicines agency (EMA), a member of the EMA scientific advice working party (SAWP) and a Pharmacometrics and Pharmacovigilance expert at the Belgian federal medicines agency (FAMHP).

S4-1

PBBM application to support formulation changes, prediction of pH related DDI and impact of beverages on exposure to acalabrutinib

Xavier Pepin, Principal Scientist Biopharmaceutics
New Modalities and Parenteral Development, Pharmaceutical Technology & Development, Operations, AstraZeneca, Macclesfield, UK

PBBM can be used to define acceptable product specifications in terms of critical material attributes or process parameters by positioning the clinical reference and operating range in a "safe space", the size of which can be supported by in-silico modelling. Pilot clinical studies are recommended where high-quality data are generated on a small number of subjects, which allows expansion to virtual trials. Variability can be assessed in silico and evidenced in vivo with selected biomarkers. Once the critical product attribute and system parameters are identified, models can be verified on clinical data and expanded to test other scenarios. One industrial case study is provided illustrating the need for biomarkers, and the approach taken to integrate in-vitro dissolution of clinical batches in a mechanistic way into the PBPK model to capture the effect of formulation, stomach pH, and consumption of beverages on the exposure.

Xavier is a pharmacist (University Paris XI). He has a Ph.D. in granulation technology (powder surface energy and liquid bridges). He has 20-year experience in the pharmaceutical industry with different jobs in preformulation, clinical & commercial development, industrial transfer, regulatory CMC and biopharmaceutics. He was the co-leader of WP4(in silico tools) for the OrBiTo IMI project 2012-2018. He has 30 publications in the field of powder surface energy, granulation technology and biopharmaceutics. His hobbies are building homes and furniture… cycling and travelling.

S4-2
Drug-drug interactions of therapeutic proteins

Antoine DESLANDES, PhD
Sanofi R&D, Centre de recherche Vitry-sur-Seine, 13, quai Jules Guesde, BP 14
94403 Vitry-sur-Seine Cedex - France

The most recent US FDA Guidance for Industry on clinical drug interaction studies does not include discussion on drug–drug interactions (DDIs) for therapeutic proteins (TPs). In addition, clinical experience suggests that the concern for drug interactions is relatively limited with TPs compared with small-molecule drugs. A recent FDA review showed that effects larger than two-fold increase in exposure appear rare and none resulted in a specific dose adjustment recommendation in the labeling for the TPs.
Currently a large proportion of approved TPs labels contain wording regarding the potential for interaction without specific DDI evaluations. There are indeed challenges in designing dedicated DDI studies, as in vitro and animal studies have limited predictive value and clinical studies also have limitations. For example, healthy volunteers are mostly inappropriate due to disease-specific differences and TPs long half-life results in parallel design and long duration of studies.
However, TPs is a rapidly evolving class of drugs and TP–drug interaction remains an area of scientific evolution from the drug development and regulatory perspectives. TP–drug interactions are usually considered in three categories: cytokine or cytokine modulators, TPs involved in a known or suspected non-CYP- or transporter-related DDI, or TPs used in combination with other drugs.
In this presentation, we will discuss examples of risk-based approaches to evaluating the potential for TP–drug interactions, which can be used to guide TP development projects.

Antoine is Scientific Advisor in the Translational Medicine and Early Development group at Sanofi R&D. His interest is in the interdisciplinary transition of biologics projects from preclinical to clinical development.
He graduated in Pharmacy, then received his PhD in Experimental and Clinical Pharmacology from the University of Paris, completed later with a Master in Modelling and Statistics (Paris V) and a Master in Immunology and Biotherapy (Paris VI)
He held different positions in MPK and translational domains in several pharma and biotech companies with increasing responsibilities. Since 2006 he works at Sanofi and has supported projects in gene therapy, immuno-oncology and HIV

S4-3
Ivabradine-metabolite PBPK/PD modelling: CYP3A4 mediated DDI risk evaluation in adults and children

Jennifer Lang, PhD[1], Ludwig Vincent, PhD[2], Marylore Chenel, PhD[2], Kayode Ogungbenro, PhD[1], Aleksandra Galetin, PhD[1]

1 Centre for Applied Pharmacokinetic Research, University of Manchester, UK
2 Technologie Servier, Orléans, France
3 Institut de Recherches Internationales Servier, Suresnes, France

DDI risk evaluation in paediatrics is not commonly carried out in clinical drug development due to ethical and practical reasons. Paediatric labelling recommendations are based on clinical DDI studies conducted in adults. Therefore, physiologically-based pharmacokinetic (PBPK) modelling can be useful to address these limitations. However, some uncertainties remain regarding physiological variations across age, especially in very young children. Maturation of the main metabolic enzyme, CYP3A4, is still not fully delineated and two hepatic ontogeny functions are currently in use. Salem ontogeny function suggests that CYP3A4 hepatic level are low in young children and reaches adult level at the age of 2.5 years, whereas Upreti ontogeny function suggests that CYP3A4 abundance exceeds adult level between 0.1 and 11 years. This presentation will demonstrate the impact of choice of hepatic CYP3A4 ontogeny function on ivabradine DDI risk with a strong CYP3A4 inhibitor (ketoconazole) in children between 6 months and 18 years. Ivabradine, a cardiovascular agent inhibiting the If current, and its main metabolite exhibit pharmacological activity and are CYP3A4 substrates. Development of a joint parent-metabolite PBPK/PD model in adults and its extrapolation to children will be illustrated, together with evaluation of the DDI risk in this special population using either Salem or Upreti ontogeny function. Implications of selection of hepatic CYP3A4 ontogeny function on paediatric DDI risk will be discussed.

Jennifer Lang is a final year PhD student at the University of Manchester under the supervision of Pr. Aleksandra Galetin and Dr. Kayode Ogungbenro and funded by the Servier laboratories. Her PhD thesis focusses on PBPK modelling of parent and metabolite with a special interest in CYP3A4- and P-gp-mediated DDI risk evaluation. Prior to her PhD, she completed a pharmacy degree at the Université Paris Descartes and a master degree at the université Paris Diderot (France). She will be joining Servier for a postdoctoral position starting in October 2020.

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STUDENTS' AWARDS ABSTRACTS

2020 First GMP Virtual Symposium

From 18th of September to
23rd of October 2020

1 Impact of G-CSF on FOLFIRINOX-induced neutropenia prevention: a population PK/PD approach

Pauline Macaire[1,2]*, Justine Paris[1,2], Julie Vincent[3], François Ghiringhelli[2,3], Leïla Bengrine-Lefevre[3] and Antonin Schmitt[1,2]

1 Pharmacy Department, Centre Georges-François Leclerc, Dijon, France (Pharmacy resident - last semester) 2 INSERM U1231, University of Burgundy Franche-Comté, Dijon, France (PhD student - third year) 3 Oncology Department, Centre Georges-François Leclerc, Dijon, France

Background: Chemotherapy-induced neutropenia is one of the most common dose-limiting toxicities of cytotoxic administration. Consequently, granulocyte colony-stimulating factor (G-CSF) is frequently prescribed to prevent chemotherapy-induced neutropenia. Nevertheless, the absence of international recommendation about prophylactic administration of G-CSF in every-2-week regimens leads to an empirical use which could be, in some situations, not fully effective for patients. This pharmacokinetic/pharmacodynamic (PK/PD) study was performed to determine effect of different G-CSF regimens on the incidence and duration of neutropenia following FOLFIRINOX administration in order to propose an optimal G-CSF dosing schedule.

Methods: A population PK/PD model was developed to describe individual neutrophils time course from absolute neutrophil counts (ANC) obtained over the first four chemotherapy cycles in 40 advanced cancer patients receiving FOLFIRINOX regimen. The structural model considered neutrophils dynamics, the stimulating effect of G-CSF on ANC and combination of neutropenic effect of the cytotoxics. Drug-induced neutropenic effects, each expressed as a linear function, were implemented separately on different sites of the neutrophil dynamics. Based on the final model estimates, simulations of 1000 virtual subjects were performed to explore different dosing schedules of G-CSF and pegylated(peg)-G-CSF administration. The incidence of all grade neutropenia and severe neutropenia (grade III/IV) as well as mean duration were then calculated for each G-CSF/peg-G-CSF regimen.

Results: Final dataset comprised 342 ANC observations from the 40 patients remaining over a median duration 3.6 cycles. The developed model successfully described the myelosuppressive effect induced by the 3 cytotoxics for all patients. Estimated baseline ANC value was 5.61 x 109.L-1 and mean transit time, defines as the average time for a cell to mature and appear in the systemic circulation, was estimated to be 141 hours. Simulations showed that peg-G-CSF administration reduced by 22.9% the risk of severe neutropenia for subjects with low ANC at the start of chemotherapy (ANC ≤ 2.5 x 109.L-1). Median duration in this group was also shortened by 3.1 days when compared to absence of G-CSF. Delayed G-CSF administration was responsible for higher incidence and longer duration of neutropenia compared to absence of administration.

Conclusions: The PK/PD model is useful in clarifying the neutrophils stimulating effect of different G-CSF formulations and highlighting how an optimal dosing schedule after the FOLFIRINOX regimen could be selected. Beyond standard risk factors of vulnerability to neutropenia, it also appears as fundamental to consider ANC baseline at each cycle as a potential risk factor of neutropenia. Simulations showed peg-G-CSF administration 24 hours after the end of chemotherapy seems to be the optimal schedule to reduce FOLFIRINOX-induced neutropenia. Through this study, we also underline that non-optimal G-CSF dosing schedules could be more harmful than no G-CSF administration.

2 Retrospective statistical power calculation for covariate detection in population pharmacokinetic analyses: A case example with a UGT1A1 metabolized drug.

Youssef Bouslikhane[1,2]*, Elisa A.M. Calvier[2], Sylvaine Cartot-Cotton[3] and David Fabre[2]
1 University of Pharmacy Paris Descartes, Master's degree 2 Sanofi R&D, Translational Medicine and Early Development, Pharmacokinetics, Dynamics and Metabolism (PKDM) Montpellier France 3 Sanofi R&D, Translational Medicine and Early Development, Pharmacokinetics, Dynamics and Metabolism (PKDM) Vitry-Alfortville France

Background: Population pharmacokinetic modelling allows for explaining PK variability of a compound by the means of covariate inclusion (i.e., covariate model building). In specific instances, the number of patients for which data has been collected in early clinical phases might be insufficient to reach the commonly admitted power of 80-90% to detect a covariate effect. Such cases might occur when the incidence of a covariate category of interest is low (e.g., low frequency of poor metabolizer profiles), or when an important between and/or within subject variability exist. Lack of power can lead to biased estimates. The current study focuses on a compound undergoing hepatic metabolism with a fraction metabolized by UGT1A1, a polymorphic enzyme, of around 54% according to in vitro predictions. PBPK predictions also revealed an impact of UGT1A1 phenotype on the compound's clearance. The aim of this work was to verify this finding on available clinical data using PopPK modelling. A secondary objective was to compute the power and required sample size for reaching an 80% power to detect metabolizing profile using a covariate on clearance.
Methods: A population pharmacokinetic model was developed with NONMEM 7.4.2 ® using a phase I study pool (N = 114). The UGT1A1 phenotype profile of the subjects was reported and assessed as a covariate to explain clearance's variability. A group of poor metabolizers (17%) was investigated against a second group including extensive and intermediate metabolizer. After a forward inclusion of the UGT1A1 covariate, multiple stochastic simulations and estimations were performed with PsN 4.9 ® for power calculation and alpha risk calibration. Regarding the power estimation, 1000 datasets were simulated from the model including the covariate (full model) and re-estimated with both full and reduced models (model without UGT1A1 covariate). The power to identify UGT1A1 effect was calculated from the change of the objective function value (OFV) between the reduced and the full model, this change (ΔOFV = OFV full model – OFV reduced model) follows a non-central chi-square distribution. Thereby, the power corresponds to the fraction of ΔOFV greater than the statistically significant criterion. Parametric power estimation was then used to generate full power curve to inform on other sample sizes.
Results: A 26% decrease in clearance for UGT1A1 in poor metabolizer subpopulation as compared to the rest of the population was estimated, with a drop in OFV of 6.7. Based on SSE results, the power for detecting this covariate was 34%. Results from a parametric power estimation suggested increasing the sample size from 114 to 300 subjects to reach the 80% commonly admitted power.
Conclusions: The SSE approach allowed us to highlight the lack of power for estimating UGT1A1 phenotype covariate despite the forward inclusion at a 5% alpha risk. In addition, parametric power estimation informed us on the requirement to include 200 additional subjects to reach 80% power level in order to detect UGT1A1 effect.

3 Interactions of carbamate pesticides with human membrane drug transporters

N. Guéniche[a]*, A. Bruyère[a], M. Ringeval[a], E. Jouan[a], A. Huguet[b], L. Le Hégarat[b], O. Fardel[c]
a Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, France
b ANSES (French Agency for Food, Environmental and Occupational Health and Safety), Fougères Laboratory, Toxicology of contaminant unit, F-35306 Fougères, France
c Univ Rennes, CHU Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et travail) - UMR_S 1085, F-35000 Rennes, France

Background: Pesticides, belonging to various chemical classes, are known to inhibit activity of drug transporters and/or to be substrates of them. Carbamates constitute a major class of pesticides derived from carbamic acid. Most of them are used as insecticides because of their ability to inhibit cholinesterase, but others are used as fungicides or herbicides. Most of studies about biological effects of carbamates currently focus on the impact on drug-metabolizing enzymes and oxidative stress. However, there was a lack of data concerning possible interactions between membrane transporters and carbamate pesticides. In this context, we sought to determine the effects of four carbamates (i.e. the insecticides N-methylcarbamates aminocarb and carbofuran, the herbicide chlorpropham and the fungicide propamocarb) towards activities of main solute carrier (SLC) (OCT1, OCT2, OAT1, OAT3, OATP1B1, OATP2B1, and OATP1B3) and ATP-binding cassette (ABC) drug carriers (BCRP, MRP2 and P-gp) involved in xenobiotics disposition.
Methods: Transport assays were conducted with transporter-overexpressing cells. Reference substrates for investigating putative modulation of transporter activity were: tetraethylammonium (TEA) (for OCT1 activity), 4-(4-diethylaminostyryl)-1-methylpyridinium iodide (4-DiASP) (for OCT2, MATE1, MATE2-K activity), 6-carboxyfluorescein (6-CF) (for OAT1 and OAT3 activity), 2',7'-dichlorofluorescein (DCF) (for OATP1B1 activity), 8- fluorescein-cAMP (8-FcA) (for OATP1B3 activity), estrone-3-sulfate (E3S) (for OATP2B1 and OAT3 activity), carboxy-2',7'-dichlorofluorescein (CDCF) (for MRP activity), rhodamine 123 (for P-gp activity), and Hoechst 33342 (for BCRP and P-gp activity). Intracellular accumulation of these reference substrates were analyzed by spectrofluorimetry, radiometry or liquid chromatography-tandem mass spectroscopy (LC-MS/MS).
Results: Results showed that none carbamate inhibited P-gp or MRP activity, whereas that of BCRP was blocked by chlorpropham (IC50=53.2 µM). Chlorpropham used at 100 µM additionally weakly reduced OATP1B1, OATP2B1 and MATE1 activity, but blocked that of OAT3 (IC50=5.0 µM). Chlorpropham nevertheless failed to trans-stimulate OAT3 activity. Propamocarb, unlike aminocarb, carbofuran and chlorpropham, was shown to cis-inhibit OCT1 (IC50=48.1 µM) and OCT2 (IC50=38.1 µM) activity, and to cis-stimulate that of MATE2-K (EC50=4.6 µM). Propamocarb however failed to trans-stimulate OCT1, OCT2 and MATE2-K activities, suggesting that these SLC transporters may not transport them.
Conclusions: Such data demonstrate that carbamates in vitro interact with drug transporters. Such interactions however depend on the nature of the carbamate and of the transporter. Further studies are required for determining the possible in vivo relevance of such carbamate- transporter relationships in terms of carbamate toxicokinetics and toxicity.

4 Pharmacokinetics/pharmacodynamics of liposomal cytarabine (Vyxeos®) in AML patients: influence of cytidine deaminase genetic polymorphisms

Mélanie Donnette[a]*, Geoffroy Venton[b], Laure Farnault[b], Bertrand Pourroy[c], Régis Costello[b], L'Houcine Ouafik[d], Joseph Ciccolini[a], Raphaelle Fanciullino[a]

a SMARTc- CRCM UMR Inserm 1068 AMU.
b Hematology Unit Assistance Publique des Hôpitaux de Marseille
c Oncopharma Unit Assistance Publique des Hôpitaux de Marseille
d Transfert Oncology Unit, Assistance Publique des Hôpitaux de Marseille

Background: Vyxeos® is a liposomal formulation of daunorubicin and cytarabine recently approved for treating adults with newly-diagnosed sAML subtypes therapy-related (t-AML) or AML with myelodysplasia-related changes (AML-MRC). The objective of this pilot study was to evaluate the influence of cytidine deaminase, the enzyme responsible for cytarabine detoxification step in the liver, on drug exposition and clinical outcome.

Methods: In this proof-of-concept study, 9 adult patients were treated with Vyxeos®. CDA status (i.e., determination of Poor Metabolizer or Extensive Metabolizer phenotypes) was evaluated before treatment by measuring residual CDA activity in serum. Pharmacokinetic sampling was performed 90min before infusion stops, then from T4H to T168H after the end of the infusion. Total cytarabine, encapsulated cytarabine and released cytarabine were discriminated and assayed using a validated LC-MS/MS method.

Results: Nine Vyxeos® patients (3M, 6F, 66 ±13 years) were included in this pilot study. Aplasia duration was significantly longer in AML-MRC patients than in AML-t (38 ±5.5 days VS. 28 ±3 days, respectively ($p<0.05$)). All AML-t had complete response after induction phase (VS. 60% in AML-MRC, $p>0.05$). Similar cytarabine exposure was measured in both population. Surprisingly, 8 out of 9 patients (i.e., 88%) were identified as CDA PM (CDA <2UI/mg). Marked differences in pharmacokinetics were observed between PM and EM patients. Total, encapsulated and released cytarabine AUC's were 2.77, 1.42, and1.46 mg/ml*h in PM patients. In EM patient, total, encapsulated and released cytarabine AUC's were 0.97, 0.76 and 0.17 mg/ml*h. When available, microscopy analysis confirmed the presence of liposomes in patients bone marrow.

Conclusion: Differences in clinical outcome between AML-t and AML-MRC patient are not supported by differences in exposure levels upon Vyxeos® administration. Surprisingly, we found that CDA status has a strong impact on cytarabine pharmacokinetics since PM patients treated with Vyxeos® present a +185% increase in cytarabine levels as compared with EM patient. This suggests that upfront CDA testing could help to predict clinical outcome.

5 Application of optimal design and control theory to inform an ideal dosing regimen for an oncological treatment, balancing tumor growth rate, safety, and resistance rate

Anne Ravix[1]*, Philippe Pierrillas[2], Henri Merdjan[2], Vincent Duval[2]
1 4th year of Bioinformatics, INSA Lyon, France – 2 Integrated Drug Development, Certara

Background: Establishing a dosing strategy frequently relies upon simulating the predicted outcomes of a range of pre-set candidate dosing scenarios. We hereby propose to back-engineer the whole process, combining optimal design and control theory. The desired outcomes are used as an input to inform a rational selection of candidate scenarios to be simulated. The methodology is applied to an oncology drug Sunitinib, a VEGF inhibitor, used to treat metastatic renal cell carcinoma, Imatinib-resistant gastrointestinal stromal tumor and pancreatic neuroendocrine tumor. With this approach, we aim to find an optimal Sunitinib dosing regimen that balances tumor shrinkage against neutropenia and resistance rate.

Methods: Sunitinib was selected for the availability of PK/PD and exposure-safety models in the literature and the difficulty to identify dosing regimens offering optimal benefit/risk ratio in oncology. The PK/PD models were implemented with RxODE R package [1]. The efficiency model describes the link between drug exposure, biomarker of vascular endothelial growth factor receptor (VEGFR3) and tumor shrinkage [2].The exposure safety model, describes the absolute number of neutrophils as a function of time, drug exposure and VEGFR3 relative change [2]. The optimization process was performed using PopED R package [3]. Several designs were tested, allowing modification of the dosing frequency, the total number of doses administered and the addition of practical constraints (capsule strengths). A cost function was used to reach the output target: in order to limit toxicity, a safety criterion was imposed, with a maximum of 13% of the population affected by grade 3/4 neutropenia (13% being the actual proportion stated in the drug label [4]). The efficacy criterion rested on the minimization of the number of patients who do not respond to treatment. According to the RECIST criterion, a patient is non-responder when the size of the tumor increases by more than 20% compared to the minimum.

Results: The optimization process was successfully implemented. Considering a design space for the dose range of 0 to 200mg, with a step of 12.5mg, the optimal regimen was 50mg once daily, with 4 weeks on and 2 weeks off schedule (6.4% non-responders and 7.6% patients with grade 3/4 neutropenia). The optimized dose regimen was identical to the one stated in the Sunitinib label. While allowing more discretization of the unit dose, down to 6.25mg increments, the optimal dosing regimen was 56.25mg once daily, with a 4 weeks on and 2 weeks off and resulted in predicted proportions of 8.5% patients with grade 3/4 neutropenia and 5.9% non- responders after the first 2 cycles.

Conclusion: Using optimization approach allowed to confirm the optimal dose of Sunitinib based on predefined criteria limiting toxicity while maximizing efficiency. This innovative approach is quite flexible, the targeted criteria can be tailored to the evaluated compound and its efficacy and safety profiles. This has potentially multiple applications: the assessment of alternative dosing to be evaluated during the development of new molecules, the combination of several toxicological criteria, in order to minimize the harmful effects and the assessment of combination therapies.

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6 Development of a new human BBB fluidic model

Nina CHOUBLIER[1]*, Xavier DECLEVES[1], Yannick PARMENTIER[2], and Claire DENIZOT[2]
** Third-year PhD student*
1 Université de Paris, UMR-S 1144 INSERM, F-75006 Paris, France
2 Centre de Pharmacocinétique et Métabolisme, Technologie Servier, F-45000 Orléans, France

Background: Neurological disorders are increasingly recognized as the world's leading causes of disability and death. The probability of success for neurological drugs is only 7% in clinical development. One of the main difficulties is the presence of the blood-brain barrier (BBB) that restricts access to the brain. The low success rate has led to an increasing demand for in vitro tools. A realistic BBB model requires the addition of a shear stress mimicking blood flow, as it positively affects endothelial cells differentiation.

Methods: We designed a dynamic device for the culture of the hCMEC/D3 cells under flow. The manufacturing process was carried out by the Adrien Roux team at the HEPIA Campus Biotech at Geneva.

Results: Our device encompasses two superposed channels representing both blood and brain compartments, communicating via a semi-permeable membrane for substrate exchanges. Culture medium circulates through the channels, thus submitting all the cells to a controlled shear stress. We specifically defined channels dimensions to ensure the laminarity and homogeneity of the flow. The design of this device allows a constant visual observation of the cell monolayer. To attest to the BBB integrity, differentiation markers can be stained by immunofluorescence and visualized directly in the chip by confocal microscopy. Finally, this chip offers an easily and reproducibly model to perform permeability assays or transporters studies.

Conclusions: This BBB model is suited for incorporation of fluid flow to study barrier function and evaluate drug passage. Our work consists now in optimizing cell culture parameters to characterize a fully differentiated BBB phenotype.

7 First in man prediction with PBPK: retrospective analysis of 27 mAbs

Carla Troisi[1,2]*, Laurent Nguyen[1] and Donato Teutonico[1]
1 Translational Medicine & Early Development, Sanofi, Alfortville, France
2 Aix-Marseille University, Marseille, France

Background: Physiologically based pharmacokinetic (PBPK) is considered a golden standard approach in the prediction of first-in-man (FIM) pharmacokinetics (PK). The application of this approach to prediction of human PK for monoclonal antibodies (mAbs) is challenging since there is no standard approach for the prediction of human Kd to FcRn, one of the most relevant parameters in mAbs PBPK models. The use of in vitro Kd measure is also challenging, because of the high variability associated to the experimental determination of this parameter and its close relationship to the intrinsic structure of the PBPK model. In this exercise a database of mAbs PK was built and analysed for different species. The objective of this work was to search for the best predictors of human FcRn Kd and hence to increase the prediction of mAbs PK in FIM.

Methods: Plasma concentrations vs time data of several mAbs were digitized based on an intensive literature search. The selected species included in the database were human, mouse, monkey and rats, and only intravenous route of administration was selected to avoid any interference with subcutaneous absorption process. The plasma concentrations data for each mAb and each species were then processed using a full PBPK distribution/elimination model within PK-SIM software and the species-specific value of Kd FcRn was estimated by data fitting. A same structural model for distribution and elimination was applied for all species and mAbs. In order to limit confounding factors, only plasma profiles not showing TMDD behaviour were selected for the Kd estimation. The obtained values for FcRn Kd in the different species were then analysed with adequate statistical tools.

Results: The database contains PK profiles of 27 mAbs: 27 for which data in humans was found, 23 in monkeys, 15 in rats and 15 in mice. Among the 27 mAbs: 9 are fully Human, 13 are Humanized, 3 are Chimeric, 1 is a peptibody and 1 is an antibody-drug-conjugated (ADC). The extrapolation of FcRn Kd from animal to human was performed by linear regression. As an alternative to the use of animal data, a straightforward prediction approach based on the median of the 27 human Kd was evaluated. With the exception of the mouse- based predictions, all other methods show results within a two-fold prediction error. Overall the best prediction was obtained with extrapolation from rat data.

Conclusions: This exercise brought to the development of a mAbs database containing 27 therapeutic mAbs which were used to define a framework for the prediction of human Kd FcRn. Thanks to this framework, it will be possible to increase the prediction accuracy of human PK for mAbs using preclinical data.

8 Therapeutic Drug Monitoring: adaptation of literature models to a target population using the PRIOR approach

Anna Chan Kwong[1,2]*, Amaury O'Jeanson[1], Patrick Nolain[3], Florence Gattacceca[2] and Sonia Khier[1]

1 Montpellier University, IMAG (Alexander Grothendieck Institute), 2 Aix-Marseille University, INSERM, CNRS, CRCM SMARTc 3 Limoges University

Background: Bayesian feedback therapeutic drug monitoring (TDM) uses population pharmacokinetic models (popPK) to predict upcoming drug concentrations and adjust dosing regimen according to previous concentration measurement(s) and dosage. For most of the drugs measured in TDM, popPK models are reported in literature. It may be of interest to adapt the literature models to the target population with the "prior approach" [1] (tweaked models). We compared the predictive ability of both literature and tweaked models on TDM concentrations of meropenem.

Methods: Blood samples of meropenem were collected in tubes with coagulation activator (silica micro-particles) from 2017 to 2019 in patients of the intensive care unit of the university health center of Montpellier (France). Plasma was analyzed with high performance liquid chromatography (HPLC) with orthophosphoric acid. The study protocol was approved by the Ethics Committee (2019_IRB-MTP_03-01). The total dataset was split into an "estimation" and a "prediction" dataset. The "estimation" dataset incorporated the patients having only one reported meropenem concentration (mono-point), as they were not eligible for evaluating predictive performance, and half of the patients having more than one reported meropenem concentration (multi-points). The remaining multi-points patients composed the "prediction" dataset. As in a cross-validation approach, multi-points patients were randomly split six times (stratified on dialysis) into the "estimation" and the "prediction" dataset. PopPK models for meropenem were selected from literature. These models were run on the "estimation" dataset with the $PRIOR NWPRI subroutine in NONMEM to adapt population parameters (tweaked model). Literature and tweaked models were used for a priori prediction (using covariates only) and Bayesian predictions (using previous observation(s) available) to predict concentrations of the "prediction dataset". This procedure was repeated for each of the six splits. Differences between observation and prediction (prediction errors) were computed for both tweaked and literature models. For each model and each split, mean prediction errors (MPE%) and root mean square error (RMSE%) from a priori and Bayesian predictions of tweaked and literature models were compared.

Results: The total dataset was composed of 115 concentrations from 58 patients (31 mono-point and 27 multi-points with two to seven observed values). For each of the six splits, the "estimation" and the "prediction" datasets were respectively composed of 44 and 14 patients or 45 and 13 patients. Six popPK models were selected in literature [2–7]. Using tweaked models compared to literature models was more valuable for a priori prediction than Bayesian prediction: overall, the MPE% and the RMSE% decreased more for a priori prediction than for Bayesian prediction.

Conclusions: For these sparse data from clinical practice, there was a tendency for tweaked models to better predict a priori individual concentrations than literature models. Thus, the "prior approach" could be a valuable tool to improve the predictive ability of literature models, in particular for the first dose to administer (a priori): this is of interest for an efficient care in critically ill patients. Sharing model codes would also facilitate the use of published models and the implementation of innovative methods to improve Bayesian feedback TDM.

9 Lipopolysaccharide-induced inflammation has no effect on the expression levels of ABC drug transporters in in vitro skin models

Manon Barthe[1,2]*, Jean-Paul Thénot[1] and Hanan Osman-Ponchet[1]
1 PKDERM Laboratories, Grasse Biotech, 45, Boulevard Marcel Pagnol, 06130 Grasse, France.
2 Master degree in pharmacokinetics, Aix-Marseille Université,

Background: Skin is the largest organ in the human body and is one of the major targets of air pollution. There is increasing evidence indicating that ATP-binding cassette (ABC) family transporters play an important role in the transdermal absorption of their substrates [1-4]. Atopic dermatitis is a chronic inflammatory disease associated with increasing production of pro- inflammatory cytokines. However, the relationship between skin inflammation and expression of ABC transporters in the skin that might change absorption of anti-inflammatory drugs is not yet known. The aim of this study was to investigate the effect of inflammation on the expression levels of ABC transporters in normal human keratinocytes (NHK) and in 3D Reconstructed Human Epidermis (RHE).

Methods: Normal human epidermal keratinocytes, (Sterlab France), were treated for 24 and 48 hours with pro-inflammatory mediator lipopolysaccharide (LPS, 100 µg/mL in culture medium). Untreated NHEK were used as control. On the other hand, 3D reconstructed human epidermis, (Sterlab France), was treated for 24 hours with LPS. Incubation was done in cell incubator set at 37°C, 5% CO2 and saturated humidity. mRNA expression of inflammation markers (TNF-alpha, CXCL8 (IL-8)), and drug transporters (ABCB1, ABCC1, ABCC2 and ABCG2) was measured by quantitative real time RT-PCR, using TaqMan® technologies.

Results: Treatment with LPS up-regulated the mRNA expression of both inflammation markers TNF-alpha and IL-8, in both in vitro skin models. The extent of expression increase ranged between 15 and 150 times, confirming the inflammatory properties of LPS in both human keratinocytes and 3D reconstructed human epidermis. However, LPS treatment did not show any significative changes of the expression of any of ABC transporters (ABCC1, ABCC2 and ABCG2) in these in vitro skin models.

Conclusions: This study clearly shows there is no relationship between inflammation induced by LPS and the expression of ABC transporters in human keratinocytes and in 3D reconstructed human

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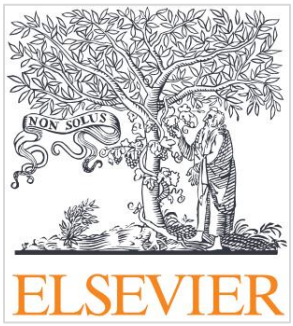

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