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Implementation of Bayesian Therapeutic Drug Monitoring in Modern Patient Care

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Prof. Lorenz Hirt

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ABSTRACT

Implementation of Bayesian Therapeutic Drug Monitoring In Modern Patient Care

The variability observed in drug exposure has a direct impact on the overall response to drug. The largest part of variability between dose and drug response resides in the pharmacokinetic phase, i.e. in the dose-concentration relationship. Among possibilities offered to clinicians, Therapeutic Drug Monitoring (TDM; Monitoring of drug concentration measurements) is one of the useful tool to guide pharmacotherapy. TDM aims at optimizing treatments by individualizing dosage regimens based on blood drug concentration measurement. Bayesian calculations, relying on population pharmacokinetic approach, currently represent the gold standard TDM strategy. However, it requires expertise and computational assistance, thus limiting its large implementation in routine patient care.

The overall objective of this thesis was to implement robust tools to provide Bayesian TDM to clinician in modern routine patient care. To that endeavour, aims were (i) to elaborate an efficient and ergonomic computer tool for Bayesian TDM: EzeCHieL (ii) to provide algorithms for drug concentration Bayesian forecasting and software validation, relying on population pharmacokinetics (iii) to address some relevant issues encountered in clinical practice with a focus on neonates and drug adherence.

First, the current stage of the existing software was reviewed and allows establishing specifications for the development of EzeCHieL. Then, in close collaboration with software engineers a fully integrated software, EzeCHieL, has been elaborated. EzeCHieL provides population-based predictions and Bayesian forecasting and an easy-to-use interface. It enables to assess the expectedness of an observed concentration in a patient compared to the whole population (via percentiles), to assess the suitability of the predicted concentration relative to the targeted concentration and to provide dosing adjustment. It allows thus *a priori* and *a posteriori* Bayesian drug dosing individualization.

Implementation of Bayesian methods requires drug disposition characterisation and variability quantification trough population approach. Population pharmacokinetic analyses have been performed and Bayesian estimators have been provided for candidate drugs in population of

interest: anti-infectious drugs administered to neonates (gentamicin and imipenem). Developed models were implemented in EzeCHieL and also served as validation tool in comparing EzeCHieL concentration predictions against predictions from the reference software (NONMEM®).

Models used need to be adequate and reliable. For instance, extrapolation is not possible from adults or children to neonates. Therefore, this work proposes models for neonates based on the developmental pharmacokinetics concept. Patients' adherence is also an important concern for drug models development and for a successful outcome of the pharmacotherapy. A last study attempts to assess impact of routine patient adherence measurement on models definition and TDM interpretation.

In conclusion, our results offer solutions to assist clinicians in interpreting blood drug concentrations and to improve the appropriateness of drug dosing in routine clinical practice.

RÉSUMÉ

Implémentation du suivi thérapeutique des médicaments dans la prise en charge moderne du patient

La variabilité observée dans l'exposition au médicament a un impact direct sur la réponse globale à celui-ci. La majeure partie de la variabilité entre la dose et la réponse au médicament se situe au niveau de la phase pharmacocinétique, c'est-à-dire au niveau de la relation dose – concentration. Parmi les possibilités offertes au clinicien, le suivi thérapeutique des médicaments (TDM) est un des outils avantageux pouvant aider à la prise en charge au niveau du médicament. Le TDM a pour but d'optimiser les traitements en individualisant les posologies en fonction des concentrations de médicaments mesurées dans le sang. Le calcul Bayesien, basé sur l'approche de pharmacocinétique de population, représente actuellement la méthode de référence pour l'application du TDM. Il nécessite néanmoins une certaine expertise et une assistance informatique, limitant la possibilité de sa large implémentation en routine.

L'objectif global de cette thèse etait l'implémentation d'outils robustes en routine afin d'offrir un TDM Bayesien au clinicien pour une prise en charge moderne du patient. A cette fin, les objectifs concrets ont été (i) de concevoir un logiciel efficace et ergonomique pour la réalisation du TDM Bayesian : EzeCHieL (ii) de fournir les algorithmes de calcul des médicaments pour la prédiction Bayesienne des concentrations des médicaments et la validation du logiciel en s'appuyant sur l'approche de population (iii) de résoudre certaines questions rencontrées en pratique clinique en s'intéressant tout particulièrement aux nouveau-nés et à l'adhésion thérapeutique.

Un état des lieux des logiciels existants a d'abord été réalisé, et a permis de définir les spécifications nécessaire à l'élaboration d'EzeCHieL. Par la suite, en collaboration étroite avec les ingénieurs en informatique, la réalisation d'EzeCHieL, un logiciel intégré, a débuté. EzeCHieL offre des prédictions bayesiennes basées sur l'approche de population et une interface utilisateur intuitive. Il permet d'évaluer si une concentration observée chez un patient est attendue, en comparaison à une population (via les percentiles), d'établir si la concentration prédite est adaptée à la concentration visée et de fournir une adaptation posologique. Il propose donc une individualisation posologique *a priori* et *a posteriori*.

L'implémentation d'une méthode de TDM Bayesienne nécessite de caractériser la disposition du médicament et de quantifier sa variabilité selon une approche de population. Des analyses de

pharmacocinétique de population ont été réalisées et les estimateurs Bayesiens fournis, pour des médicaments candidats dans les populations d'intérêt : anti-infectieux chez les nouveau-nés (gentamicine et imipenème). Les modèles ainsi développés ont été implémentés dans EzeCHieL et servent également d'outils de validation en comparant les concentrations prédites par EzeCHieL aux concentrations prédites par le programme de référence (NONMEM®).

Les modèles nécessitent d'être adéquats et fiables. L'extrapolation n'est, par exemple, pas possible à partir des adultes ou nouveau-nés. Ce travail propose donc des modèles pour les nouveau-nés, basés sur le concept de la pharmacocinétique développementale. L'adhésion thérapeutique est aussi un problème majeur dans le développement de modèle et dans la réussite de la thérapie médicamenteuse. Une dernière étude a tenté d'évaluer l'impact de l'adhésion thérapeutique mesurée en routine sur la caractérisation des modèles et sur l'interprétation des concentrations sanguines de médicament.

En conclusion, nos résultats proposent des solutions pour assister les cliniciens dans l'interprétation des concentrations sanguines de médicament et pour améliorer l'adéquation des posologies dans la pratique clinique quotidienne.

RÉSUMÉ LARGE PUBLIC

Implémentation du suivi thérapeutique des médicaments dans la prise en charge moderne du patient

Les individus ne sont pas égaux face aux traitements qui leur sont prescrits. Ainsi pour la même dose d'un médicament administré, l'exposition, caractérisée par la concentration sanguine du médicament, sera variable d'un individu à l'autre. La majeure partie de cette variabilité réside dans la phase pharmacocinétique (processus d'absorption, de distribution et d'élimination du médicament), c'est-à-dire au niveau de la relation dose – concentration. Parmi les possibilités offertes au clinicien, le suivi thérapeutique des médicaments (TDM) est un des outils avantageux pouvant aider à la prise en charge médicamenteuse. Le TDM a pour but d'optimiser les traitements en proposant des posologies (quelle dose, à quel intervalle?) individualisée, en fonction des concentrations du médicament mesurées dans le sang. Pour tenir compte de ces mesures de concentration, le calcul Bayesien peut être employé. Il se base sur les données pharmacocinétiques en rassemblant des données des individus au sein d'une population. Il représente actuellement la méthode de référence pour l'application du TDM mais nécessite néanmoins une certaine expertise et une assistance informatique, ce qui limite son application dans la pratique quotidienne.

L'objectif global de cette thèse était l'implémentation d'outils robustes en routine afin d'offrir un TDM Bayesien au clinicien pour une prise en charge moderne du patient. A cette fin, les objectifs concrets étaient (i) de concevoir un logiciel efficace et ergonomique pour la réalisation du TDM Bayesien : EzeCHieL (ii) de fournir les algorithmes de calcul pour la prédiction Bayesienne de la concentration des médicaments, en s'appuyant sur l'approche de population (iii) de résoudre certaines questions rencontrées en pratique clinique, (cas des nouveau-nés et de l'adhésion thérapeutique càd prise correcte de son traitement par le patient).

Après avoir réalisé un état des lieux des logiciels existants a pour fournir les spécifications nécessaires à l'élaboration d'EzeCHieL, une collaboration étroite avec les ingénieurs en informatique a permis la réalisation d'EzeCHieL. EzeCHieL permet d'évaluer si une concentration observée chez un patient est « normale », en comparaison avec ce qui serait attendu dans la population, si la concentration est adaptée par rapport à la concentration de médicament visée et de fournir une adaptation posologique si nécessaire.

L'implémentation d'une méthode de calcul Bayesienne pour le TDM nécessite de caractériser la pharmacocinétique du médicament et de quantifier la variabilité observée entre les individus et chez un même individu. Une approche de population est alors de rigueur. Des analyses de population ont été réalisées et les estimateurs nécessaires au calcul Bayesien fournis pour des médicaments candidats. Ce travail s'est particulièrement intéressé aux anti-infectieux chez les nouveau-nés (gentamicine et imipenème), en se basant sur le développement physiologique.

Une dernière étude a tenté également d'évaluer l'impact de l'adhésion thérapeutique mesurée en routine sur la caractérisation des modèles pharmacocinétiques et sur l'interprétation des concentrations sanguines de médicament.

En conclusion, nos résultats proposent des solutions pour assister les cliniciens dans l'interprétation des concentrations sanguines de médicament et pour améliorer l'adéquation des posologies dans la pratique clinique quotidienne.

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Fuchs A, Giannoni E, Guidi M, Decosterd LA, Pfister M, Widmer N, Buclin T, Csajka C. Population pharmacokinetic study of imipenem in neonates (*in preparation).*

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Fuchs A, Rotzinger A, Cavassini M, Buclin T, Csajka C, Schneider MP. Impact of medication adherence measurement on antiretroviral drug pharmacokinetics and interpretation of drug concentration levels. European society for patient adherence, compliance, and persistence. 21-22 November 2014, Lausanne (Switzerland).

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ABBREVATIONS

AIC	Akaike's information criterion
ART	Antiretroviral Therapy
ATV	Atazanavir
AUC	Area Under the Curve
BSV	Between Subject Variability
bBW	birth Body Weight
BW	Body Weight
CDSS	Clinical Decision Support System
CHUV	Division of Clinical Pharmacology of the Lausanne University Hospital
CI	Confidence Interval
C_{ipred}	Individual Predicted Concentration
CL	Total Clearance
Cmax	Maximum concentration
Cmin	Minimum concentration
CML	Chronic Myeloid Leukaemia
C_{obs}	Observed Concentration
CRT	Creatinine
CSEM	Swiss Center of Electronics and Microelectronics
C_{trough}	Trough concentration
CWRES	Conditional Weighted Residuals
CV	Coefficient of Variation
D1	Zero order constant of absorption
EBE	Empirical Bayes Estimates
EPFL	Swiss Federal Institute of Technology Lausanne
EFV	Efavirenz
ETV	Etravirine
FOCEI	First Order Conditional Estimation with Interaction
GA	Gestational Age
GFR	Glomerular Filtration Rate
GIST	Gastrointestinal Stromal Tumours
GUI	Graphical User Interface

HEIG-VD	Vaud School Business and engineering
HES-SO-VS	University of Applied Sciences and Arts Western Switzerland Valais – Wallis
HIV	Human Immunodeficiency Virus
HIT	Health Information Technology
HPLC	High-Performance Liquid Chromatography
bHT	birth Height
HT	Height
IQ	Inhibitory Quotient
ISyPeM	Intelligent Integrated Systems for Personalized Medicine
IIV	Inter-individual Variability
Ka	First order constant of absorption
LC-MS/MS	Liquid Chromatography coupled with tandem Mass Spectrometry
LOQ	Limit Of Quantification
LPV	Lopinavir
MAP	Maximum A Posteriori
MDRD	Modification of Diet in Renal Disease
MEMS	Medication Event Monitoring System
mHealth	Mobile Health
MSE	Mean Squared Error
MPE	Mean Prediction Error
MIC	Minimum Inhibitory Concentration
NNRTI	Non Nucleoside Reverse Transcriptase Inhibitors
NONMEM	Non Linear Mixed Effect Modelling software
NPDE	Normalized Prediction Distribution Error
TDM	Therapeutic Drug Monitoring
OF	Objective Function
PD	Pharmacodynamics
PDs	Pocket Doses
PDA	Patent Ductus Arterious
PE_i	Relative Prediction Error
PI	Percentile Interval
PIs	Protease Inhibitor
PK	Pharmacokinetics

PMA	Postmenstrual Age
PNA	Postnatal Age
pcVPC	prediction-corrected Visual Predictive Checks
popPK	Population Pharmacokinetics
Q	Intercompartmental clearance
RMSE	Root Mean Squared Error
TCI	Target Concentration Intervention
TDM	Therapeutic Drug Monitoring
TKI	Tyrosine Kinase Inhibitors
SNHL	Sensorineural Hearing Loss
Vc	Central Volume of distribution
Vd	Volume of distribution
Vp	Peripheral Volume of distribution
Vss	Volume of distribution at Steady-State

NONMEM Symbols

Δ	Delta: difference
ε	Epsilon: residual error of an observation y, also called random effect
η	Eta: inter-individual, random error in NONMEM models
ω	Omega:standard deviation of parameters θ generated by NONMEM
σ	Sigma:standard deviation of residual error ε
θ	Theta: fixed effects parameters generated by NONMEM
j	Observation
i	Subject (i.e. individual)

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CHAPTER I. GENERAL INTRODUCTION

From Bayesian estimators to dosage individualization

I.1. Drugs and variability in the therapeutic response

Drug development progressively reaches a fair degree of reliability regarding standard dosage recommendations. However, it still devotes insufficient attention to heterogeneity in drug response among individuals in terms of both efficacy and safety, which is common and noticed for a long time. In 1923, Banting and Macleod were awarded the Nobel Prize in Physiology and Medicine for the discovery of insulin, and the modern era of tailored therapy started when they administered the first insulin doses to a patient adjusted to blood sugar level [1]. Already in 1785, William Withering titrated the dose of foxglove, against its clinical effects and toxicity [2]. Formal individualization of digitalis treatment by drug concentration measurement began in the end of the 60's [3, 4] when drug assays became available. These are only typical examples among many others. Sources of variability are multiple including genetic polymorphisms, drug-drug interactions, disease conditions, specific patients' characteristics, etc. In the differences observed in drug response, pharmacokinetic (PK) considerations, related to drug disposition and metabolism, are of major importance. PK describes the fate of drugs in the body by quantifying the absorption, distribution, metabolism and excretion processes. It allows to devise the time-course of systemic exposure of a drug (and/or its metabolites) reflected by plasma concentration curves. The relationship between plasma drug concentrations and reproduction of a clinically relevant outcome, either the pharmacodynamic (PD) phase, or response biomarkers (as PD surrogate) is called PK/PD [5].

The largest part of variability in drug response resides in the PK phase, i.e. in the dose-concentration relationships. In a population, the total variability is made-up of predictable and unpredictable variability. The unpredictable variability, i.e. the random variability, is in turn made up of both inter-individual -which is not predictable from patients' characteristics and describes variability between individuals- and intra-individual variability – which describes the variability around each individual average parameter [6].

To consider variability in drug response is not so important for drugs with a wide therapeutic interval in which case the "one size fits all" approach holds. However, this issue is particularly acute

for drugs with a therapeutic window narrower than the random population variability [6]. This situation often leads to challenges in optimizing a dosage regimen for an individual patient (**figure 1.1**). Drug therapy individualization aims of both optimizing drug efficacy and minimizing its harms, by prescribing the right drug at the right dose to the right patient [7]. Thus, it also belongs to what has been recently called personalized medicine. An approach to drug therapy individualization is to design an appropriate dosage regimen for a given patient, based on dose-concentration relationship. Dosage individualization based on the measurements of drug concentration gave rise to the process of what is now called *Therapeutic Drug Monitoring* (TDM). However, in day-to-day practice, drug individualization is often left to prescribers based on their own experience, and patient's clinical status and characteristics, relying on empirical drug monitoring procedure [5].

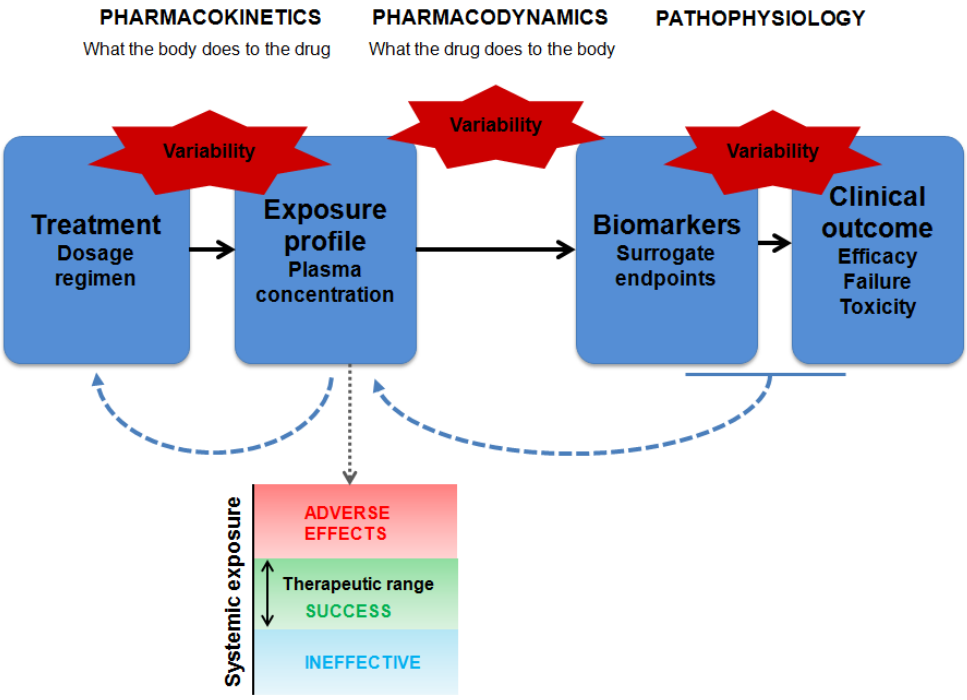

Figure 1.1. Pharmacokinetics to pharmacodynamics (solid arrows), back to the design of dosage regimen (blue dashed arrows) and relationship with drug therapeutic range concept.

I.2. Therapeutic Drug Monitoring

I.2.1. Basic concepts

As mentioned above, TDM represents the feedback strategy of tailoring dosing regimen based on plasma drug concentration measurements, representing additional information to guide drug therapy. It is indeed established that for selected drugs, response can be optimised using this approach. For instance, this is current practice for lithium, digoxin, aminoglycosides, immunosuppressants, and antiepileptics. Monitoring of protease inhibitors (PI), non- nucleoside reverse transcriptase inhibitors (NNRTI), tyrosine kinase inhibitors (TKI) and other anti-infectious drugs is also progressively adopted in some institutions including ours [8]. Drug candidates for TDM need to satisfy a number of criteria [8, 9] as presented in **table 1.1**.

Table 1.1. Characteristic requirements for a drug to be a candidate for TDM

Analytical criteria
Sensitive and specific analytical method available
Pharmacokinetic (PK) criteria
Good knowledge of the PK of the drug of interest
Large interindividual variability
Low intraindividual variability
Low predictability of PK from dose
Pharmacodynamic (PD) criteria
Good knowledge of the PD properties of the drug of interest
Good relationship between drug concentrations and pharmacological effect
Narrow therapeutic index
Known target concentrations
Clinical criteria
Adequate and easily monitored biomarker not available
Clinical drug response not easily assessable or not sufficient alone
Duration of therapy of a sufficient length
Good interpretation of concentration measurements available

More precisely, TDM can be divided in two types [10]:

- *a priori* TDM based on prior knowledge on the patient characteritics to define initial dosage regimen and relying on population PK/PD relationships

- *a posteriori* TDM based on plasma drug concentrations, in order to achieve plasma concentration within a target range [11, 12]. As illustrated in **figure 1.2**, it includes:

- A pre-analytical step: blood sample and request on a laboratory form with essential information (dosage regimen, time of sampling, last time of dosing, patients characteristics, other administered drugs).
- An analytical step: rapid, sensitive and specific analytical methods and instruments are key for providing reproductible and reliable data that can be used for individualization.
- A clinical step: drug concentration are interpreted together with target range and clinical individual situation. Dosage adjustment can be advised if the concentration is out of target

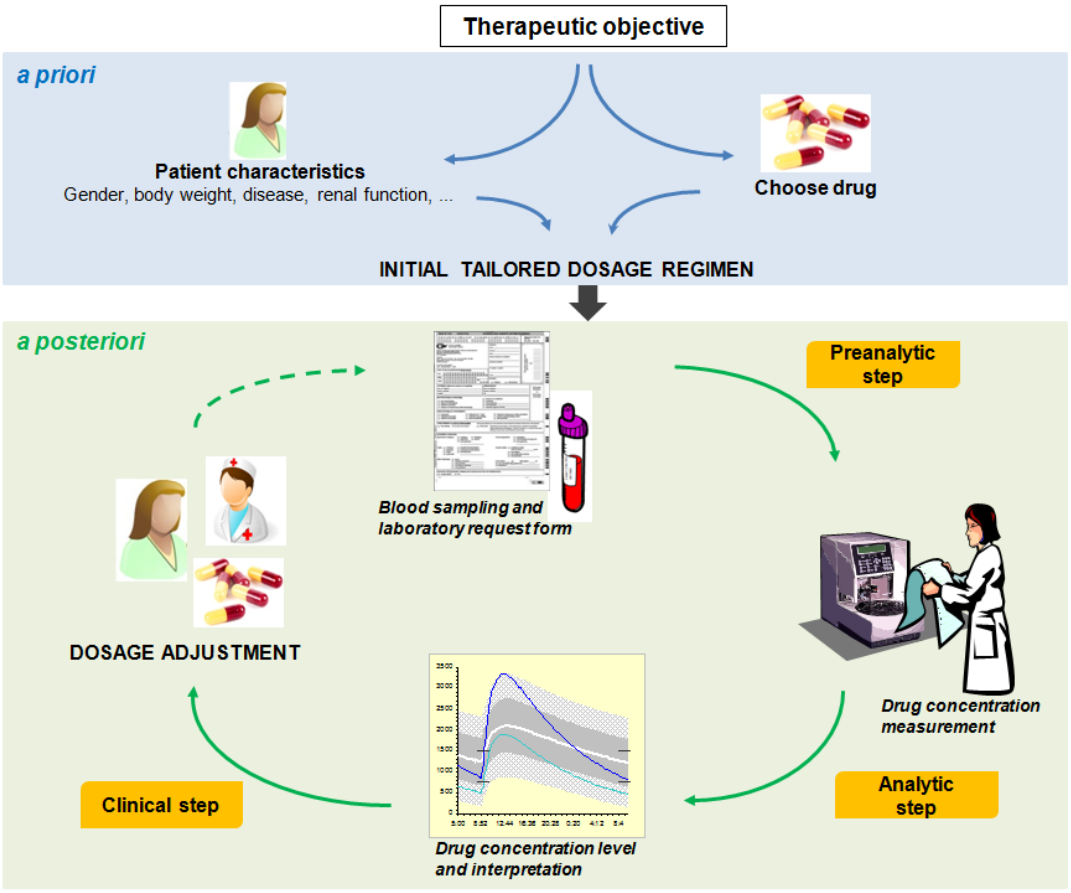

Figure 1.2. Major steps in TDM

I.2.2. Pharmacokinetic targets

A target concentration represents the value, or the range of value, with the greatest probability of therapeutic success at a given time [13]. The pharmacokinetic targets depend of the considered

drugs. The most common target is the trough concentration (C_{trough}), just before the next dose. For anti-infectious drugs, target also depends of the minimum inhibitory concentration (MIC): for instance, peak concentration over MIC (aminoglycosides), percentage of time over the MIC (carbapenems). For immunosuppressants, although it is debated, many studies suggested that Area Under the Curve (AUC) is a better predictor of success than C_{trough} [14]. Average concentration can also be considered (digoxin). The target concentration may also depend on the indication. This is the case for digoxin depending whether it is being used for atrial fibrillation or congestive heart failure. For some antibiotics, it may depend of the severity and the site of infection additionally to the pathogen involved.

Thus, for drug concentration interpretation, it requires to sample at an optimal time, which is linked to the PK target and it should be performed at steady-state. In practice, this is not always possible to sample patient at optimal time, and in this case, concentration prediction at the time of interest may be beneficial.

I.2.3. Methods for dosage regimen initiation and adjustment

Rather than identical standard dose for all individual patients, nomograms have been proposed to facilitate the determination of initial dosing. The sources of variability in the response are anticipated. When a plasma concentration is available, the proportional method can be used to calculate an adjusted dosage to reach the desired concentration, from the initial observed concentration. This method relies on a simple rule of three, but it assumes that kinetics is linear, steady-state is achieved, and that either nominal dose or dosage interval would be modified [15-17]. Regression methods have also been proposed, that consist of determining the slope of elimination (in $time^{-1}$) from at least two measured concentrations during the post-distributive phase, from the same interval of dose. The most popular example is certainly the Sawchuk-Zaske method for aminoglycosides [18]. Finally, the most recent pharmacokinetic method based on Bayesian approach is generally more accurate and more robust [19-21]. The Bayesian strategy relies on the population PK/PD studies which is further developed below. A modern trend of TDM is given in **figure 1.3**.

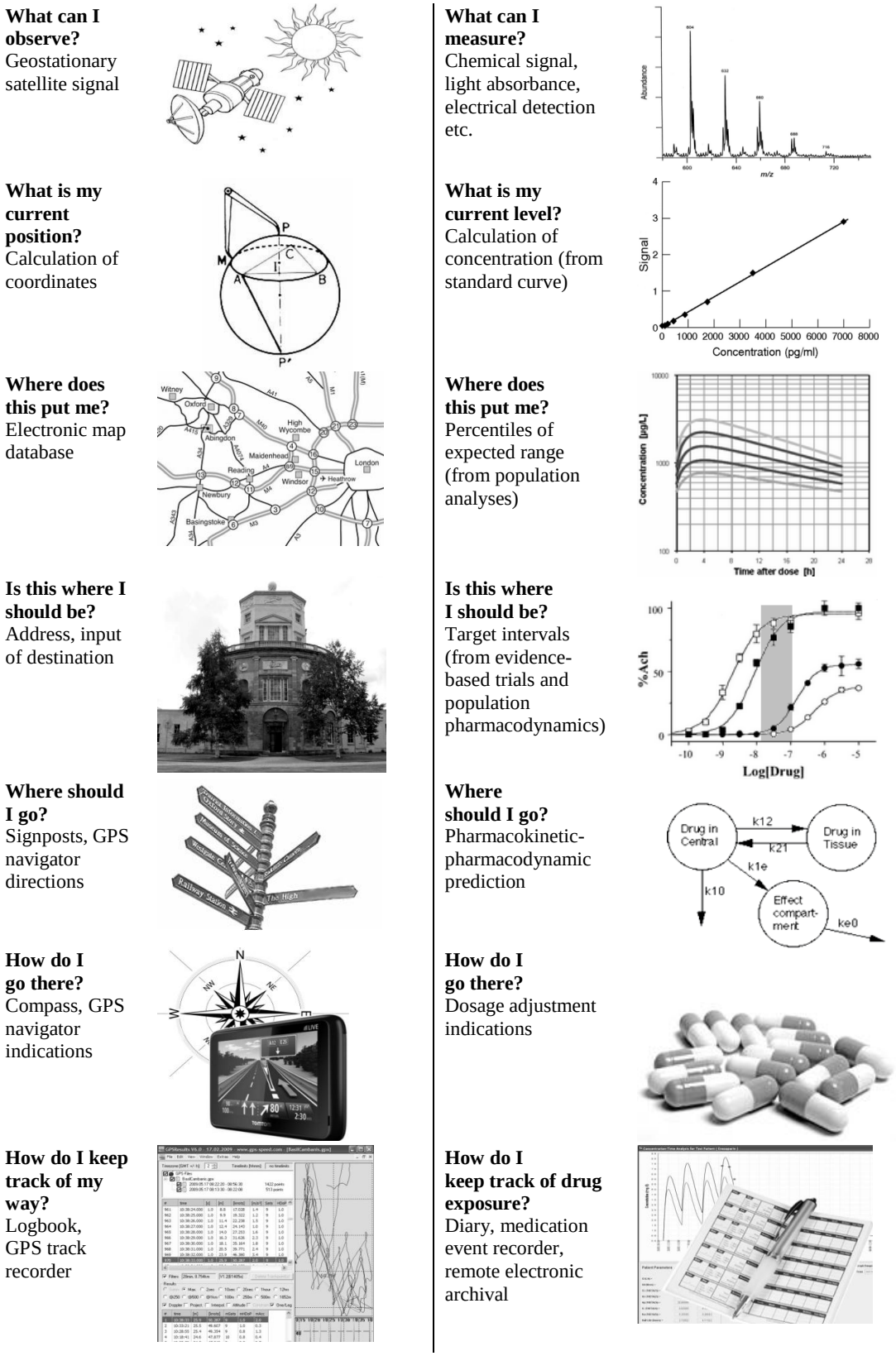

Figure 1.3. Modern trend of TDM. A. Sequential steps of modern navigation, as currently implemented in GPS-based satellite navigation devices. B. Potential modern methods of monitoring drug therapy, mapped on to the methods of navigation. (Reprinted from An agenda for UK clinical pharmacology, Monitoring drug therapy, Buclin et *al.,* BJCP, 2012;73(6):917-23. Copyright (c) 2012, The Authors).

I.3. Population approach and modeling: concept and benefits

I.3.1. Models and compartments theory

Model is useful as a representative description of a system, especially designed to facilitate calculation and prediction. In pharmacokinetics, it aims to show the dose-concentration relationship over time of the drug. Compartment theory is often used in PK, in order to describe the fate of a drug: in this case, drug distribution within the body is approximated by a model constituted of compartments, represented by boxes. In the boxes, the drug appears kinetically distributed. It provides a means for estimating the associated parameters such as clearance and volume of distribution. An example of a two-compartment model is given in **figure 1.4** that includes a central compartment, of which plasma is a part and a peripheral compartment, but do not necessarily represent any anatomical region of the body [22, 23]. In the population approach, it is called the structural model and it can be stated as differential equations (see below).

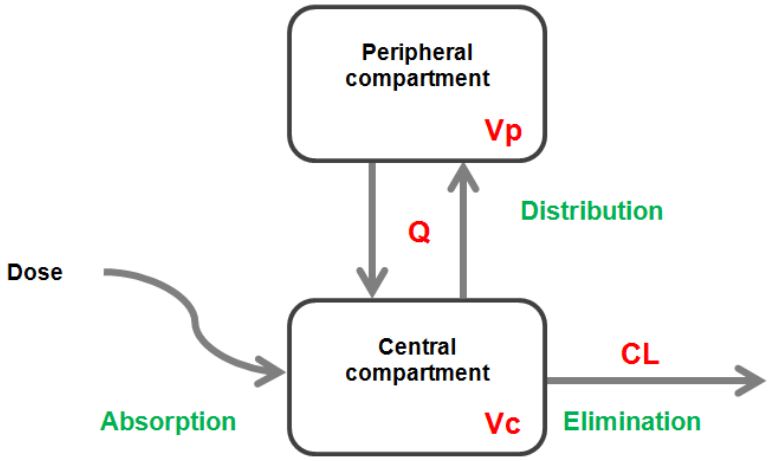

Figure 1.4. Schematic two-compartments model for an intravenous administration with pharmacokinetic parameters: **Vc** = Central volume of distribution, **Vp** = peripheral volume of distribution, **Q** = intercompartmental clearance, **CL** = total clearance

I.3.2. Population pharmacokinetic modeling

In the early 70's, clinical PK largely benefited of population PK modeling emergence. Its objective is to describe plasma concentration-time profile with mathematical and statistical models using

sparse blood samples in a whole population. Development of the fixed-effects model allows indeed simultaneous analysis of data collected in a population. However, most of the models used in PK are nonlinear with time, and in such cases, mathematical calculation is complicated. In the 70's and early 80's, Sheiner and Beal developed the first method adapted to nonlinear mixed effect model, at the University of California, San Francisco: here was born population PK. They also proposed the first **non**linear **m**ixed **e**ffect **m**odeling software: NONMEM® [24]. In addition to providing the average behaviour of the group (the mean plasma concentration-time course), population PK provides an opportunity to estimate variability on various PK parameters, identify its sources and quantify the unexplained part of variability [25].

Population PK is usually characterized in terms of:

(i) **Fixed effects:** representing the population average of the model parameters θ (clearance and volume of distribution). These parameters are susceptible to various factors, such as physiological characteristics (age, gender, body weight, renal status, etc), genetic characteristics, or drug-drug interactions. These last factors are the fixed effect covariates, z_i.

(ii) **Random effects:** this is the part of the variability that is not explained by the above fixed effect and permits quantification of:

- The *interindividual* variability (also called the between subject variability), which is the variability between two different individuals. It is expressed by ω^2, which is the variance of the fixed effect parameter θ. For an individual i, $\theta_i = \theta + \eta_i$ where η_i follows a normal distribution with a variance ω^2.

- The *intraindividual* variability (also called the residual unexplained variability), which is the variability within the same individual over time i.e. between two given moments. It is expressed by σ^2. For an observation j, the corresponding prediction $\hat{y}$ by $y_{ij} = \hat{y} + \varepsilon_{ij}$ where ε_{ij} follows a normal distribution with a variance of σ^2.

Thus, the general mixed effects model is written:

$$\boldsymbol{y_{ij}} = \boldsymbol{f}(\boldsymbol{x_{ij}}, \boldsymbol{\phi_i}) + \boldsymbol{\varepsilon_{ij}}$$

And the parameter model:

$$\boldsymbol{\phi_i} = \mathbf{g}(\boldsymbol{z_i}, \boldsymbol{\theta}) + \boldsymbol{\eta_i}$$

Where y_{ij} is the jth observation in an individual i, x_{ij} is a known quantity (time or dose), ϕ_i is the pharmacokinetic parameter vector for an individual i, and ε_{ij} represents the residual error; g is a structural model which is function of fixed effects covariates z_i, and fixed effects parameters θ; finally, f represents the pharmacokinetic model (like one, two or three compartments, linear or non-linear kinetics). In this general model, residual error ε_{ij} is additive, and means that each measurement is assumed to be equally precise for all values of y_{ij}. When error changes with differing values of y_{ij}, ε_{ij} is assumed to follow a log-normal distribution with median 1 and a constant coefficient of variation. Combinations of additive and log-normal errors can also be used [26].

The model that best fits the analyzed data is determined by the maximum likelihood approach. NONMEM® estimates the best values of θ, ω^2, σ^2 that give the lowest value of the objective function (OF). Complementary to the maximum likelihood approach, diagnostics graphics and values of coefficients of variation will be analyzed to determine the final model [26].

The advantages of population PK reside in being able to treat sparse data, and thus the possibility to use the information generated during patient routine care. Estimation of random and fixed effects allows development and improvement in dosing strategies for specific population of patients (neonates, paediatrics, elderly, dialysis, disease,…) who will eventually received the drug of interest. As it will be presented in the following paragraph, it permits Bayesian feedback analysis to be performed for TDM [25].

I.4. From population to individual: Bayesian forecasting

To forecast individual PK parameters with precision in a given patient is central to make optimal dosage decision. The Bayesian approach is more accurate and precise for this purpose as it estimates individual PK parameters that will be most consistent with serum level predicted by the model and the actual measured concentration. It balances deviation of the individual's model-predicted concentration ($\hat{C}$) from observed concentration (C_{obs}) and the deviation of the individual's estimated parameters values (P_k) from the population parameter value ($\widehat{P_k}$). It uses the *prior* probability distribution of the individual's parameters set in the light of the observed concentration to give the *posterior* distribution. The *posterior* distribution has a different mode than the prior one, and its new mode is used for the next forecasting round (**figure 1.5**). It takes into account uncertainty over individual parameters and measurements error [27-29].

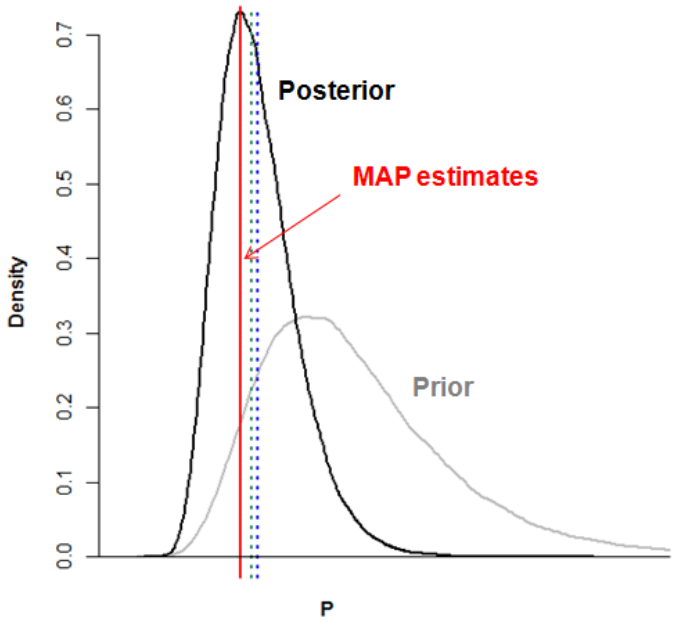

Figure 1.5. Parameter density for *a priori* (grey) and *a posteriori* (black) distribution, with a posteriori mode (red line), a posteriori median (green dotted line) and a posteriori mean (blue dotted line).

Bayesian optimization criterion is based on the maximum a posteriori (MAP), for normal distribution assumption, and minimizes the following expression [29] for estimates of parameters P:

$$OBJ_{MAP}(P) = \sum_{j=1}^{n} \frac{\left[C_{obs,j} - f(P, t_j)\right]^2}{{\sigma_j}^2} + \sum_{k=1}^{m} \frac{\left[P_k - \widehat{P_k}\right]^2}{\omega_k^2}$$

$\boldsymbol{OBJ_{MAP}}$	Optimization criterion: P function to minimize
$\mathbf{P}$	Parameters (clearance(s), volume(s) of distribution, etc)
$\boldsymbol{C_{obs,j}}$	Observed concentration at time t_j
$\boldsymbol{f(P, t_j)}$	$\hat{C}$ = model-predicted concentration
$\boldsymbol{{\sigma_j}^2}$	Residual error variance on $C_{obs,j}$
$\boldsymbol{P_k}$	Individual's estimated parameter values
$\boldsymbol{\widehat{P_k}}$	Population parameter values
$\boldsymbol{\omega_k^2}$	Parameter residual variances

Individual parameters values, individual-predicted concentrations and residuals-parameters values are thus estimated by the so-called *post hoc* estimation (or empirical bayes estimates (EBE) estimation). It is used for the refinement of a patient dosage regimen that can be based only on one measured concentration. This process is presented in **figure 1.6.**

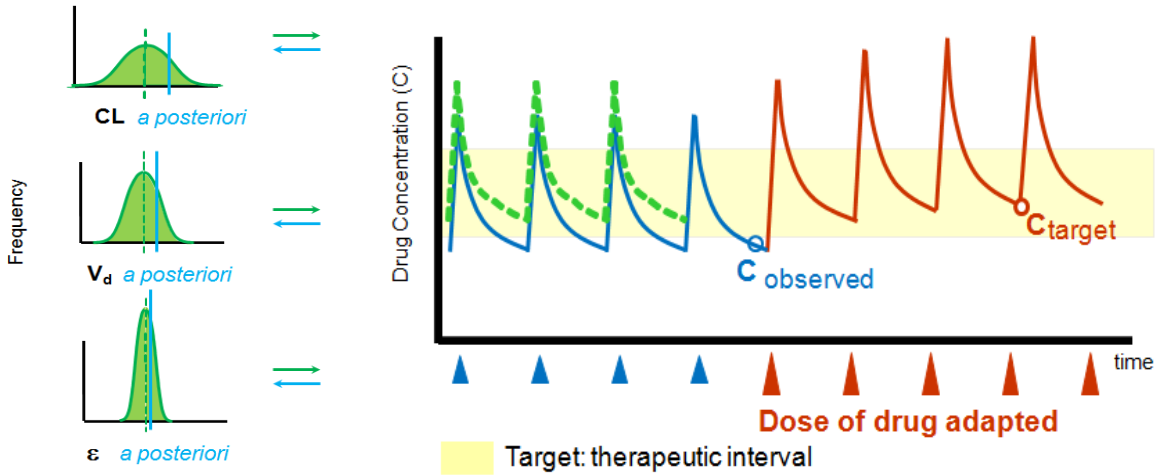

Figure 1.6. Bayesian strategy for dosage adaptation**:** from *a priori* parameters to *a posteriori* individual parameters used for dosage regimen refinement. *(adapted from the courtesy of Pr. T. Buclin)*

I. 5. Implementation of Bayesian estimator for dosage individualization

I. 5.1. Computer tools and new technologies

Bayesian forecasting method is computational demanding and necessitates intensive numerical integration [30]. Thus, its implementation in the health care system context requires appropriate computing platforms for integrating all information gathered, adequate resources and effective communication. The 20th century saw the advent of computer, and computerization in medicine has evolved with time and the modernization of health care facilities since the 60's [31]. It also benefited from the development of Internet and the Web. As we have moved to the 21st century, we have come to rely more and more on the Internet and Web 2.0. Medicine is not left behind, witness of the development of Health 2.0, eHealth, Health Information Technology (HIT), mobile Health (mHealth) [32, 33]. HIT can be defined as a diverse set of technologies for transmitting and managing health information for use by consumers, providers, and all other groups with an interest in health and health care, such as payers and insurers. HIT displays a variety of systems, such as computerized storage and reporting of laboratory results, electronic health records, or novel systems that permit interoperability, i.e. permit clinicians to share information about patients across institutional boundaries and even all over the globe. HIT has improved quality and efficiency, and eventually reduced health care costs. Its effective use also resides in its ability to retrieve data, organize them, apply algorithms, and provide the results to clinicians when and where they need it [34]. Products and services based on HIT remains relatively small and undeveloped in medicine compared to most other sectors of the economy [35]. The most advanced progression into these new possibilities is represented by mHealth. mHealth technology that encompass Smartphone and embedded tablets are slowly changing healthcare, with more than 17,000 applications today available for mobile devices, for a large panel of tasks either for clinicians, hospitals or directly for patients [36]. Use of mHealth technology leads to "*put doctor in patients pocket and to jump to personalized medicine*" [35].

I. 5.2 NanoTera project – Intelligent Integrated Systems for Personalized Medicine

Intelligent Integrated Systems for Personalized Medicine (ISyPeM) is a multi-disciplinary and multi-institutional project involving the Division of Clinical Pharmacology of the Lausanne University Hospital (CHUV), the School Business and Engineering Vaud (HEIG-VD), the University of Applied Sciences and Arts Western Switzerland Valais – Wallis (HES-SO-VS), the Swiss Federal Institute of Technology Lausanne (EPFL), and the Swiss Center of Electronics and Microelectronics (CSEM), as presented in **figure 1.7.**

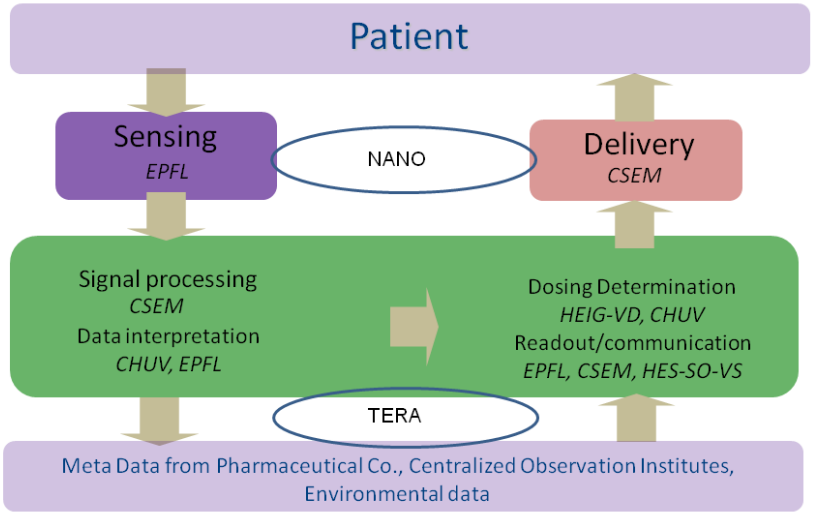

Figure 1.7. ISyPeM - A multidisciplinary and multi-institutional project to advance state-of-art personalized medicine by creating new technologies.

This project is part of the Nano-Tera initiative. Nano-Tera is a Swiss collaborative research enterprise that aims to bring new technological evolution using engineering and information technology to improve health and security and to extend the management of energy and the environment.

The aim of the specific 2-step ISyPeM project[1,2] is to advance state-of-art personalized medicine while benefiting from technological advances. This project involves many facets, ranging from analytic and miniaturized monitoring test development at the point of care, to new drug delivery mechanisms.

[1] ISyPeM 1: http://www.nano-tera.ch/projects/405.php
[2] ISyPeM 2: http://www.nano-tera.ch/projects/368.php

The present thesis focuses only on the contribution of the Division of Clinical Pharmacology (CHUV) to this project. Our division has a longstanding experience on drug dosage individualization, along with technical competences in population PK/PD. As previously mentioned, monitoring relies almost exclusively on empirical procedure in the medical community, and drug monitoring still represents a significant challenge for modern health care. Translation of concentration measurements values into personalized treatment advices requires yet the integration of efficient and ergonomic computer tools into the system, with communication capabilities, which are nowadays becoming a standard in many aspects of medical care. Thus, development of an easy-to-use and efficient clinical decision support system (CDSS) [37] for health care providers appears crucial and lead to EzeCHieL subproject in 2010. It results from close collaboration between the division of Clinical Pharmacology and the software engineers from HEIG-VD, who are in charge of software development. **Figure 1.8** represents CHUV contribution to ISyPeM and especially where EzeCHieL realization currently stands. Later, it will be integrated into others ISyPeM devices, once available.

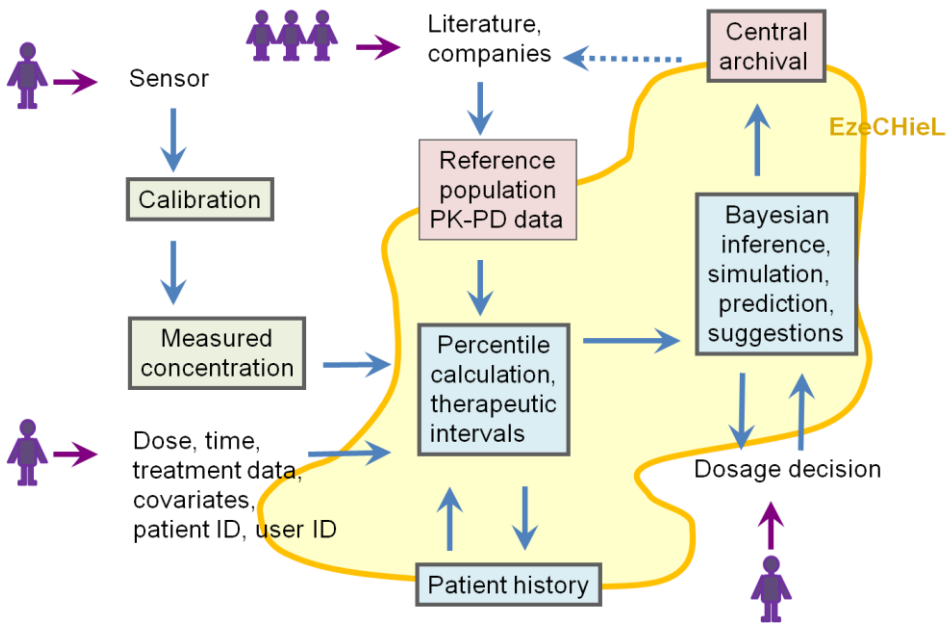

Figure 1.8. Contribution of CHUV in ISyPeM : EzeCHieL and project perimeter
(Courtesy of Pr. T. Buclin, Lausanne)

I. 6. Examples of some pharmacokinetic issues in clinical practice

I. 6.1. Special group of patients: focus on neonates

Certain patients' group (elderly, pediatrics, critically ill, patients with renal failure, obese) are difficult to study because of ethical and logistic issues. During drug development, studies deal with more or less selected subgroups, most of the time quite homogenous (healthy volunteer, patient with few associated co-morbidities). Much of the drug PK is thus unknown once it is released on the market [38].

For instance, no consensus has been reached for dose selection in children but this is often obtained from extrapolation in another population of reference, where the relations between covariates and parameters is characterised. Implicitly, this means that the following hypotheses are accepted: the structural model, variability and covariance are identical; there is continuous covariate-parameters relationship; the correlation between covariate and parameters is identical in the new population; and there is no other significant covariate in the population of extrapolation. However, it does not take into account the developmental change across paediatric populations [39] [40]. There are biological basis for using size and maturation to describe PK in this population and, actually, size and age are considered as primary covariates for PK model.

Body size (body weight (BW)) is the most important predictor for elimination process [41]. Most body size relation is often described following an allometric relation: $CL_i = CL_{std} \times \left(\frac{BW_i}{BW_{std}}\right)^{0.75}$. Volume shows direct proportionality to body weight: $V_i = V_{std} \times \left(\frac{BW_i}{BW_{std}}\right)^{1}$ [42]. The value of the coefficient of 0.75 used to scale the process of clearance is an empirically derived constant that has also been discussed throughout the literature, and it cannot be applied solely for infants without a maturation function. Maturation (Age) is used to describe processes that are associated with time course and not dependent of size. Maturation of clearance starts before birth, taking into account gestational age, additionally to age, thus often leads to better prediction, especially because birth may occur prematurely [43]. There are examples of allometric extrapolation from adult to teenager or children. But there is no universal method of extrapolation in infants (< 2 to 5 years old) due to

growth and organ maturation process. Regarding the important need of information for these groups, use of information generated during the routine care of patient to obtain estimates is advocated and is facilitate by population method and modeling [44]. Neonates are of particular interest; since birth seems also to have consequences on maturation that is poorly documented [41, 42].

I. 6.2. Medication adherence

Medication adherence implies persistence, which refers to continuing the treatment for the prescribed duration and, execution which refers to the patterns of patient adherence behavior (percentage of days with correct dosing, percentage of correct dosing intervals, drug holidays) [45]. The ultimate consequence of poor medication adherence is its contribution to a negative therapeutic outcome, especially in chronic disease. While a number of covariates related to the clinical response are studied to the clinical response, patient adherence is rarely measured or taken into consideration. However, addition of adherence in the PK/PD picture shows how it complicates both: drug pharmacokinetic characterization and dosage regimen definition (**figure 1.9.** adherence in the PK/PD concept).

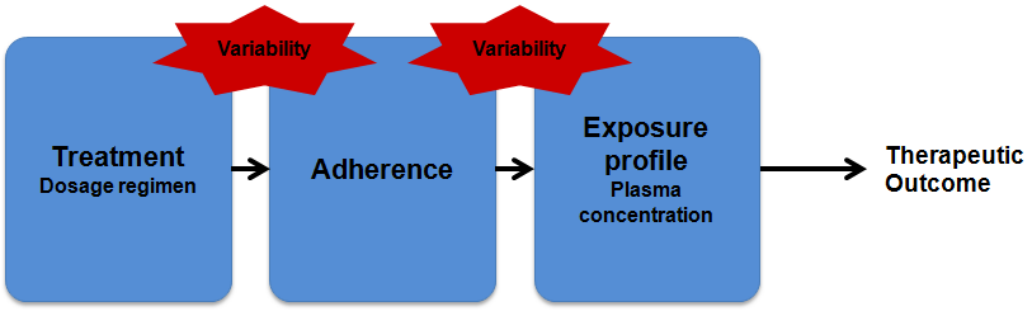

Figure 1.9. Adherence in the PK/PD picture

Deviation from taking medication as prescribed is a source of variation in drug exposure and thus in the global pharmacotherapy. It can lead to an incorrect description of the PK/PD models. Assuming that medications are taken exactly as prescribed when it is not the case can lead to biased model parameter estimates and to misleading clinical outcome interpretation. Quantitative

measurement of medication adherence can decrease the residual variability up to 50% [46] and can substantially remove noise in the PK/PD models [47].

Patterns of non adherence also influence TDM intervention. Most TDM intervention assumes a full adherence and steady-state condition and the "white coat compliance" (defined as an improved medication adherence just before a clinic visit) makes less reliable TDM measurements [48]. Individual Bayesian calculations are affected if a wrong dosing history is assumed. In returns, it can biased dosage recommendation [49].

Consequences of poor adherence depend of drug's PK and PD properties. Antimicrobials and antivirals are frequently unforgiving. Half-life is often quite short, and the rate of potential mutation in pathogens is high, which makes essential to maintain an effective concentration throughout the dosing interval. Even so, there is a lack of research combining medication adherence variables with PK, and a poor understanding of the impact of such model [50].

I. 7. Objectives of the thesis

The overall objective of this research is to provide advances in Bayesian drug dosage individualization and to allow its implementation in the routine care.

To that endeavour, the purposes of this thesis are:

i. To elaborate an efficient and ergonomic computer tool for TDM, EzeCHieL (chapter II), by:
- Systematically reviewing currents programs available in practice, in order to evaluate needs, to provide specifications and to support development of EzeCHieL.
- Participating actively in the elaboration of EzeCHieL particularly in the conception, testing and validation of the software, in close collaboration with the engineers.

ii. To provide drugs' algorithms for Bayesian forecasting and validation, relying on population approach (chapter III).

iii. To address some practical issues met during TDM intervention such as better understanding causes of variability in drug exposure (specific population, adherence), and to optimise TDM intervention via EzeCHieL (Chapter III and Chapter IV).

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CHAPTER II. COMPUTER TOOLS

Chapter II in the thesis context

The global project of this thesis arose from the observation that an adequate tool to offer Bayesian TDM at large scale was missing

The first part of this chapter is presenting a review of the current software tools available regarding TDM. In the last decades, several programs have yet been designed to assist clinicians in interpreting blood drug concentrations and to improve the appropriateness of drug dosing in routine clinical practice. The purpose of this review was to establish the current stage of the existing software to evaluate the limits of these current tools and to propose specifications for the development of our new tool, EzeCHieL.

Following this review, the question was "what can we do yet"? The second part of this chapter is presenting the concept of EzeCHieL, and intuitive and flexible software intended to assist clinicians in TDM interpretation. Different capabilities embeds by the software regarding drug exposure prediction, drug treatment indication and interoperability amongst others are under elaboration. Its current stage of realization, since the beginning of its development in 2010 is given.

Own contribution:

First part: Participation to protocol elaboration. Programs' identification and collection. Extensive programs' testing and comparison. Contact with software distributors. Drafting of the article and publication process.

Second part: Participation in program conception. Extensive program testing and validation. Close collaboration with software engineers. Drafting of the article.

II.1. BENCHMARKING THERAPEUTIC DRUG MONITORING SOFTWARE: A REVIEW OF AVAILABLE COMPUTER TOOLS

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ABSTRACT

Therapeutic drug monitoring (TDM) aims to optimize treatments by individualizing dosage regimens based on the measurement of blood concentrations. Dosage individualization to maintain concentrations within a target range requires pharmacokinetic and clinical capabilities. Bayesian calculations currently represent the gold standard TDM approach but require computation assistance. In recent decades computer programs have been developed to assist clinicians in this assignment. The aim of this survey was to assess and compare computer tools designed to support TDM clinical activities. The literature and the Internet were searched to identify software. All programs were tested on personal computers. Each program was scored against a standardized grid covering pharmacokinetic relevance, user friendliness, computing aspects, interfacing and storage. A weighting factor was applied to each criterion of the grid to account for its relative importance. To assess the robustness of the software, six representative clinical vignettes were processed through each of them. Altogether, 12 software tools were identified, tested and ranked, representing a comprehensive review of the available software. Numbers of drugs handled by the software vary widely (from two to 180), and eight programs offer users the possibility of adding new drug models based on population pharmacokinetic analyses. Bayesian computation to predict dosage adaptation from blood concentration (a posteriori adjustment) is performed by ten tools, while nine are also able to propose a priori dosage regimens, based only on individual patient covariates such as age, sex and bodyweight. Among those applying Bayesian calculation, MM-USC*PACK© uses the non-parametric approach. The top two programs emerging from this benchmark were MwPharm© and TCIWorks. Most other programs evaluated had good potential while being less sophisticated or less user friendly. Programs vary in complexity and might not fit all healthcare settings. Each software tool must therefore be regarded with respect to the individual needs of hospitals or clinicians. Programs should be easy and fast for routine activities, including for non-experienced users. Computer assisted TDM is gaining growing interest and should further

improve, especially in terms of information system interfacing, user friendliness, data storage capability and report generation.

II.1.1. Introduction

The monitoring of drug therapy aims to forecast treatment success, failure or toxicity, and to adjust prescriptions as a consequence. Circulating drug concentration is a traditional pharmacokinetic surrogate used for this purpose, in what is called therapeutic drug monitoring (TDM) [1]. TDM assumes that circulating drug concentrations better predict the effect of pharmaceutical agents and clinical outcome than doses. Practically, TDM approaches attempt to optimize individual dosage regimens through the maintenance of concentrations within a given therapeutic range [2]. Dosage individualization consists either of a priori adjustment (without blood drug concentration measurement) based on demographic, biological, pharmacogenetic and clinical covariates, or of a posteriori adjustment based on drug concentration determination [3]. TDM-guided dosage individualization is currently applied to a number of drugs such as antibacterials, anticonvulsants, digoxin and immunosuppressants [4]. Major benefits for patients reside in optimizing the drug concentration exposure, leading to more rapid and sustained therapeutic control and to improved safety, which might even reduce the duration of hospitalization [1, 5]. Maintaining optimal drug concentrations is, however, a complex and demanding task. It requires solid knowledge of evidence-based clinical guidelines, clinical pharmacology and pharmacokinetics, as well as definite mathematical skills for dosage calculation [5]. It therefore represents a time-consuming activity for healthcare professionals and often requires the intervention of a specialist [1]. In such circumstances, computer-assisted decision making [6] is advantageous, as algorithms implemented enable the automated calculation of doses, while integrating patients' individual factors such as age, bodyweight, sex, kidney function, disease and drug interactions along with drug concentration results [7, 8]. Whereas most industries have experienced an information technology revolution since the 1980s, healthcare systems are generally moving rather slowly in that direction [9]. The

main healthcare domain currently undergoing profound transformation is the field of electronic medical records and of networks to share these medical data [9, 10]. Dispensation and dosing of drugs also represent a field of interest in which intelligent technologies could be useful [10]. In parallel, technological efforts towards the miniaturization of monitoring tests (e.g. TDM determinations) are necessary [11], along with the development of robust and user-friendly computer tools to provide seamless monitoring services in clinics [1]. Indeed, in recent decades, several programs have been designed to assist clinicians in interpreting blood drug concentrations and to improve the appropriateness of drug dosing in routine clinical practice [12-19]. Recently, computer-assisted decision tools for monitoring gained renewed attention, holding further potential for TDM-guided dosing optimization. In 1993, Buffington et al. [12] published a review of computer programs designed for TDM-guided dosage optimization available in the USA. Since then, however, few evaluations on this type of software have been presented, and no further review has ever been published to our knowledge. The aim of this survey is to provide an updated comparative evaluation of all software designed for routine TDM-guided dosage adjustment that is widely available throughout the world.

II.1.2. Search strategy and selection criteria

A literature search for clinical pharmacokinetic software programs was performed through MEDLINE (1966 to October 2012) and Google using the following keywords: therapeutic drug monitoring, software, program, computerized, clinical pharmacokinetics, computer assisted decision-making, dosing, drug dosage. The web portal of David Bourne's pharmPK forum [20] was also used as a resource for program identification. As programs widely differ in their features, their expected characteristics had to be assessed along multiple axes. This led to the design of a comprehensive evaluation grid to standardize the comparison of software. Criteria were defined based on the authors' experience in routine TDM practice. General characteristics addressed were as follows: user interface, visual aspect, user friendliness; possibility of interfacing with other

hospital software (e.g. laboratory software or patient's medical records); possibility to store patient's or user's information; the quality of report generated for physicians; the cost; and computational aspects such as import and export functions. To take into account the variety of fee schemes, prices were calculated for a 5-year annual subscription. Pharmacokinetic aspects addressed were as follows: drugs and type of population covered by the programs; type of models, calculation approaches, simulation capabilities; modularity; quality of pharmacokinetic plots generated; and further utilities such as creatinine clearance calculation. The full grid of criteria is available in **Tables 2.SI** and **2.SII** of the Online Resource. The evaluation of all software programs was performed on a standard personal computer by one pharmacist user, backed up by two clinical pharmacologists experienced in computing and the clinical practice of TDM. A score was assigned to each criterion, ranging from 1 (for the lowest performance) to 5 (for the highest performance). For binary items (yes/no), a score of either 2 or 4 was allocated and for ternary criteria a score of 1, 3 or 5 was allocated to balance the marks attributed. Scoring definitions are detailed in the Online Resource (**Table 2.SI**). The scoring approach had to be balanced, since criteria obviously differ in their importance. In that endeavour, five physicians, five pharmacists and five computer engineers were asked to attribute a weight from 1 to 3 to each criterion (1 for low importance, 2 for useful but not essential and 3 for essential). A final weighting factor for each criterion was then calculated by arithmetic average. Finally, a ranking of the software programs could be established by summing the weighted scores to obtain a global score for each program. Scores by category were also calculated in order to appraise more finely the various facets of the programs. When characteristics of programs were unclear, contact with the authors or developers was sought to clarify relevant points. Validation by the author or by the software developing company was proposed and the grid was distributed to those willing to participate. They were asked to fill it in using the explanatory table sent along with the grid (**Table 2.SI**). This allowed a double-control and confirmation of missing information. To improve the robustness of our evaluation, six clinical vignettes, inspired by

real clinical TDM cases encountered in our routine activity, were also tested. These cases aided the evaluation of the software based on systematic testing of real-life situations. They also provided an insight of a priori and a posteriori predictions offered, and of the type of specific cases that could typically be handled by the programs.

II.1.3. Therapeutic drug monitoring software

II.1.3.1. History and evolution

USC*PACK© was the first available software dedicated to monitoring and dosage adjustment. Developed by the Laboratory of Applied Pharmacokinetics at the University of Southern California (Los Angeles, CA, USA) and launched in 1973 [21], it is still in use and evolving. It represents a comprehensive software that includes MM-USC*PACK© (now called RightDose™) and is designed for clinical practice and dosage adjustment. Later, in 1982, the Department of Pharmacology and Pharmacotherapy at the University of Groninigen (Groningen, The Netherlands) developed MwPharm©. MediWare (Charles University, Prague, Czech Republic), now hosting the program, was established in 1987. Abbott Laboratories also developed a software package in the early 1990s called Abbottbase Pharmacokinetic Systems or PKS [18]. It was widely used, at least in the USA, during the 1990s [12]. The program distribution has, however, been discontinued for some years. Similarly, there are other programs that existed in the 1990s but are no longer available (e.g. SeBAGEN [22], ATM [13], Simkin [23]). Either they are not marketed any more, or their development was merged with other software. For example, Kinetidex® has been Thomson Reuters' software since 2001, resulting from a merge between Simkin and Micromedex®. In the meantime, other initiatives have appeared, mostly from the academic field. A pharmacist from Creighton University (Omaha, NB, USA) developed multiple programs dedicated to assisting hospital pharmacy practice under the global name RxKinetics© Software. Among them, three programs are intended for dosage adjustment, with the first one, Kinetics©, launched in 1986. More recently, programs have been developed in Asia. JPKD® for desktop and TDM for R (which is a variant of

JPKD® developed as a plug-in for the R statistical program) were both developed by Kaoshiung Medical University (Kaoshiung, Taiwan) and released in 2006. New initiatives are still emerging, the latest of which comes from the University of Otago (Dunedin, New Zealand) and the University of Queensland (Brisbane, QLD, Australia), which released the first version of TCIWorks in 2011.

II.1.3.2. Widely available software packages

Twelve clinical pharmacokinetic programs were identified: MM-USC*PACK©, MwPharm©, TCIWorks, JPKD®, TDM for R, Antibiotic Kinetics©, APK©, Kinetics©, Kinetidex®, T.D.M.S. 2000™, DataKinetics™, RADKinetics. Antibiotic Kinetics©, APK© and Kinetics© belong to the RxKinetics© programs. Specific versions reviewed are indicated in **Table 2.1.1**. Moreover, major features are described for each software in **Tables 2.1.2** and **2.1.3**. All criteria considered are presented in the detailed evaluation grid accessible in the Online Resource (**Table 2.SII**), with their associated weight. A summary of the results, scored by category and ranked, is shown in **Table 2.1.4**. We were able to contact authors or the developing company for 11 of the 12 programs (only developers from RADKinetics could not be reached because of broken links on their website and unavailability of contact information). Some developers declined participation, considering either that it was difficult to self-rate items or that our demand included requests for information viewed as proprietary. Eventually, five developers provided feedback for MM-USC*PACK©, MwPharm©, Antibiotic Kinetics©, APK©, Kinetics©, JPKD®, TDM for R, and T.D.M.S. 2000™. Among these 12 programs, DataKinetics™ is no longer marketed. A website still exists for RADKinetics and the program can be downloaded, but there is apparently neither support nor updates anymore. There has been no update for JPKD® since 2007, but support is still available.

Table 2.1.1. Descriptive characteristics of the program

characteristic	MwPharm©	MM-USC* PACK©	TCIWorks	RxKinetics Programs©			JPKD®	TDM for R	Kinetidex®	TDMS 2000™	Data Kinetics™	RAD Kinetics
				Antibiotic Kinetics©	APK©	Kinetics©						
Author(s)	D.K.F. Meijer, et al.	R.W. Jelliffe, M. Neely, A. Bustad	S. Dufull, PhD L. Van Den Berg, C. Kirkpatrick	R. Tharp	R. Tharp	R. Tharp	Y. Lee, J.M. Lai Y.H. Lu et al.	M. Chen, Y. Lee	R.K. Klasco (and authors of SimKin Program)	P. O. Anderson, A. Gupta	NA	R. Rademacker
Company/ Institution	University of Groningen (developer), Faculty of Medicine of Charles University, Pragues and Mediware (marketer)	Laboratory of Applied Pharmacokinetics, School of medicine, USC	School of pharmacy, University of Otago School of pharmacy, University of Queensland	School of pharmacy and health profession, Creighton University	School of pharmacy and health profession, Creighton University	School of pharmacy and health profession, Creighton University	Graduate College of Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung	Graduate College of Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung	Thomson Reuters	Healthware Inc.	MDK Inc. Developper, ASHP Marketer	NA
Location of company/ Institution	The Netherlands / Czech Republic	USA	New Zealand / Australia	USA	USA	USA	Taiwan	Taiwan	USA	USA	USA	USA
Date of the first version	1991	1973	2010	1999	1999	1986	2006	2006	NA	1986	NA	NA
Version reviewed	4.0	15.2	1.0	2.3.9	3.5.3	2.2.5	3.0	2.2.1	11	11.02	5.0.15	2.0.1
Computer language of the source program	C#	C++ / Matlab	Java	Pascal	Pascal	Visual Basic	Java	R	NA	C++	NA	NA
Still marketed	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Websites	mediware.cz	lapk.org /software.php	tciworks.info	rxkinetics.com	rxkinetics.com	rxkinetics.com	jkpd.kmu.edu.tw/jpkd/	pkpd.kmu.edu.tw/tdm/	truvenhealth.com/products/	tdms2000.com		showcase.netins.net/web/radman/

NA not available

Table 2.1.2. Features of the programs: general characteristics

Characteristic	MM-USC *Pack©	MwPharm©	TCIWorks	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	T.D.M.S. 2000™	Data Kinetics™	RAD Kinetics
User Interface												
Platform	Windows®	Windows®	Windows® / Mac® / Linux	Windows® / mobile device (no iOS®) / Mac® / Linux	Windows® / Mac® / Linux	Windows®	Windows® / mobile device	Windows® / mobile device	Windows®(no international version)	Windows®	Windows® / mobile device (no iOS®)	Windows® (old version)
User friendliness	Need practice	Need practice	Need practice	Very easy	Not user friendly	Very easy	Very easy	Very easy	Easy	Need Practice	Easy	Easy
Clinical manual	No	No	Limited	No	No	Yes	Yes	Yes	Yes	Limited	Limited	No
Interfacing												
	No	Yes, with Mirth™ Connect technology	No	No	No	Yes, only to collect some patient data	Yes, only to collect some patient data	Yes, only to collect some patient data	No	No	No	No
Storage												
Patient records / Database	Yes, on local files (no real database)	Yes	Yes	No	No	No	Consultations only	Yes	Yes	Yes	Consultations only	Consultations only
Report generation												
	Yes	Yes, customizable	Yes, customizable	Yes	No	Yes	Yes, customizable	Yes, customizable	Yes, customizable	Yes, customizable	Yes, customizable	Yes
Cost[a]												
	Donation US$595	US$1,530	Free	Free	Free	US$125	US$150	US$250	US$1,520 annually	US$600 annually	US$900	US$100
Computational aspect												
GUI	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Data import / export	Export	Export	No	Export	No	No	Administrative data only	Administrative data only	No	No	No	No
Technical manual	Sparse	Yes	Getting started guide	Yes	No	Yes	Yes	Yes	Yes	Getting started guide	Yes	No

GUI graphical user interface

[a] Cost indicated for a single seat license

Table 2.1.3. Features of the programs: pharmacokinetics

Feature	MM-USC *Pack©	Mw Pharm©	TCI Works	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	TDMS 2000™	Data Kinetics™	RAD Kinetics
Population and drugs												
Add drug model interface	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	No
Models												
A priori regimen proposal	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Bayesian analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No
First dose handled	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	No	No
Non steady state situation handled	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Modularity												
Possibility of user-defined parameters	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No
User-defined boundaries value target	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Plot												
PK Plot generation	Yes	Yes	Yes	Not for all drugs	No	Yes	Yes	Yes	Yes	Yes	Yes	No
Percentiles	Yes	No	No	No	No	No	No	No	No	No	No	No
Various												
Creatinine clearance calculation	Jelliffe	Cockroft & Gault	Cockroft & Gault	None	None	Cockroft & Gault / Schwartz / Jelliffe	Cockroft & Gault / MDRD / Schwartz / Jelliffe / Salazar & Corcoran	Cockroft & Gault / MDRD / Jelliffe / Salazar & Corcoran	Cockroft & Gault / Schwartz	Cockroft & Gault / Schwartz	Cockroft & Gault / Schwartz / Jelliffe	Cockroft & Gault

MDRD Modification of Diet in Renal Disease, *PK* pharmacokinetic

II.1.3.3. Software requirements and individual characteristics

General characteristics

Nowadays, all of the recent program versions run on the Windows® operating system (Microsoft Corp., Redmond, WA, USA). Kinetidex® runs only on US-English Windows®. Kinetics© is sold only in the USA, Canada and the UK (as it uses a dot to separate decimals instead of a comma as in other countries). As users of personal digital assistants, smartphones and Mac® computers (Apple, Cupertino, CA, USA) dramatically increased over the last few years; this should also be taken into consideration. At present, JPKD®, APK© and Kinetics© have developed an application for mobile devices. TCIWorks, JPKD® and TDM for R can be run on Mac OS X® environment (Apple). The Internet is the most rapid and convenient media for presentation and distribution of software. All of the software packages are hosted on websites, ranging from a simple advertisement for Kinetidex® to a comprehensive source of information with technical information, including teaching topics and/or screenshots, for JPKD® or MM-USC*PACK©. Most programs are easy to download through the Internet, at least as demonstration versions. The importance of support documentation should not be underestimated and a user manual should be part of the software bundle. Technical and sometimes clinical manuals are included with most software packages. However, there is a large discrepancy between software, ranging from a 'getting started' guide for T.D.M.S. 2000™, MwPharm© or TCIWorks, to a comprehensive manual directly integrated into the software withword search capability for the RxKinetics©, DataKinetics™ and Kinetidex® programs. In addition to documentation, JPKD® and TDM for R publish video demonstrations on their respective websites. Kinetidex® and DataKinetics™ also provide sample cases that are included in their documentation. Only a few of the programs include information on drugs' pharmacokinetics, or even sometimes TDM itself (e.g. the RxKinetics© programs and DataKinetics™). In addition, convenient contact details for support are important. The RxKinetics© programs and the new version of MM-USC*PACK© (now known as RightDose™) also offer access to a users' forum for

questions and discussions. Another requirement for TDM software is the ability to interface with laboratory information management systems, especially for collecting blood drug concentrations, receiving administrative and clinical patient data, and sending reports to patient's electronic records. Although interfacing with hospital information systems may be challenging, since they differ worldwide, initiatives such as Health Level Seven International (HL7; http://www.hl7.org/) aim to standardize electronic health data transfer. Additionally, interfaces have been developed in recent years for applications that do not support HL7 standard and thus allow interoperability. MwPharm© is the only program that can be relatively easily interfaced with hospital information systems through the Mirth™ Connect technology (Mirth Corp., Irvine, CA, USA). For administrative and some demographic data, the software designers behind RxKinetics© have developed a basic interface to allow a health information system to dump such data into the software. Users may ideally wish to record their patients' administrative and clinical data, as well as concentration measurements and predictions issued. MwPharm©, TCIWorks, Kinetics©, Kinetidex® and T.D.M.S. 2000™ have full patient databases that store patients' administrative data, as well as dosages and drug concentration results that were entered for dosage individualization. USC*PACK© does not have a fully integrated database but can save patients' data on a local file on the user's personal computer. Some other programs only have an administrative database that records patients' basic data. Another issue is the confidentiality of data: APK®, Kinetics© and MwPharm© use an encrypted database. Software must be able to generate reports that can be transmitted to physicians and have the ability to save the possible associated advice consultation into the patient's medical records. Quality and readability of the report generated vary widely between programs, from TDM reports that are not transmissible to physicians to clear, printable reports with a highly structured core (it should be noted that TDM for R does not generate any kind of report). Essential information comprises patient administrative and clinical data, history of drug dosages and concentration measurements, and a clearly readable pharmacokinetic interpretation. In addition,

some reports can include a free text field that can be filled in by the consultant. Reports ideally need to be customizable to better meet each institution's visual identity guidelines. Another important issue that users face during the choice of software is its cost. Surprisingly, costs are not consistently weighted with regards to software capabilities. Some are free (TCIWorks, JPKD®, TDM for R), others are subject to a one-off donation (MM-USC*PACK©), while others require a first-year subscription fee followed by a license charge for subsequent years, which basically includes provision for updates. Graphical user interface (GUI) is a must-have nowadays. Each program has a unique graphical design that makes it more or less user-friendly but definitely facilitates navigation across windows, files or menus. Only TDM for R is based on a command-line interface. For research purposes, import/export capabilities could represent a valuable feature. Few programs offer this facility: JPKD® allows for exporting data in comma-separated variables (CSV) format; MwPharm© offers import and export possibilities in structured text (TXT) format; extraction of administrative data is possible from APK©, in CSV format, but as it concerned only administrative data, it was not considered as data exportation for the purpose of this evaluation. APK© was noted to have the best result in the 'general characteristics' category, closely followed by MwPharm© (Table 2.1.4). APK© offers a simple solution and is remarkably flexible, particularly for non-experienced users, while having a favourable cost–quality ratio. MwPharm© and TCIWorks also offer many interesting features but represent more sophisticated tools.

Table 2.1.4. Weighted scores for each category and overall category rounded to unit and ranking

	MM-USC *Pack©	Mw Pharm©	TCI Works	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	TDMS 2000	Data Kinetics™	RAD Kinetics
General characteristics												
User interface	79 (10)	95 (4)	89 (7)	90 (6)	73 (11)	105 (3)	111 (1)	106 (2)	92 (5)	80 (9)	83 (8)	61 (12)
Interfacing	13 (5)	26 (1)	13 (5)	13 (5)	13 (5)	18 (2)	18 (2)	18 (2)	13 (5)	13 (5)	13 (5)	13 (5)
Storage	34 (7)	46 (1)	30 (8)	16 (10)	16 (10)	16 (10)	46 (2)	46 (2)	36 (5)	34 (6)	37 (4)	29 (9)
Report	16 (10)	58 (1)	45 (7)	36 (8)	13 (12)	34 (9)	56 (2)	56 (2)	50 (6)	50 (6)	53 (4)	16 (10)
Cost	26 (4)	19 (8)	28 (3)	23 (6)	23 (5)	23 (5)	28 (1)	28 (1)	12 (12)	19 (8)	16 (10)	16 (11)
Computational aspects	60 (3)	59 (4)	78 (1)	66 (2)	53 (10)	58 (5)	58 (5)	58 (5)	51 (11)	55 (9)	58 (5)	41 (12)
Total	228 (10)	304 (3)	284 (4)	244 (9)	191 (11)	253 (7)	317 (1)	311 (2)	253 (6)	251 (8)	259 (5)	176 (12)
Pharmacokinetic aspects												
Population and drug	59 (7)	76 (1)	60 (6)	70 (2)	40 (11)	53 (9)	65 (3)	56 (8)	62 (3)	63 (4)	49 (10)	33 (12)
Models	191 (1)	179 (3)	184 (2)	120 (9)	117 (10)	139 (8)	148 (7)	153 (6)	174 (4)	174 (4)	117 (5)	98 (12)
Modularity	48 (7)	43 (8)	53 (1)	53 (1)	33 (11)	48 (4)	48 (4)	48 (4)	49 (3)	39 (9)	33 (11)	38 (10)
Plot	42 (1)	34 (3)	37 (2)	26 (10)	15 (11)	32 (6)	32 (6)	32 (6)	34 (3)	34 (3)	32 (6)	15 (11)
Various	22 (9)	34 (2)	25 (7)	19 (11)	19 (11)	25 (5)	25 (5)	23 (8)	31 (4)	33 (3)	35 (1)	20 (11)
Total	363 (2)	366 (1)	358 (3)	288 (9)	225 (11)	297 (8)	317 (6)	311 (7)	350 (4)	342 (5)	266 (10)	204 (12)
Authors												
Expertise of authors	51 (1)	51 (1)	49 (3)	32 (9)	32 (9)	37 (6)	37 (6)	37 (6)	23 (12)	42 (5)	42 (4)	32 (9)
Global score	641 (5)	720 (1)	692 (2)	564 (10)	448 (11)	587 (8)	671 (3)	659 (4)	627 (7)	636 (6)	567 (9)	412 (12)

All data given as weighted score (rank). Rankings were given from1 for the best classified to 12 for the worst classified

Pharmacokinetic aspects

The number of drugs covered by each program varies from two for RADKinetics to more than 180 for MwPharm© (**Table 2.1.5**). The drug of interest can be chosen in the library offered by the program. For some programs, even definitions of specific populations for drug use are available (e.g. neonates). Few programs take into account drug and/or disease interactions: T.D.M.S. 2000™, MwPharm©, JPKD® and Kinetidex®. Moreover, in the last decade, important progress has been achieved in the field of pharmacogenetics, which can be used for a priori dosage regimen adaptation in some clinical situations [24]. Integrating a TDM and pharmacogenetics approach therefore appears more and more suitable for optimization of pharmacotherapy in the context of

personalized medicine [25, 26]. Additionally, some food-drug interactions are progressively being discovered, which involve various mechanisms such as an increase or decrease of bioavailability or an induction or inhibition of metabolism [27, 28]. The most famous examples are probably those involving grapefruit or alcohol [29]. When sufficiently described and quantified, pharmacogenetic features and these interactions should certainly be included in TDM programs in the near future. A fundamental pharmacokinetic aspect of programs concerns the possibility for the user to add their own drug models. In eight programs (MwPharm©, MM-USC*PACK©, TCIWorks, Antibiotic Kinetics©, APK©, Kinetics©, JPKD®, T.D.M.S. 2000™), a new model for a drug or a population can be defined within an 'add drug model interface' provided, by entering model parameters either from a single population pharmacokinetic study or from a systematic pharmacokinetic review of studies. For example, APK© offers pre-defined parameter fields using a one-compartment model where the values have to be entered, whereas some other programs can handle multicompartmental models or different types of administration. USC*PACK© employs a non-parametric adaptive grid (NPAG) program[30], which makes it more complicated for non-experienced users but has the great advantage of accommodating any kind of model of up to three compartments. Conversely, TCIWorks offers a very simple and intuitive tool for the user to add his/her own model of up to two compartments. Moreover, it offers the possibility to freely import and export drug models plugged in as extensible markup language (XML) data format and thus easily shares drugs models. APK©, Antibiotic Kinetics© and RADKinetics account only for intravenous administration owing to the fact that drugs handled by these programs are only given through this route of administration. Only the more sophisticated packages (i.e. MM-USC*PACK©, TCIWorks, MwPharm©, Kinetidex®, T.D.M.S. 2000™) are able to handle data for drugs administered by continuous intravenous infusions. Those same programs are also able to deal with non-steady state and irregular regimens, which represents a substantial feature. In fact, they offer a convenient interface to enter concentrations with detailed information on dosage history. It is

worth noting that APK© and Kinetics© can deal with non-steady state situations, but require three concentration–time data points. APK© is also able to deal with a first dose, but requires at least two concentration–time data points to perform calculations, and would not use a Bayesian analysis in that case, but rather a simple regression approach. It is crucial that programs document the prediction and individualization methods employed to ensure accuracy and appropriateness. Equations are, however, detailed in only a minority of support sources, namely in T.D.M.S. 2000™, DataKinetics™, MwPharm© or RxKinetics©. Whereas in the 1990s only half of the programs offered Bayesian prediction [12], nowadays such approaches are widely implemented; ten of 12 programs offer such techniques. This is particularly convenient for routine practice because of the limited number of samples required and the flexibility of sampling times. It is worth noting that only MM-USC*PACK© uses a non-parametric approach, which provides the advantage of assuming no distribution and of allowing subpopulation clusters[31], which is not easily achievable with normal or log-normal distribution assumptions [32]. Nine of the computer tools are able to compute an a priori regimen and, among those, seven are also able to estimate a loading dose. For users who would not know concentration targets, default therapeutic range targets are often provided by the software. To be easily used according to up-to-date institution recommendations or specific patient cases, therapeutic targets should be readily modifiable, which is the case in most software packages. Pharmacokinetic curve plotting is offered by all software except JPKD® (which proposes it only for aminoglycosides), RADKinetics and TDM for R. Only MM-USC*PACK© offers the option to include the population variability through adding percentiles to plots. From a clinical point of view, it is essential that clinicians be aware of the creatinine clearance of certain drugs. Many programs, in addition to Cockroft-Gault, suggest other creatinine clearance calculations such as Schwartz, Cockroft-Gault adjusted to bodyweight, MDRD or Jelliffe's equations. TDM for R and JPKD® do not provide this parameter. Regarding this 'pharmacokinetic aspects' category, the most

sophisticated programs had the highest scores: MwPharm©, MM-USC*PACK© and TCIWorks (**Table 2.1.4**).

Authors

All programs have been developed by pharmacists and/or medical doctors, usually supported by skilled computer specialists. They were all developed in an academic environment (except perhaps for Kinetidex®, for which no information could be obtained). TCIWorks received grant support from a pharmaceutical company (Pfizer) among other academic sponsors. Only two programs have been described in the literature in the past (USC*PACK© [21] and MwPharm© [19]), but the publications concern old versions. Literature regarding the use of the programs is also quite poor. However, among the literature that does exist, USC*PACK© is the best furnished, particularly regarding its use in clinical practice [33-36]. TCIWorks has also recently started to be documented as well [37, 38].

2.1.3.4. Clinical vignettes

Clinical vignettes were tested in each program whenever possible (see **Table 2.SIII** in the online Resource), in order to again insight into dose adjustments and predicted concentrations. These results are only presented for descriptive purposes. As much as possible, vignettes were entered into each program in the same manner. However, difficulties were encountered, such as (i) introduction of a first dose or interruption of treatment, especially when a dosing interval or a delay before restarting treatment was indicated; (ii) drug administered in neonates and low bodyweight patients; and (iii) administration by continuous intravenous infusions. Nevertheless, when vignettes were able to be processed, most of them roughly converged to a similar prediction, except for phenytoin (a drug characterized by non-linear kinetics), where extrapolated concentrations were aberrant in some programs.

Table 2.1.5. Drugs supported by the programs

Drug	MM-USC *PACK©	Mw Pharm©	TCI Works	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	TDMS 2000™	Data Kinetics™	RAD Kinetics
Cardiovascular system												
Digoxin		✓		✓	✓			✓	✓	✓	✓	
Quinidine		✓								✓		
Procainamide		✓										
Others		42										
General anti-infectives for systemic use												
Ceftazidime		✓										
Aminoglycoside				✓	✓						✓	
Streptomycin		✓										
Tobramycin	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	
Gentamicin		✓	✓	✓		✓	✓	✓	✓	✓	✓	✓
Amikacin	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	
Netilmicin		✓				✓	✓	✓			✓	
Vancomycin	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓
Kanamycin		✓										
Indinavir				✓	✓							
Ritonavir				✓	✓							
Zidovudine		✓										
Enfuvirtide				✓	✓							
Others		36								3		
Antineoplasic and immunomodulating agents												
Imatinib mesylate				✓	✓							
Ciclosporine		✓		✓	✓							
Tacrolimus				✓	✓							
Everolimus				✓	✓							
Sirolimus				✓								
Others		10										

Table 2.1.5. (continued)

Drug	MM-USC *PACK©	Mw Pharm©	TCI Works	JPKD®	TDM for R	Antibiotic Kinetics©	APK©	Kinetics©	Kinetidex®	TDMS 2000™	Data Kinetics™	RAD Kinetics
Nervous system												
Acetylsalicylic acid (aspirin)		✓										
Paracetamol		✓										
Phenobarbital		✓								✓		
Phenytoin		✓		✓	✓					✓	✓	
Carbamazepine	✓	✓		✓	✓							
Valproic acid	✓	✓		✓	✓				✓			
Lithium		✓		✓	✓					✓		
Others		42										
Respiratory system												
Theophylline		✓		✓	✓				✓	✓	✓	
Aminophylline					✓			✓				
Oxtryphilline					✓							
Others		2										
Miscellaneous												
Others drugs		30					1	2				
Other one compartment							✓			✓	✓	

Drug classified according to WHO Anatomical Therapeutic Chemical classification

✓ Drug handled by the software

II.1.3.5. Overall classification

From a global benchmarking point of view, MwPharm© and TCIWorks turned out to be the best ranked TDM programs. Because they represent sophisticated tools, they fulfil many of the criteria considered: both are complete software offering calculation of patient parameters, a priori and a posteriori dose suggestions, a structured patient database and good quality reports. However, such tools can be rather complex to use, which is especially true for MwPharm©, whereas TCIWorks is more intuitive. MwPharm© benefits from a large drug library, but, unfortunately, no description of the drug models is available, which means that not all drugs are easily usable. TCIWorks does not have a drug library yet. USC*PACK© should also be considered as a comprehensive software; however, despite its large number of users worldwide, it lacks user friendliness and flexibility compared with other programs and provides no structured database or report transmissible to practitioners. The success of the software definitely lies in its good pharmacokinetic capabilities and its long experience. The three RxKinetics© programs, Antibiotic Kinetics©, APK© (the third best classified program) and Kinetics©, offer simpler but very flexible solutions, particularly for non-experienced users, with a good cost/capabilities ratio. Antibiotic Kinetics© is the least sophisticated of the three, and is unable to save any patient or consultation data. APK© and Kinetics© provide patient records and reports of good quality. These computer tools aim to deal with daily clinical practice. T.D.M.S. 2000™ and Kinetidex® also offer nice features with Bayesian analysis, a database, and the ability to detail complete patient dose administration and concentration measurements. However, these programs are expensive. User friendliness could be improved for most software, especially T.D.M.S. 2000™. JPKD® and TDM for R allow a simple adaptation from a single measurement at steady state. JPKD® is a simple, intuitive, convenient and free tool. Conversely, TDM for R requires the user to already be an experienced R user.

II.1.4. Discussion

Overall, for many years now, lots of effort has been put into the development of computer tools throughout the world to facilitate the practice of TDM and to provide reliable dosing optimization advice with convenient and complete software. This article presents a comprehensive review of the characteristics of the available software. From simple, efficient and low-cost programs (JPKD®, APK©) to comprehensive packages (MwPharm©, TCIWorks, USC*PACK©), the panel of available tools is fairly variable. Each software tool must be regarded with respect to the individual needs of hospitals or clinicians. Major limitations to achieve this benchmark probably reside in the uniqueness associated with each of these programs. Depending on the intended users, specific TDM practice, whether it is to be used in clinical research or not, etc., a certain tool would better fit one institution than another. In this article, we followed a general and consensual strategy, and our grid focuses on all aspects that we considered, as clinical pharmacologists, as being required by an 'ideal' TDM software tool for a large population of potential users. The weight assigned, by three different types of professionals (physicians, pharmacists, computer engineers), attempts to balance these aspects of the tools. This should, however, not prevent individual users from defining their own weighting factors (even 0) for **Table 2.SII** in the Online Resource and to obtain a global score that would better reflect their own needs. Our grid, used to rank the software, is a complete and detailed list describing characteristics of the programs assessed; however, it only focuses on dosage optimization in the context of TDM. Thus, it may possibly have missed some features that make each program unique. MwPharm© and TCIWorks were found to provide optimal characteristics for TDM but to represent sophisticated tools that offer detail beyond the traditional needs for drug adjustment. For simple adaptation based on one concentration, simpler tools such as JPKD® or APK© may be sufficient for many clinicians. TCIWorks is in an early stage of its development and looks promising. It has more flexibility and is more intuitive for users than most other programs presented in this review. Its developers aimed to implement target concentration intervention

(TCI) rather than TDM. TCI is an evolving concept that proposes targeting of a concentration associated with a desired effect rather than a traditional therapeutic range [39]. Moreover, future versions of TCIWorks should include the possibility to add a pharmacodynamic block to models. Although MM-USC*PACK© was not among the best ranked programs, it is used worldwide and is still often considered as a reference for precision and prediction (MwPharm© [40] or Abbottbase PKS [41] were previously compared to it). Moreover, in addition to the clinical interface for dosage adjustment, USC*PACK© offers a full modeling tool employing the NPAG algorithm. Customized pharmacokinetic/pharmacodynamic models can be built up through a graphical approach by placing boxes on the screen and connecting them with arrows (USC*PACK BOXES). Additionally, USC*PACK© also offers programs for infectious disease and cardiology. Finally, new features are under development (interfacing, database search function, and drug and disease interactions). It is also worth noting that other types of tools than stand-alone TDM programs do exist. A good example is the ISBA ImmunoSuppressant Bayesian dose Adjustment) web portal from Limoges University Hospital in France (https://pharmaco.chu-limoges.fr/), which proposes TDM adaptation for ciclosporin, tacrolimus, mycophenolate mofetil and, coming soon, for aminoglycosides and glycopeptides, methotrexate and anticancer agents. When dosage adjustment for one of these drugs is desired, the user fills in a data entry sheet on the portal to give information about patient clinical evolution, the context of the request, drug intake and blood drug concentration. Adaptation is then proposed based on Bayesian estimation and validated by a pharmacologist. It is then sent to the applicant via an electronic standardized report, normally in 24 h. A similar portal exists for fluorouracil dosage optimization, called ODPM (Onco Drug Personalized Medicine), which has been developed by the Cancerology Institute of the West Paul Papin and University of Angers, France (http://www.odpm.fr/). Web portals could therefore represent an alternative to autonomous software despite their requirement of remote human third-party intervention. Bayesian dosing optimization is widely applied now, being considered the gold standard. For instance, the

pharmacokinetic Bayesian method is recommended in the ‘‘Australian Therapeutic Guidelines: Antibiotics’’ [42, 43] . The use of this approach allows computation of a priori dosage regimens based on the individual’s characteristics, the use of random time sampling, performance of clinical interpretation in non-steady-state situations, and more accurate predictions [44]. However, such complex mathematical calculations would not be possible without computer tools, and this is why all currently marketed TDM programs now integrate it. To date, the usefulness of TDM remains controversial, with studies showing positive, negative or no significant impact on patient outcomes [45]. Despite the heterogeneity of the data, TDM services have been used since the 1970s in clinical practice, after some early trials with lithium and digoxin in the 1960s [1, 45]. This has been encouraged by the introduction of computerization, especially in Europe (notably in The Netherlands [46]), Australia [47] and the USA [48, 49]. Computer-assisted advice should indeed be part of a global multidisciplinary TDM strategy, as foreseen some decades ago [50]. Even though it was reported that unassisted clinicians tend to use suboptimal loading, maintenance and total doses than when computer support is available [5, 51], dosage optimization programs do not replace clinicians with pharmacokinetic skills. Physicians and other specialists involved in patient care should be aware of the potential of TDM and increasingly take advantage of these powerful computer tools. In the late 1990s, Bates emphasised the importance of educational approaches to change physicians’ opinions and interventions, in addition to the efficiency of computer tools [52]. Despite the growing availability of dosage adjustment tools, there is still room for improvement. Programs should ensure user friendliness through smart design and flexibility, enabling easy and quick use in routine activities, including by non-experienced users. Expected pharmacokinetic variability should be displayed, e.g. via visual representation of percentiles. More importantly, to be used in hospitals, the program should interface with other applications, in particular with laboratory information management systems, patient administrative databases and electronic medical records. Moreover, the ability to export data should enable further research. Accurate

Bayesian approaches should be routinely preferred for optimal dosing regimen prediction. Comprehensive but clear and pedagogical printed reports, customizable for institutions, should be produced. Support should ideally be provided both by the developers and by a community users group, with access to clinical and technical documentation. Finally, TDM applications should become easily portable to ubiquitous and user-friendly mobile devices, in order to be used directly at the point of care, at the patient's bedside [53] or even by the patients themselves.

II.1.5. Conclusion

While the 12 presently available TDM programs reviewed here reveal an encouraging evolution, none of them yet fulfils all of the requirements of an ideal tool [8]. The major challenge currently is to develop programs with comprehensive clinical and research capabilities, while still showing simplicity, flexibility and user friendliness that would make these tools easy to run by all types of users.

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Supplementary Material 1

Table 2.SI: Mark definition of the evaluation grid

From 5, the highest performance to 1, the lowest performance	
1. General characteristics	
a) User interface and utilization	
Platforms supported (*Windows, MacOS, Unix/Linux, iOS, webOS, Android, Symbian*)	**1** = DOS **2** = Windows but old version or not international version **3** = Windows **4** = Windows + (mobile device *or* Linux and Mac) **5** = Windows + mobile device + Linux + Mac
Easy download through Internet	**2** = No (or not online, CD Rom) **4** = Yes
Easiness of installation	**1** to **5** :1 = Difficult, 5 = very easy
Network installation	**2** = No **4** = Yes
General user friendliness	**1** to **5** :1 = Not user friendly, 5 = most user friendly
Global visual appeal	**1** to **5** :1 = not visually appealing; 5 = visually appealing
Wizard step-by-step interface for inexperienced users	**1** = No **3** = Few wizard for basic step **5** = Clearly with ordered wizard for each step
Multiples languages localizations (*en, fr, es, others*)	**2** = No **4** = Yes
Possibility of new language insertion by users	**2** = No **4** = Yes
Multiple users accommodation (*users database; password*)	**1 =** No password **2** = Administrator login **3** = Password to protect the patient database **4** = Login for the program (and possibly plus a password). Password for specific features, particularly database edits (patient, drug, user base). Possibility to add user **5** = Password for database protection and possibility for every user to have its own database. Administrator login for specific features (drug model for example). Password for the program available on request
Quality of clinical manual	**1** = No clinical manual **3** = No specific clinical data, precision of what equation for which drug. Suggestion of volume of distribution for example **5** = Well documented. Easy accessible with information available for each drugs
Web support	**1** = Bad **2** = Many things not working in it **3** = Simple commercial advertisement **4** = Good, but no screenshots **5** = Good, with screenshots o*r* good, no screenshot, but with thumbnails linking to teaching documentation
Possibility of easy contact with the company/authors	**1** = No **2** = Support website has several broken links. Difficult to contact a real person **3** = Yes initially, then progressively more difficult to find support with clear answers **4** = Yes, but sometimes difficult to find the correct person to contact for help with specific issues **5** = Yes
User group active on Internet (*forum, blog, usenet*)	**2** = No **4** = Yes

b) Interfacing	
Lab software interfacing to collect concentration measurements	**2** = No **4** = Yes
Medical record interfacing to collect patients' administrative and clinical data	**2** = No **4** = Yes
Interfacing with medical information systems to issue reports	**2** = No **4** = Yes
c) Storage	
Patient historical record	**1** = No records are saved **2** = Administrative data are saved **3** = Consults/Report saved, can be loaded; display, in the search field, the dose that has been proposed **4** = Consults saved, can be loaded; display, in the search field, the dose that has been proposed. If printed, PK parameters are saved **5** = Records are stored (concentrations included)
Database search by patient, drug, date, user, free text…	**1** = No database **2** = File Name **3** = Sorted either by ID or by patient (user's choice) / or patient browsing / or by patient name and patient number **4** = Drug and patient **5** = By patient, drug, date, medical record, simulation name
Storage of user identity	**1** = No record of the user **3** = If indicated for the consult **5** = Yes (with login)
Tools for statistics of use	**2** = No **4** = Yes
Encoded database	**1** = No database **2** = Not encrypted **3** = password protected **4** = Password protected if desired **5** = Encrypted
Possibility of data collection in a remote central database and confidentiality	**2** = No **4** = Yes
d) Report	
Global readability	**1** = No report **2** = Information available but not clearly presented. Not transmissible as it stands in the ward **3** = Information is classified into sections, but not well (include patient data and recommendations). Readability could be improved **4** = Information is classified into sections (include patient data and recommendations) **5** = Easily readable, customizable, all essential information present
Inclusion of PK plot	**1** = No **3** = Only for some drugs **5** = Yes
Inclusion of a free text field	**1** = No **3** = Note box printed in the report, but must be filled out by hand **5** = Note box can be edited directly in the software. Comments will be printed in the report
Display of user identity	**1** = No **2** = Devoted space on the printed consult, but it must be filled in by hand **3** = Yes, asked just before printing or name indicated as a consultant (also asked before to be integrated in the consult) **4** = Yes, the name of the person logged is printed in the consult or the name indicated as the consultant **5** = Institution logo display

d) Report (continued)	
Customizable template	**1** = No **2** = Word document generated that can be modified **3** = Header, footer **4** = Header, footer, logo **5** = Header, graph in option, predefined comments that can be customized, many items to tick that will be printed
Conversion	**1** = No conversion, no PDF **3** = PDF Format **5** = More formats
e) Cost	
Price of a standard license (over 5 years)	**1** = Very expensive (≥ 5000 $US) **2** = Expensive (2000 – 4999 $US) **3** = Medium (500-1999 $US) **4** = Cheap (< 500 $US) **5** = Free
Academic license at reduced cost	**2** = No **4** = Yes
Maintenance contract proposed	**1** = No **2** = Included in a paid contract **3** = Updates on websites **4** = Updates button implemented in the software, that check directly online (free) / to download on website **5** = Updates button implemented in the software + email sent let us know (free)
f) Computational aspects	
List of changes and bug fixes between versions	**2** = No **4** = Yes
Access to previous versions	**2** = No **4** = Yes
Availability of program sources	**2** = No **4** = Yes
Graphic user interface (GUI) tools embedded	**2** = No **4** = Yes
Necessity of a runtime framework support (Java, .NET, VBRUN, SQL based…)	**2** = Yes **4** = No
Capacity of structured data import	**1** = No **3** = Yes, TXT, Access™ or CSV format **5** = Yes, TXT, Access™ or CSV format and XML format for models
Capacity of structured data export	**1** = No **3** = Yes, TXT, Access™ or CSV format **5** = Yes, TXT, Access™ or CSV format and XML format for models
Verbose bug output to user	**1** = No **3** = Yes, but not easily understandable **5** = Yes
Quality of technical manual	**1** = No technical manual **2** = Basic **3** = Exists but is difficult to find (scattered) **4** = Getting started guide good but difficult to find in-depth information **5** = Clear and easy to find. Index. Comprehensive

2. Pharmacokinetic aspects	
a) Population and drug	
Number of drugs	**1** = Gentamicin + vancomycine **2** = Aminoglycoside + / - vancomycine **3** = Aminoglycoside + classic drugs requesting TDM (for example digoxin, lithium, phenytoin …) **4** = Aminoglycoside + classic drugs that need TDM + anti-HIV / anti-cancer drugs **5** = Many drugs (all kind)
Definition of different populations	**1** = No different population **2** = Very basic (edit drug model suggest different doses for pediatrics and adults) / Vd adapted with corrected factor for elderly and obese (age, weight) **3** = Different population (disease) **4** = Different population (disease) and CRT clearance calculation with Schwartz or (Cockcroft-Gault) CG formula. No interface to add our own drug/population model **5** = Yes, population taking into account age (includes neonate models) and pathology or disease state. More importantly, one can define different populations via the "add drug" interface
Standard covariates used (age, sex, body weight)	**1** = No **3** = Yes **5** = Yes with height optional (except for Schwartz calculation)
Weight range (eg obese, preterm, neonate)	**1** = Inferior range limited (< **2** kg) **3** = Large weight range but CRT clearance does not take into account age (example Schwartz formula) **5** = Large weight range and Schwartz calculation possible
Readable PK parameters sets	**2** = No or no population parameters **4** = Yes
Literature references on drug PK parameters used	**1** = No references **3** = References without any specification of the drug or drug specific references but at least some of the information is not cited. **5** = Precise references
Possibility of new drug and/or population insertion and user-friendliness	**1** = No **2** = Possible but complicated. Requires knowledge of a programming language **3** = Yes, but not flexible since only predefined parameters can be inserted **4** = Yes. Flexible, and relative simple **5** = Easy insertion
b) Models	
Compartment models	**1** = No compartment **3** = 1 compartment **5** = From 2 compartments to 3 compartments possible
IV bolus, infusion, extravascular, and other absorption models	**1** = IV bolus **3** = Oral / IM / IV bolus / Short IV infusion **5** = Oral / IM / IV bolus / Short IV infusion / Continuous IV infusion
Non-linear PK models	**2** = No **4** = Yes
A priori regimen proposal	**2** = No **4** = Yes
A priori loading dose proposal	**2** = No **4** = Yes
Number of observations that can be entered	**1** = 1 **3** = Few **5** = Unlimited (sometimes depends of the menu used)

b) Models (continued)	
Use of < LOQ observations	**2** = No **4** = Yes
Non Bayesian calculations	**2** = No **4** = Yes
Bayesian analysis capabilities	**2** = No **4** = Yes
Individual parameters generation	**1** = No **3** = Not for all drugs **5** = Yes
Concentration profile simulation (Cmax, Cmin)	**1** = Not for all drugs **3** = Yes, but no plot **5** = Yes
A posteriori regimen proposal	**2** = No **4** = Yes
A posteriori re-loading dose or treatment interruption proposal	**1** = No **3** = Yes, but does not take into account an interruption in treatment **5** = Yes
First dose handled with extrapolation to steady-state	**1** = No **3** = Option with 2 / 3 points (regression) **5** = Yes
Non-steady state situations and irregular regimens handled	**1** = No **3** = Not for all drugs or not for irregular regimen **5** = Yes
Possibility to adjust/specify the dosage and obtain concentration simulation	**1** = No **3** = Yes but not convenient, or not possible to modify the dose **5** = Yes
Possibility to re-perform population analysis from drug concentration history	**1** = No **3** = Basic (often problematic with sparse data) **5** = Interface for modeling included in the software
c) Modularity	
Possibility of new model definition	**2** = No **4** = Yes
Parameterizable covariates	**2** = No **4** = Yes
Choice between population values or user defined parameters	**1** = No or No population parameters **3** = Yes, by changing the value in the appropriate field **5** = Yes, by ticking "user defined" (default population parameters still visible)
User-defined boundaries value target	**1** = No **3** = Yes but not simple. Cannot be adapted for each case because this requires a change in the settings **5** = Yes
Default boundaries value target	**2** = No **4** = Yes
Inter-operability with other software	**2** = No **4** = Yes

d) Plot	
Generation of PK curves	**1** = No **3** = Only for aminoglycosides **5** = Yes
Prediction intervals/percentiles on PK plot	**2** = No **4** = Yes
Global on screen readability	**1** to **5** :1 = Less readable; 5 = best readable
Interactive clickable graph	**2** = No **4** = Yes
e) Various	
Capability of drug interactions integration	**2** = No **4** = Yes
Capability of disease state effects integration	**2** = No **4** = Yes
Methods of creatinine clearance calculation	**1** = No CRT clearance calculation **2** = Jelliffe **3** = Only CG **4** = CG and adjusted CG, or CG and Schwartz **5** = Many, including Schwartz, CG and adjusted CG
Concentration unit conversion and/or parameterization	**2** = No **4** = Yes

3. Expertise of authors	
Computer scientists/engineers	**1** = No **3** = Yes, single person with computing certificate **5** = Yes, team of computer scientist
Pharmacists/MDs	**2** = No **4** = Yes
Academic relations	**2** = No **4** = Yes
Industrial relations	**2** = No **4** = Yes
Scientific publications describing the software	**2** = No **4** = Yes
Published clinical research validating the software	**2** = No **4** = Yes

Supplementary Material 2

Table 2.SII.a: Evaluation Grid. General characteristics

	WT*	MM-USC Pack	Mw Pharm	TCIworks	JPKD	TDM for R	Antibiotics Kinetics	APK	Kinetics	Kinetidex	T.D.M.S	Data Kinetics	RAD Kinetics
1. General characteristics													
a) User interface and utilization													
Platforms supported (Windows, MacOS, Linux, iOS, webOS, Android, Symbian)	2.4	3	3	4	5	4	4	4	3	2	3	4	2
Easy download through Internet	1.7	4	4	4	4	4	4	4	2	2	4	4	4
Easiness of installation	2.1	4	3	3	4	4	4	4	4	4	3	3	5
Network installation	1.8	2	4	4	2	2	4	4	4	4	4	4	2
General user friendliness	2.8	3	3	4	5	2	5	5	5	4	3	4	4
Global visual appeal	2.1	3	4	5	3	2	3	3	3	4	2	4	2
Wizard step-by-step interface for inexperienced users	2.1	1	3	1	3	1	3	3	3	3	1	1	1
Multiples languages localizations (en, fr, de, es, others)	1.5	2	4	2	2	2	2	2	2	2	2	2	2
Possibility of new language insertion by users	1.3	2	2	2	2	2	2	2	2	2	2	2	2
Multiple users accommodation (users database; password)	2.2	1	5	3	1	1	1	4	4	4	1	3	1
Quality of clinical manual	2.5	1	1	1	1	1	5	5	5	5	3	3	1
Web support	2.0	5	5	5	5	5	5	5	5	3	5	2	1
Possibility of easy contact with the company/authors	1.7	5	5	4	5	5	5	5	5	3	5	2	1
User group active on Internet (forum, blog, usenet)	1.7	4	2	2	2	2	4	4	4	2	2	2	2

	WT*	MM-USC Pack	Mw Pharm	TCIworks	JPKD	TDM for R	Antibiotics Kinetics	APK	Kinetics	Kinetidex	T.D.M.S	Data Kinetics	RAD Kinetics
b) Interfacing													
Lab software interfacing to collect concentration measurements	2.2	2	4	2	2	2	2	2	2	2	2	2	2
Medical record interfacing to collect patients' description data	2.2	2	4	2	2	2	4	4	4	2	2	2	2
Interfacing with medical information systems to issue reports	2.2	2	4	2	2	2	2	2	2	2	2	2	2
c) Storage													
Patient historical record	2.9	5	5	5	1	1	1	4	4	5	5	3	3
Database search by patient, drug, date, user, free text	2.5	2	4	3	1	1	1	3	3	5	3	3	3
Storage of user identity/address	2.2	1	1	1	1	1	1	5	5	1	1	3	1
Tools for statistics of use	1.2	4	2	2	2	2	2	2	2	2	2	2	2
Encoded database	1.9	2	5	?	1	1	1	5	5	?	2	4	2
Possibility of data collection in a remote central database (confidentiality over the net)	1.9	2	4	2	2	2	2	2	2	2	2	2	2
d) Report													
Global readability	2.7	2	4	5	4	1	4	4	4	5	4	3	2
Inclusion of PK plot	2.6	1	5	5	3	1	5	5	5	5	5	5	1
Inclusion of free a text field	2.6	1	5	1	3	1	1	5	5	5	5	5	1
Display of user identity/address	2.0	1	5	1	1	1	2	5	5	2	2	3	1
Customizable template	1.5	1	4	3	1	1	1	5	5	3	5	2	1
Conversion (txt, pdf, doc)	1.9	1	3	5	3	1	1	1	1	1	1	5	1

	WT*	MM-USC Pack	Mw Pharm	TCIworks	JPKD	TDM for R	Antibiotics Kinetics	APK	Kinetics	Kinetidex	T.D.M.S	Data Kinetics	RAD Kinetics
e) Cost													
Price of a standard license (over 5 years)	2.3	3	2	5	5	5	4	4	4	1	2	3	4
Academic license at reduced cost	2.3	4	4	4	4	4	2	4	4	2	4	2	2
Maintenance contract proposed	2.4	4	2	3	1	1	4	4	4	2	2	2	1
f) Computational aspects													
List of changes and bug fixes between versions	1.8	2	2	2	4	4	4	4	4	2	4	4	2
Access to previous versions	1.6	2	2	4	2	4	2	2	2	2	2	2	2
Availability of program sources	1.7	2	2	4	2	4	2	2	2	2	2	2	2
Graphic user interface (GUI) tools embedded	2.6	4	4	4	4	4	4	4	4	4	4	4	2
Necessity of a runtime framework support (Java, .NET, VBRUN, SQL based)	1.3	4	2	2	2	4	4	4	4	2	4	4	4
Capacity of structured data import	2.8	3	3	5	1	1	1	1	1	1	1	1	1
Capacity of structured data export	2.8	3	3	5	5	1	1	1	1	1	1	1	1
Verbose of bug communication to user	2.0	5	3	5	5	3	5	5	5	5	5	5	5
Quality of technical manuals	2.5	3	5	4	5	2	5	5	5	5	4	5	2

Table 2.SII.b: Evaluation Grid. Pharmacokinetic aspect

	WT*	MM-USC Pack	Mw Pharm	TCIworks	JPKD	TDM for R	Antibiotics Kinetics	APK	Kinetics	Kinetidex	T.D.M.S	Data Kinetics	RAD Kinetics
2. Pharmacokinetic aspects													
a) Population and drug													
Number of drugs	2.6	3	5	1	4	4	2	2	3	3	3	3	1
Definition of different populations	2.8	4	5	5	5	1	2	2	2	4	4	1	1
Standard covariates used (age, sex, body weight, creatinine)	2.7	3	3	3	3	3	3	3	3	3	3	5	3
Weight range (eg obese, preterm, neonate)	2.8	3	5	3	3	3	1	5	1	5	5	5	3
Readable population PK parameters sets	2.8	4	4	4	2	2	4	4	4	4	4	2	2
Literature references on drug PK parameters used	2.6	3	3	1	5	1	5	5	5	3	1	1	1
Possibility of new drug and/or population insertion and user-friendliness	2.6	2	3	5	4	1	3	3	3	1	3	1	1
b) Models													
Compartment models (1, 2, 3 cpt)	2.4	5	5	5	3	3	3	3	5	3	5	3	3
IV bolus, infusion, extravascular, and other absorption models	2.9	5	5	5	3	3	1	1	3	5	5	3	1
Non-linear PK models	2.4	4	2	4	4	4	2	2	2	4	4	4	2
A priori regimen proposal	2.3	4	4	4	2	2	4	4	4	4	4	4	2
A priori loading dose proposal	2.3	4	4	4	2	2	4	4	4	4	4	2	2
Number of observations that must /can be entered	2.0	5	5	5	1	5	3	3	3	5	3	3	1
Use of <LOQ observations	1.8	2	2	2	2	2	2	2	2	2	2	2	2
Non Bayesian calculations	2.5	4	4	4	4	2	4	4	4	2	4	4	4
Bayesian analysis capabilities	2.9	4	4	4	4	4	4	4	4	4	4	2	2

	WT*	MM-USC Pack	Mw Pharm	TCIworks	JPKD	TDM for R	Antibiotics Kinetics	APK	Kinetics	Kinetidex	T.D.M.S	Data Kinetics	RAD Kinetics
Individual parameters generation	2.8	5	5	5	5	5	5	5	5	5	5	3	5
Concentration profile simulation (Cmax, Cmin)	2.9	5	5	5	3	3	5	5	5	5	5	1	3
A posteriori regimen proposal	3.0	4	4	4	4	4	4	4	4	4	4	4	4
A posteriori re-loading dose or treatment interruption proposal	2.5	5	5	5	1	1	1	3	3	5	5	1	1
First dose handled with extrapolation to steady-state	2.7	5	5	5	1	1	3	3	1	5	5	1	1
Non-steady state situations and irregular regimens handled	2.3	5	5	5	1	1	3	3	3	5	5	3	1
Possibility to play with adjust/specify and obtain concentration simulation	3.0	5	5	5	5	3	5	5	5	5	3	5	3
Possibility to re-perform population analysis from drug concentration history	1.8	5	1	1	1	1	1	3	3	1	1	1	1
c) Modularity													
Possibility of new model definition	2.3	4	4	4	4	2	4	4	4	2	2	2	2
Parameterizable covariates	2.5	4	2	4	4	2	2	2	2	2	2	2	2
Choice between population values or user defined parameters	2.6	1	3	3	3	1	3	3	3	5	3	1	1
User-defined boundaries value target	2.6	5	3	5	5	5	5	5	5	5	5	5	5
Default boundaries value target	2.4	4	4	4	4	2	4	4	4	4	2	2	4
Inter-operability with other software	1.7	2	2	2	2	2	2	2	2	2	2	2	2

	WT*	MM-USC Pack	Mw Pharm	TCIworks	JPKD	TDM for R	Antibiotics Kinetics	APK	Kinetics	Kinetidex	T.D.M.S	Data Kinetics	RAD Kinetics
d) Plot													
Generation of PK curves	2.9	5	5	5	3	1	5	5	5	5	5	5	1
Prediction intervals/percentiles on PK plot	2.6	4	2	2	2	2	2	2	2	2	2	2	2
Global on screen readability	2.6	5	4	5	3	1	3	3	3	4	4	3	1
Interactive clickable graph	1.9	2	2	2	2	2	2	2	2	2	2	2	2
e) Various													
Capability of drug interactions integration	1.9	2	2	2	4	4	2	2	2	4	4	4	2
Capability of disease state effects integration	2.1	2	4	2	2	2	2	2	2	4	4	4	2
Methods of creatinine clearance calculation	2.5	2	5	3	1	1	5	5	4	4	5	4	3
Concentration unit conversion and/or parameterization	2.3	4	4	4	2	2	2	2	2	2	2	4	2

* WT = weight applied

Table SII.c: Evaluation Grid. Expertise of authors

	WT*	MM-USC Pack	Mw Pharm	TCIworks	JPKD	TDM for R	Antibiotics Kinetics	APK	Kinetics	Kinetidex	T.D.M.S	Data Kinetics	RAD Kinetics
3. Expertise of authors													
Computer scientists/engineers	2.4	5	5	5	1	1	3	3	3	5	3	5	1
Pharmacists/MDs	2.5	4	4	4	4	4	4	4	4	?	4	4	4
External relations: Academic	2.2	4	4	4	4	4	4	4	4	?	4	4	4
External relations: Industrial	1.3	2	2	4	2	2	2	2	2	2	2	2	2
Scientific publications describing the software	2.0	4	4	2	2	2	2	2	2	2	2	2	2
Published clinical research validating the software	2.3	4	4	4	2	2	2	2	2	2	4	2	2

* WT = weight applied

Supplementary Material 3

Clinical vignette presentation

Gentamicin Vignette (1)

SL is a 15-year old girl (born July, 1997) with cystic fibrosis. She weights 49.5 kg and is 155 cm tall. Her serum creatinine is 0.6 mg/dl. She was started on gentamicin 500 mg IV every 24 hours 3 days ago. Her serum drug level measured just before the 4th dose is 0.27 mg/L and 34.9 mg/L 30 min after the infusion end.

What is the posology recommendation given by the program after fitting these serum concentrations?

What would be the Cmax and Cmin extrapolated for a dose of 400 mg every 24 hours after fitting these serum concentration, for a target peak concentration of 25 mg/l and a target trough concentration of 0.5 mg/l?

Gentamicin Vignette (2)

ZS is a newborn girl (gestational age of 37 weeks). She weights 2.27 kg and she is 40 cm tall. Her serum creatinine is 0.25 mg/dl. Because of suspicion of neonatal infection, she received 9 mg gentamicin at her birthday, synergistically with amoxicillin. 30 min and 11 hours after the infusion end, her serum drug levels are respectively 8 mg/L and 3 mg/L.

What is the posology recommendation given by the program after fitting these serum concentrations measured after a first dose and not at steady state, for a target peak concentration of 6 mg/l and a target trough concentration of 1 mg/l?

What would be the Cmax and Cmin extrapolated for a dose of 8 mg every 24 hours after fitting serum concentration?

Digoxin Vignette

VC is a 73-year old patient (born April, 1939) suffering from atrial fibrillation. He weights 92.7 kg and is 182 cm tall. His serum creatinine is 1.93 mg/dl. He is treated by digoxin 0.250 mg once a day for several months. At time of a routine control, 23h45 after his last dose, his serum drug level is 0.9 µg/l.

What is the *a priori* posology recommendation from the programs (before fitting any concentration) for a target average concentration of 1 µg/l (Cmin = 0.8 µg/l and Cmax = 2 µg/l)?

After fitting serum concentration, what is the extrapolated concentration if a dose of 0.125 mg every 24 hours is imposed?

Vancomycin Vignette

PJ is a 57-year old patient (born July, 1955) with ruptured infra-aortic aneurysm and amputation of both legs. He weights 62.5 kg and he is 172 cm tall. His serum creatinine is 3 mg/dl. He was started

vancomycin IV 1000 mg every 24 hours for 3 doses. Afterward vancomycin was stopped. 35h45 hours after the last administration, his serum drug level is 20.2 mg/l.

When should the treatment be started again if the target residual concentration is 15 mg/l?

What is the posology recommendation given by the programs after fitting this serum concentration?

Tacrolimus Vignette

BI is a 57-year old patient (born January, 1955) that had a kidney transplant 2 days ago. He weights 82.2 kg and is 175 cm tall. He is receiving 6 mg of tacrolimus per 24 hours in continuous infusion. Treatment started 2 days ago at 1 pm. His albumin concentration is 36 g/l, his hematocrite is 31 % and his creatinine clearance is 1.93 mg/dl. The patient is also receiving diltiazem. Today, at noon, his serum drug level is 19.1 µg/l.

What is the posology recommendation given by the programs, after fitting this serum concentration, for a target concentration of 10 µg/l?

Phenytoin Vignette

CA is a 10-year old girl (born May, 2002) suffering from emphysema. She weights 37.6 kg and is 140 cm tall. Her albumin is 38 g/l, her hematocrite 34% and her creatinine is 0.4 mg/dl. She is receiving oral phenytoin for 7 days at a regimen of 150 mg every 12 hours. 12 hours after her last dose intake, her serum level is 34.7 mg/l.

What is the posology recommendation given by the programs after fitting this serum concentration for a target concentration of 15 mg/l?

What would be the extrapolated concentration Cmin for a dose of 125 mg every 12 hours after fitting serum concentration?

Table 2.SIII: Results from clinical vignette

			Gentamicin Vignette (1)											
			MM-USC PACK	**Mw Pharm**	**TCI Works**	**JPKD**	**TDM for R**	**Antibiotic Kinetics**	**APK**	**Kinetics**	**Kinetidex***	**TDMS***	**Data Kinetics**	**RAD Kinetics**
Proposed dose (mg)	Bayesian		367.8	603.9	360	318.48	Does not work	377	377	384	340	380	/	Not able
	Regression		/	302.8	460	343.65		355	355	355	/	355	318.9	
Interval (h)	Bayesian		24	15.68	24	19.01		20	20	20	12	10.9	/	
	Regression		/	18.82	24	8.86		19	19	18	/	19.9	19	
Imposed dose (mg)			400	400	400	400	400	400	400	400	400	400	400	400
Imposed interval (h)			24	24	24	24	24	24	24	24	24	24	24	24
Extrapolated concentration	Bayesian	Cmax (mg/l)	27.19	16.23	33	28.74	Does not work	26.3	26.3	25.7	28.6	33	/	Not able
	Regression		/	32.55	42.2	31.03		27.9	27.9	28	/	42.2	31	
Extrapolated concentration	Bayesian	Cmin (mg/l)	0.13	0.12	0	0.13		0.2	0.2	0.1	0	0	/	
	Regression		/	0.45	0	0.22		0.2	0.2	0.2	/	0	0.24	

* For cystic fibrosis

			Gentamicin Vignette (2)											
			MM-USC PACK	**Mw Pharm**	**TCI Works**	**JPKD**	**TDM for R**	**Antibiotic Kinetics**	**APK**	**Kinetics**	**Kinetidex**	**TDMS**	**Data Kinetics**	**RAD Kinetics**
Proposed dose (mg)	Bayesian		4.9	5.5	Not able	Not working	Does not work	/	/	NA	6	6	/	Not able
	Regression		/	5.4		8.04		5.7	5.7		/	6	6.1	
Interval (h)	Bayesian		24	19.71		Not working		/	/		24	20.3	/	
	Regression		/	19.63		19.68		24	24		/	20.2	20	
Imposed dose (mg)			8	8	8	8	8	8	8	8	8	8	8	8
Imposed interval (h)			24	24	24	24	24	24	24	24	24	24	24	24
Extrapolated concentration	Bayesian	Cmax (mg/l)	9.61	8.23	Not able	Not working	Does not work	/	/	NA	8.4	8.1	/	Not able
	Regression		/	8.31		5.62		8	8		/	8.3	7.5	
Extrapolated concentration	Bayesian	Cmin (mg/l)	1.39	0.92		Not working		/	/		0.7	0.9	/	
	Regression		/	0.90		0.13		0.9	0.9		/	0.9	0.83	
Remarks					Not able to handle neonate					Only for adults	Taking back treatment right away	Model adapted for neonates		

Digoxine Vignette												
	MM-USC PACK	**Mw Pharm**	**TCI Works**	**JPKD**	**TDM for R**	**Antibiotic Kinetics**	**APK**	**Kinetics**	**Kinetidex**	**TDMS**	**Data Kinetics**	**RAD Kinetics**
A priori proposed dose (mg)	Does not work	Does not work	NA	No a priori regimen	Not able	NA	NA	0.138	0.125	0.204	0.148	NA
Interval (h)								24	24	24	24	
Imposed dose after fitting (mg)	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.13	0.125	0.125	0.125	0.125
Imposed interval (h)	24	24	24	24	24	24	24	24	24	24	24	24
Extrapolated concentration Cmin (µg/l)	Does not work	Does not work	NA	0.45	0.45	NA	NA	0.5	0.6	0.6	0.5	NA

Vancomycin Vignette												
	MM-USC PACK	**Mw Pharm**	**TCI Works**	**JPKD**	**TDM for R**	**Antibiotic Kinetics**	**APK**	**Kinetics**	**Kinetidex**	**TDMS**	**Data Kinetics**	**RAD Kinetics**
Time for retake (h)	NA	(J4) Time to hold: 12.25	NA	Not able	Not able	Not able	Time to hold: 14.9	Time to hold: 14.6	Not able to take treatment interruption into account	Not able	Not able	Not able
Dose for retake (mg)		768.6		515.39	361.1	721	721	757		475	495	400
Next interval regimen (h)		35.71		32.84	24	39	39	42		24	24	24
Remarks				Interval indicated = 48 h	Interval indicated = 24 h	Interval indicated = 48 h	Interval indicated = 48 h	Interval indicated = 48 h				

Tacrolimus Vignette												
	MM-USC PACK	**Mw Pharm**	**TCI Works**	**JPKD***	**TDM for R***	**Antibiotic Kinetics**	**APK**	**Kinetics**	**Kinetidex**	**TDMS**	**Data Kinetics**	**RAD Kinetics**
Proposed dose after fitting (mg)	NA	NA	NA	3.9	3.24	NA	NA	NA	NA	NA	NA	NA
Interval (h)				24	24							
Remarks				Not able to handle continuous infusion (sampling time indicated = 23 h)	Not able to handle continuous infusion (sampling time indicated = 23 h)							

*diltiazem interaction taken into account in the program

Phenytoin Vignette												
	MM-USC PACK	**Mw Pharm**	**TCI Works**	**JPKD**	**TDM for R**	**Antibiotic Kinetics**	**APK**	**Kinetics**	**Kinetidex**	**TDMS**	**Data Kinetics**	**RAD Kinetics**
Proposed dose (mg)	NA	NA	NA	133.08	158.75	NA	NA	NA	NA	178	132	NA
Interval (h)				12	12					24	/	
Imposed dose (mg)				125	125					125	125	
Imposed interval (h)				12	12					12	/	
Extrapolated concentration Cmin (mg/l)				11.31	-9.22					1092.9	11.9	
Remarks				12 h manually indicated for interval	12 h manually indicated for interval							

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II.2. The Development Of EzeCHieL: An Integrated, User-Friendly Software For Individualized Drug Dosing Regimen Calculation and Bayesian Therapeutic Drug Monitoring

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Under preparation

ABSTRACT

EzeCHieL is a program that aims to support clinicians in the clinical interpretation of blood drug concentration measurements. It is designed to be an easy-to-use pharmacokinetic tool for experienced as well as inexperienced users to tailor drug dosing regimen to specific patient, either based or not on blood drug concentration measurements in the frame of therapeutic drug monitoring. With the program, the user is able (i) to assess the expectedness of an observed concentration in a patient compared to the population via percentiles (ii) to assess the suitability of the predicted concentration at a time of interest according to the therapeutic interval (iii) to provide dosing adjustment advice if appropriate. EzeCHieL provides population-based predictions and Bayesian forecasting for routine use. The realization of the program is still under development. It will be a fully integrated software, affording powerful calculation, interactive graphical display, interfacing capabilities with hospital information system compliant with HL7 language, a local patient and drug history database, a central database for data collection in the research framework, report generation and useful extra tools. The tool is almost accomplished. We present the current stage of development of EzeCHieL and expected coming features.

II.2.1. Introduction

The aim of Therapeutic Drug Monitoring (TDM) is to optimise dosing regimens for individual patients based on the determination of plasma drug levels, in order to ensure effective drug concentration exposure whilst avoiding toxicity. TDM has been recognised to be beneficial in the management of various medical conditions, and dosage individualization guided by plasma drug measurement is currently applied to a number of drugs [1-3]. Additionally, recent refinements of analytical techniques increase the availability of drug assays, therefore putting an increasing emphasis on the value of TDM. The number of drug measurements performed in medical laboratories is globally expanding. However, measuring drug concentrations without providing appropriate clinical interpretation of the results leads to poor benefit to the patient.

TDM necessitates consistent concentration–effect relationships and is best suited for drugs with a narrow therapeutic index that demonstrate a high inter-individual variability. It requires a good understanding of the relationship between drug dosing regimens and resulting blood concentration profiles, namely pharmacokinetics (PK).

While most TDM interventions still rely on an empirical approach in daily practice, during the last decades it greatly gained from the emergence of population PK. From reference population data, a population PK model for a drug can incorporate patients' descriptors (for instance body weight, creatinine clearance, disease, etc) and be fitted to drug concentration values (making it possible to quantify the residual unexplained variability). Once well characterized, such a model can be used as a prior to build up a formal interpretation of a given patient's concentration value, as it allows individual Bayesian parameter estimation, simulations, concentration predictions and ultimately dosing suggestions. Another advantage of this approach is the possibility to accommodate **random** concentration values, which can be then extrapolated at a specific time for comparison with the desired targets. Population-based interpretation and Bayesian forecasting rest on mathematical modeling and non-trivial calculations. Thus it requires appropriate computing facilities, which are however largely available nowadays.

A number of more or less sophisticated programs have been proposed during the past years to perform this task [4]. It appears however that there is still an important room for improvement in this type of software for routine use. Clinicians without special training in PK need a simple, user-friendly and easily accessible informatics tool. Additionally, such a program should provide accurate Bayesian predictions, interfacing with information systems, data storage capabilities and automatic report generation [4]. Computer assisted TDM is gaining growing interest, in parallel with the expansion of drug measurements.

Like other institutions, the University Hospital of Lausanne has faced the need of a computer tool to assist TDM intervention. In the early 1990s, Borradori et *al*. showed an association between high aminoglycoside exposure and sensorineural hearing loss (SNHL) in preterm infants [5], stressing the importance of monitoring carefully the concentration exposure to these antibiotics. It led to the design of a small PC program locally available, that helped in the calculation of dosage adaptations for aminoglycoside antibiotics and vancomycin. The proposed program, written in Microsoft Visual Basic for DOS, implemented a classical two-points approach: it was able to compute individual values of clearance and distribution volume from peak and trough concentrations measured after first dosing or during a repeated doses regimen. These estimates served to determine the dose amounts and dosing intervals required to bring the steady-state peak and trough levels near preset target values considered as usually efficient and safe.

Further initiatives have then been undertaken with regard to antiretroviral therapy (ART). ART substantially improves survival in patients infected with HIV. A relationship between plasma levels and efficacy/toxicity has been established for certain classes of antiretroviral drugs. Drug concentration measurement is recognised as providing useful information to guide therapy for these antiretroviral agents, known for a high pharmacokinetic variability, potential interactions and complexity of use in polytherapy. Trough concentrations (C_{trough}) are traditionally preferred for interpretation, as target values have been proposed for them. However, in practice, blood samples are often drawn at various times due to modalities of treatment intake and medical visit schedules.

To overcome this issue, in the end of the 1990s, our institution undertook further initiatives to provide assistance in the interpretation of plasma levels. From in-house developed population models, percentiles curves covering the whole dosing interval were established to propose reference concentration values under standard dosage regimens at steady-state [6]. In the absence of better validated therapeutic intervals, this did help to at least evaluate the *expectedness* of an observed concentration under a given dosage regimen at any time between two dose intakes. This represents a rudimentary TDM referring to population PK [7]. It has been applied to a various number of antiretrovirals as well as to tyrosine kinase inhibitors (TKI). A more formal Bayesian approach has been developed for efavirenz using a simple nomogram, taking advantage from the fact that all inter-individual PK variability for this drug could be assigned to its relative bioavailability [8].

Further efforts have been made to improve the interpretation of randomly measured concentrations while ensuring accurate prediction of C_{trough} using a Bayesian approach. For imatinib, the first commercialized TKI, a Bayesian maximum a posteriori (MAP) estimation method base on a population pharmacokinetic model was developed and implemented in Excel (Microsoft® Office 2007, Microsoft Corporation, Redmond, WA, USA) [9]. Additionally to prediction, it was used with success to optimize dosages when necessary [10, 11].

In the spirit of the last decades of innovative improvements to develop TDM for new drugs and to support clinicians in TDM interpretations, our division is now at the initiative of the development of a new computer program, called *EzeCHieL*. The main goal of EzeCHieL is to support the medical community for the clinical interpretation of randomly measured drug concentrations, using population-based reference percentiles and Bayesian predictions. Moreover, this computer tool aims to suggest individualised dosing adjustments if necessary, and should straightforwardly accommodate any candidate drug. Such aspirations require an easily accessible, integrated and user-friendly tool implementing Bayesian MAP estimation that can be used by inexperienced as well as experienced users.

The objectives of this paper are to provide an outline of the desired tool and to present the pharmacological specifications required to succeed in the aforementioned tasks. We will then report on the state of progression of EzeCHieL development since the beginning of the project in 2010.

II.2.2. General conceptual approach

EzeCHieL is designed to address three major questions which should be raised following drug concentration measurement, and which delineate the intellectual process behind therapeutic drug monitoring:

- **Is the patient's concentration expected**? *To answer this question, EzeCHieL shall locate the patient's concentration value within the percentiles of distribution of concentrations expected under the given dosage, which graphically summarize the variability in drug exposure among the population.* EzeCHieL will compute *population*, *individual a priori* percentiles, from a given population pharmacokinetic model, using simulation algorithms. In addition, once one or several blood samples of a patient have been measured, the program will confront them to prior individual patient's parameters and compute *a posteriori* percentiles deduced from Bayesian MAP estimation. The *expectedness* of a concentration can thus be evaluated at different levels: either compared to the population or to the patient him- or herself. Moreover, besides this *empirical Bayesian* approach, a *full Bayesian approach* should be made available, which incorporates not only reference population PK parameters (average values, covariates coefficients and variability) but also an estimation of their own uncertainty (standard errors and correlations between estimates).
- **Is the patient's concentration suitable**? *To answer this question, EzeCHieL shall assess whether the patient's concentration profile meets, at a time of interest, the targeted therapeutic value and interval.* Based on a concentration measurement, Bayesian prediction allows to extrapolate the concentration at the time referred for defining target exposure (e.g. peak or trough time, or average concentration i.e. AUC). This extrapolation can then be compared to the target

concentration or interval. EzeCHieL should accommodate not only standard target ranges, but also values depending on a defined covariate or entered specifically for a given patient (e.g. minimum inhibitory concentration for anti-infective drugs)

- **How should the dosing regimen be adjusted**? *To answer this question, EzeCHieL will help the prescribed to choose the most appropriate dosing schedule to reach and to maintain the patient's concentration profile within the targeted therapeutic range.* EzeCHieL thus offers a reverse PK calculation algorithm that starts from concentrations to derive dosages, so to suggest an appropriate dosing schedule for the desired target.

All the above mentioned capabilities should largely rely on data visualisation with generation of concentration curves and target ranges. Other desired aspects include an easy-to-use interface and a flexible architecture allowing evolutions. EzeChieL will be able to handle various types of pharmacokinetic models, so that it can include a large library of drugs, and the users can add their own drug models. Interfacing with laboratory and patient information systems is also a major aspect of the development. Generation of high quality reports enabling a clear rendering of the results is a must-have. Finally, pharmacokinetic data gathered during the daily practice of TDM should be saved and used to continuously increase our knowledge and refine our drugs model through further research.

II.2.3. Software Development

Platform supported and installation requirement

EzeCHieL is designed to be a stand-alone cross-platform application that runs on any modern system (Windows, Mac and Linux, and soon on iOS and Android platforms). It is written in C++ using the Qt framework. The program is available in English or French and updates are easily downloaded on its the website (http://www.ezechiel.ch/).

User interfaces

The program is intended to provide a user-friendly tool that uses a graphical user interface (GUI), menu-driven with docks and panels (**figure 2.2.1**). It offers a step by step wizard (**figure 2.2.2**) that facilitates navigation for inexperienced users. Control via the command line interface is also however possible. From the GUI, patients and physician are added into the suitable panel.

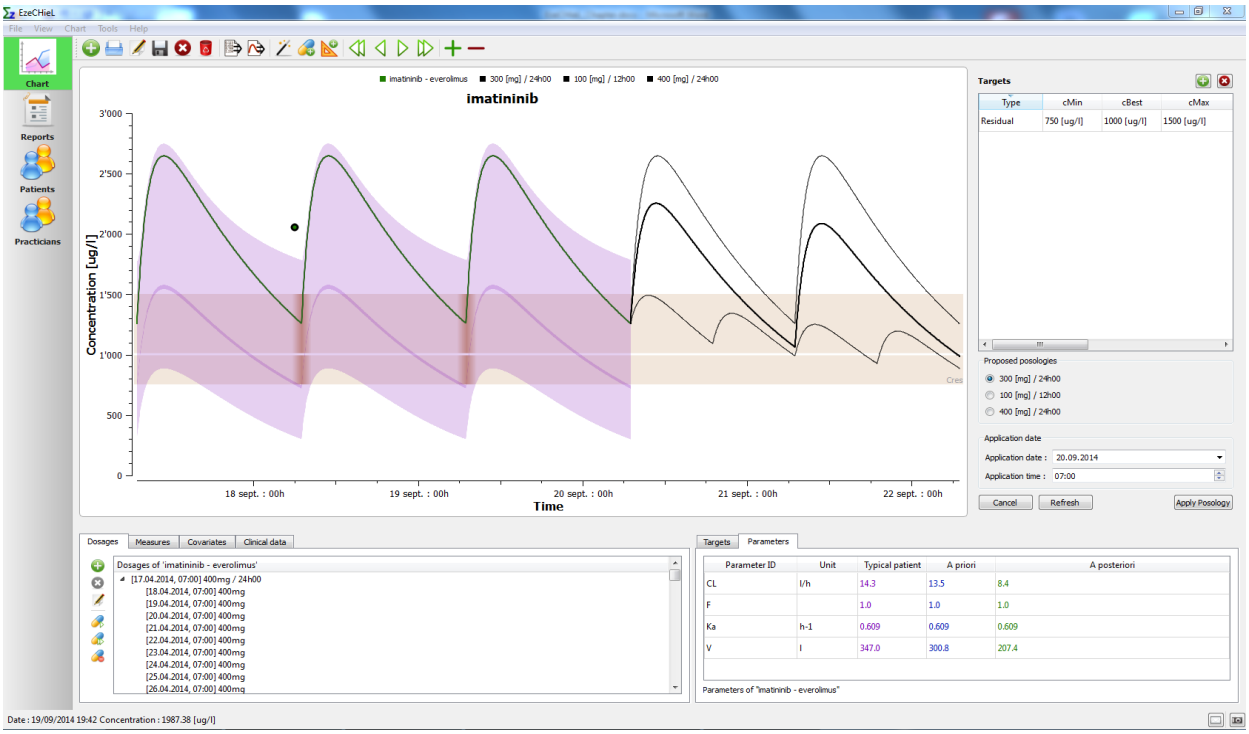

Figure 2.2.1. Graphical User Interface of EzeCHieL. On the left: patients, practitioner, report and chart panels. On the top: various menu docks. On the bottom, left: drug dosing history, concentration measurements, and covariates tabs. On the bottom, right: Target concentration prediction(s) and population, *a priori* and *a posteriori* pharmacokinetic parameters. On the right: Drug dosing suggestions panel. Chart: therapeutic interval i.e. target (horizontal shaded area). Chart, on the left: population prediction with the typical patient (purple line) and the 10^{th}-90^{th} percentile (shaded purple area). Observed concentration (green point) with *a posteriori* patient prediction based on Bayesian estimation (green line). Chart, on the right: concentration over time from dosing suggestion.

To handle a TDM intervention, EzeCHieL starts by creating a concentration profile curve. The first step consists in indicating the drug of interest and the appropriate reference population. Then the user enters dosing regimen information, covariates (patient descriptors) for the chosen drug and measured drug concentration. The program will then calculate the patient's PK parameters for the given drug through MAP Bayesian estimation and draw the corresponding PK curve. Further actions encompass the localisation of the patient within the population (percentiles display), the

comparison of extrapolated concentration with reference target, the provision of dosage adjustment suggestions, and the generation of an intervention report. Further features of the program and more details regarding these steps are given in the next paragraphs.

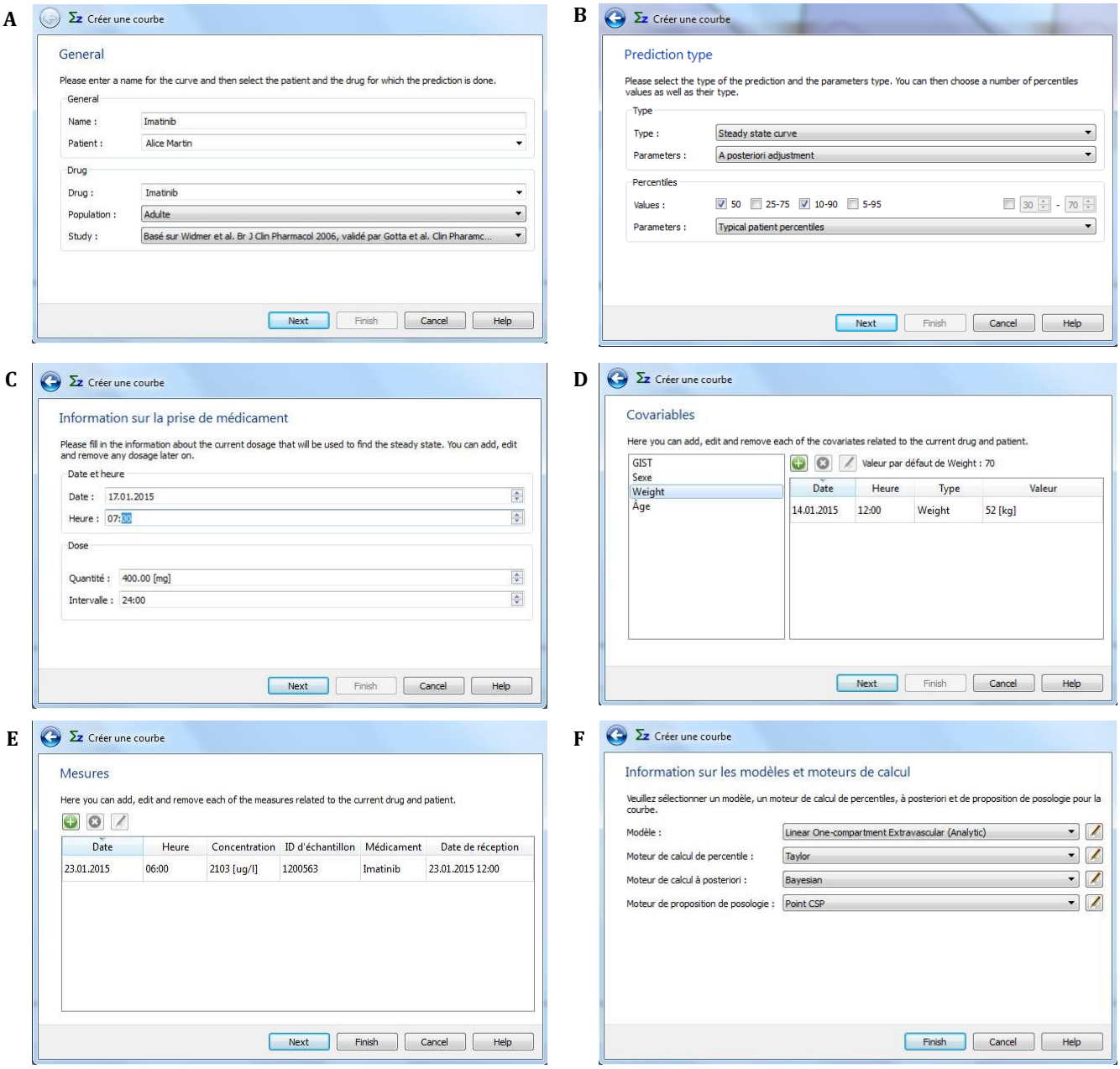

Figure 2.2.2. Step by step wizard for data entry during TDM intervention. A. Patient and drug information. B. Type of concentration prediction. C. Drugs schedule and dosage information. D. Covariates information. E. Drug concentration measurements information. F. Advance setting for experienced user regarding calculation algorithms

Modular architecture

EzeCHieL architecture is designed to be very flexible. A concept of plugins which articulate around a central core has been chosen. These plugins implement various components such as PK model calculation, percentiles calculation, Bayesian derivation algorithms, reverse calculation for individualised dosage suggestion.

Pharmacokinetic models and drug description

In the software, a PK model is made up of a set of parameters either defined for integrated closed-form PK equations in terms of clearance, volume of distribution, constant of absorption, etc. or in terms of microconstants used for the integration of differential equations. Inter-individual variability can be associated with each parameter. Correlation between parameters is also supported by the program. Parameters are then used to calculate the predicted concentration profile and to build up a curve. All type of PK models will be handled by EzeCHieL including: one- two- three- linear and non-linear compartment model with first or zero order absorption and double gamma absorption for extravascular and intravenous administrations. Further PK models could be implemented upon request to the developers.

An extended markup language (XML) file is written for each drug and is associated with a type of aforementioned PK model. This XML file specifies the set of parameters for the drug and the population considered, along with both inter- and intra-patient variability stemming from the population analysis. In addition, it contains information on drug dosage forms available, resulting dosage steps considered reasonable, acceptable intervals of time, usual infusion time if appropriate, and drug concentration targets. The XML file also includes the full covariate model description. In case of missing data for a given patient, default values, corresponding to the mean value from the original population data, can be assigned. EzeCHieL will include a rich library of drugs but users will be able to implement their own drugs, either directly into a drug XML file template or using a dedicated drug model editor made available. The architecture of calculation is given in **figure 2.2.3.**

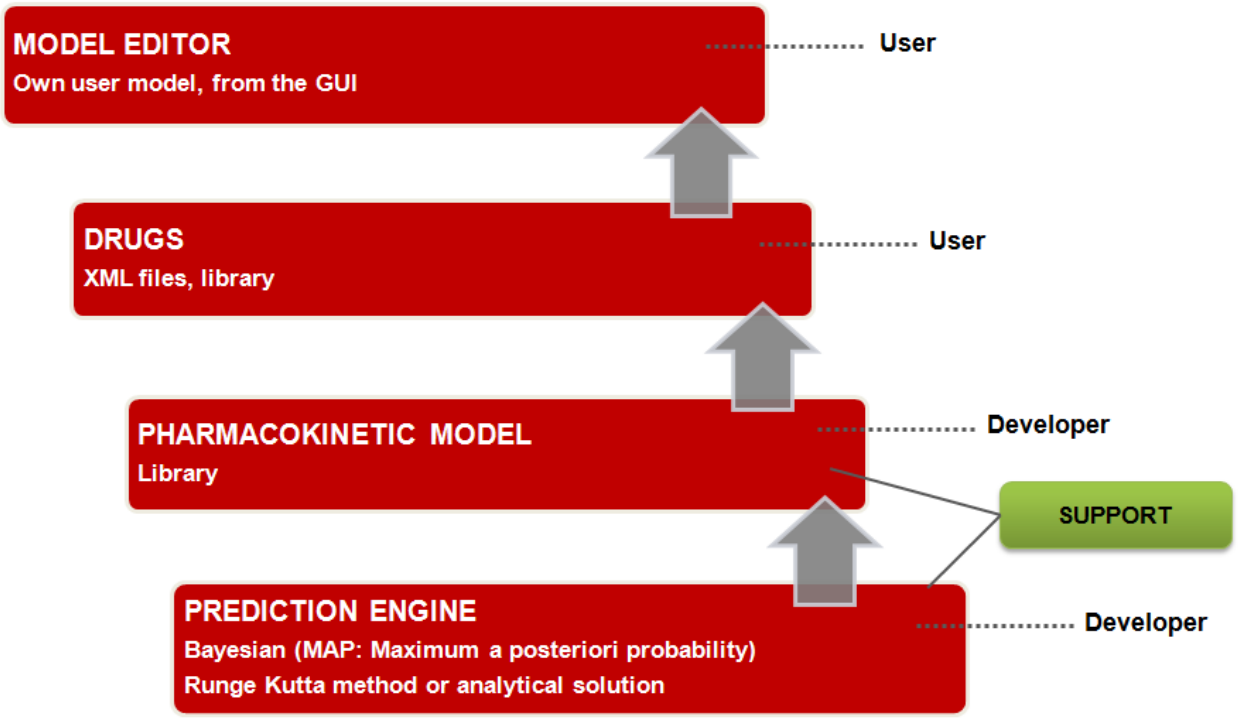

Figure 2.2.3. Layers architecture of prediction calculation and drugs descriptors

Population prediction and Bayesian individualization

Individualization is based on the availability of a reference population PK model including assumptions of parameters' distribution. Once a concentration measurement is available its clinical interpretation relies on Bayes' theory. Several steps are outlined here for this interpretation:

- typical patient

From the prior knowledge of the distribution of PK model parameters in the general population of interest (i.e. the original population dataset previously mentioned), the average *typical patient* is represented (this patient usually corresponds to the reference values of covariates relevant for the model). The typical patient is thus representative of a patient whose characteristics affecting the drug kinetics (i.e. covariates) are not known.

- a priori

The prior knowledge of the distribution of PK model parameters now incorporates the knowledge of the patient's covariates relevant for the model, in order to determine the patient's *a priori*

parameters (i.e. before any concentration is evaluated). The resulting predicted PK profile allows for example planning the initial dosing regimen.

- a posteriori: **Bayesian estimation**

Once one or several drug concentration measurements are available, individual PK parameters can be estimated by Bayesian calculations based on their maximum *a posteriori* probability (MAP). This approach combines the measured drug concentration(s) and the prior knowledge of the distribution of model parameters estimated in the population of interest. It searches for the best combination of parameters that can account for the concentration(s) observed in the given patient, weighted by the prior knowledge of their respective variability in the population. This approach can be applied with any number of drug concentration measurements.

At each level, starting from the typical patient to the *a posteriori* analysis, the degree of uncertainty regarding the fate of drug concentrations is reduced for a given patient.

Percentiles

Around all the above PK model based predictions, percentiles of distribution can be generated, which describe the respective spread of their uncertainty. Thus, a *typical patient* exposure profile should be complemented with the variability observed in terms of concentration over time exposure in the whole population, which encompasses both explained and unexplained between-patient variability, along with the within-patient or inter-occasion or residual variability. Individual a priori percentiles are based on the knowledge of covariates and do not incorporate anymore the population variability explained by the covariates. Individual a posteriori percentiles still reduce the role of unexplained between-patient variability, since the patient has now been characterized by individual monitoring. In case of a large number of concentration measurements, these individual a posteriori percentiles end up in containing only the residual variability. The former two percentiles can be used to compare the adequacy of a single individual random concentration with the population of reference [7, 12], while the latter one rather informs about the expectedness of a new concentration value for a given individual having already been sampled. Percentiles are

implemented in the program under two distinct methods of calculation, named “Monte Carlo” and “Taylor-inspired”. The Monte Carlo method is based on a large number of simulations of concentrations from random patients drawn from a probability distribution relying on both inter- and intra-individual variability. The Taylor method uses error propagation calculations via the first (and possibly via the second) order approximations of the Taylor series. Monte-Carlo tends to rebuild the true distribution of concentrations (when N is sufficiently large), while the Taylor-inspired methods are less accurate but faster. Methods of percentiles calculation are also implemented as plugins in the program.

Curve fitting and prediction engine

A PK model for a given drug is originally defined by a system of differential equations. Solving the system of differential equations allows fitting a curve and so predicting a patient’s concentration over time. The curve to fit can be calculated either by the Runge Kutta integration method, using the original differential equations plus a set of initial conditions (at time t=0), or by the calculation of the analytical solution (closed-form equation) of the differential equation if it exists; this is typically not the case for non-linear kinetics, which make TDM of additional value for the corresponding drugs (e.g. phenytoin). Analytical solutions are preferable when they are available, for speed calculation considerations, but EzeCHieL offers both approaches.

Drug dosing regimen calculation and targets

Finally, from the individualized PK parameters, EzeCHieL will generate drug dosing suggestions to reach drug target concentration. It displays a certain number of acceptable dosing regimens that can achieve the desired PK target exposure. Nominal dose and time interval suggestions are constrained to satisfied only relevant combinations based on practical and galenic consideration entered in the drug’s XML file. The user can evaluate the choice on a chart that displays the result of the dosing suggestions. Relevant predicted concentration at steady-state are calculated and displayed. Population target values (and intervals) are handled, including with possible dependence on pharmacodynamic covariates, but the user can also define a patient’s own desired target.

Drug dosing, measure history

The dosing regimen and concentration measurements values are displayed on the GUI. Drug dosing can easily be modified to fit all actions taken for a patient (missed dose, treatment, interruption, nominal dose and/or interval modification). A new drug concentration measurement can readily be added. Any covariates value modification can be simply handled via this panel as well.

Covariates

Covariate values are also displayed in a tab on the GUI. Similarly, they can easily be modified or added. EzeChieL aims at defining global covariates, i.e those most commonly encountered in PK models, that could thus be used in different drug model for a given patient (like body weight or glomerular filtration rate, etc). More specific covariates are requested according to the chosen drug. Regarding covariates derived from other parameters, the program will offer interactive calculations directly accessible for: creatinine clearance, body mass index (BMI), body surface area (BSA), or different type of body weight (BW).

Graphical display

Drug concentration over time is displayed on dynamic graph from the fitted model. Changes in covariates or drug dosing (dose, interval) are clearly labelled. Multiples curves can be added, as well as percentiles. Targets are clearly depicted. Cursor can be moved along the patient curve, indicating the predicted concentration at any time. User can choose between linear and logarithmic scale. A colour code is set up for different elements.

Report

Reporting and saving results is of major importance. Comprehensive reports, customizable for a given institution or practitioner, can be generated to document TDM intervention. They shall include administrative information regarding patient, physician and user, laboratory data, dosing recommendations if appropriate, dosing regimen graphs, population and individual PK data, and free text that can be added by the user. As most of the data used in the reports is already stored in

the database and they can be retrieved to prefill many of a report's fields. Customization of the report as a shorter version is also possible, through the masking of selected segments. The report is implemented using a combination of HTML5 technology, CSS and Qt's webkit features.

Database

All clinical useful data need to be saved. Data such as patient data (personal information, some from medical records) and practitioner data are stored in a local SQLite database. Patient data are saved and current dosing adjustment can also be saved for a future dosage monitoring. It is also possible to interface EzeCHieL with the hospital information system *(see below)*.

For research purpose, EzeCHieL shall also transfer any collected data regarding drug concentration and useful PK information (essentially covariates) to be aggregated in a remote central database. Such sharing feature will be used to develop and continuously improve existing models.

Data interoperability and confidentiality

Seven International (HL7; http://www.hl7.org/), the standard language for electronic health data transfer and probably the most commonly encountered in the medical field, is supported by EzeCHieL trough the Mirth™ Connect technology (Mirth Corp., Irvine, CA, USA). It enables data to be interfaced with hospital information system including laboratory systems and the patient electronic medical records. To satisfy privacy and security requirements, all data stored locally are encrypted, and data transferred will be digitally signed. Regarding data aggregated for research purpose, the following approaches will be combined: pseudonymization (by applying the multi-key searchable encryptation scheme to the identifiable patient's information) and anonymization, using generalization technique.

Export functions

Curves can be exported as points, with many exportation options to satisfy user's preference (**figure 2.2.4**). Graphs can be exported as image or PDF documents, reports as PDF or ODT.

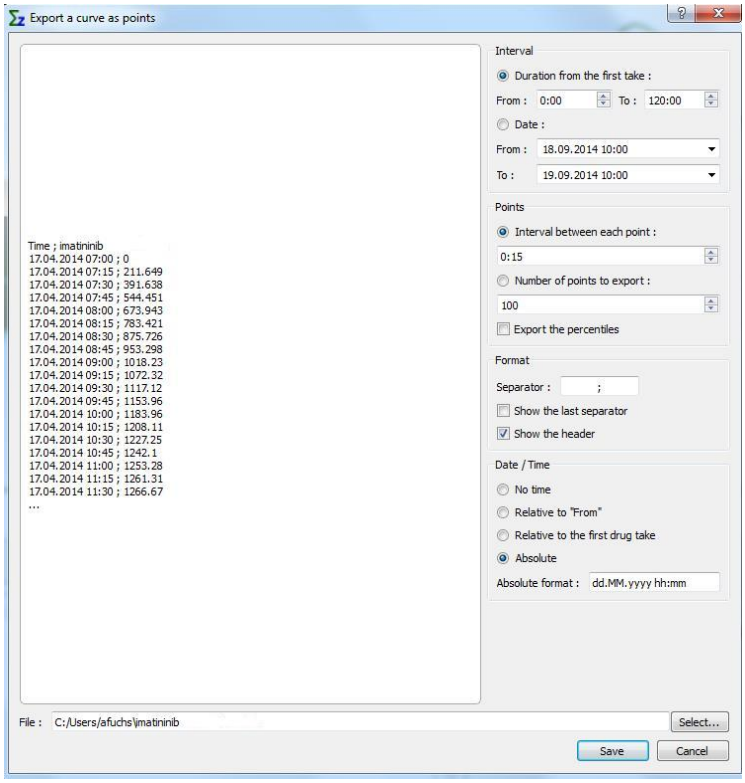

Figure 2.2.4. Options panel for curve exportation

Support

First, a user manual is provided (free access on the program's website) made up of a quick start guide to rapidly handling a TDM intervention. It is worth noting that EzeCHieL is probably intuitive enough to handle a TDM intervention without going through the user manual. The second part of the manual gives deeper information on all aspects of the program: calculation motor and equations, drugs library, model edition, validation of the program, interoperability, database, export, etc. A website and a user group are under realization. Finally, the long term support will be ensure via a system of start up, to continuously maintain and develop the program, and will offer to users an opportunity for contact and request.

II.2.4. Progress report

The current stage of realization, since the beginning of its development in 2010 is given in the following progress grid, and also including future developments.

Table 2.2.1. Progress grid of EzeCHieL development

Item	Specification	Current status
Platforms	- PC/Windows	**OK** with Qt platform
	- Mac	**OK** with Qt platform
	- Linux	**OK** with Qt platform
	- Android smartphone/tablet	*Envisaged later*
	- iOS iPhone/iPad	*Envisaged later*
User interfaces	- Fully functional command line interface (console mode)	**OK**
	- Graphical user interface (all features for specialized users)	Well advanced
	- Wizard for every-day use by non-specialists	Well advanced
	- Service to be interfaced with e-environments	*Envisaged later*
	- Preferred language settings (translations)	Translation underway
	- Global ergonomics	Well advanced
Modular architecture	- Central core, including:	Underway
	- Report generator	Awaits finalization
	- License/security	Underway
	- Configuration/setup	Underway
	- User interfaces	See below
	- Drug description XML files	
	- PK models plugins	
	- Posterior estimation plugins (Bayes engine)	
	- Percentiles calculation plugins	
	- Report generators/templates	
	- Dosage adjustment plugins (reverse engine)	
	- Internal database	
	- Data interchange with external system.	
	- Data export to remote databases	
PK model types	- Closed integral form:	**OK**, to be expanded
	- 1, 2 compartments 1st-order for Bolus, infusion, and extravascular	**OK**
	- 3 compartments 1st-order, Bolus	To be implemented
	- 0-order absorption	To be implemented
	- lag time	To be implemented
	- Differential form (Runge-Kutta 4th-order):	**OK**, to be expanded
	- 1, 2, 3 compartments 1st-order, Michaelis-Menten and mixte (1st order with Michaelis-Menten)	Almost finalized
	- Bolus, infusion, extravascular 1st-order *and* 0-order absorption, Michaelis-Menten absorption	To be done
	- Treatment start and steady-state	Almost finalized
	- Versatility, ease of future model implementation	**OK**

Item	Specification	Current status
Drug description (XML)	- Drug database	**OK**
	- Data structure definition	
	- popPK parameters, variability	**OK**
	- Covariates with formulae (on PK parameters and on PD parameters = individual targets)	**OK**
	- popPK variability without covariates	To be done
	- Var-covar matrix of estimates	To be done
	- Forget function for past measurements	To be done
	- Separate library of units	**OK**
	- Drugs XML file validation tool	**OK**
	- Abundant comments (self-explanatory)	**OK**
	- Structured references	To get structured
	- Interactive drug file editor	To be made soon
	- Data accountability management	Key to be added
	- Web-based central repository	Website to develop
Prediction engines	- Analytical approach based on moment match (Taylor-inspired)	
	- 1st order	**OK**
	- 2nd order	Awaits finalization
	- Simulation approach (Monte-Carlo)	**OK**
Posterior estimation plugins	- Empirical Bayesian calculation	
	- Based on Baye's objective function	**OK**
	- Allowing for covariances between PK parameters	**OK**
	- Allowing for additive, proportional, or mixed additive+proportional distributions for PK parameters and residual error	**OK**
	- *Should meet NONMEM MAP values*	To be checked
	- Full Bayesian calculation (takes into account variance-covariance matrix)	To be implemented
Percentiles	- Empirical Bayesian percentiles	
	- Population (without covariates)	To be implemented
	- Typical patient (covariates centered)	**OK**
	- Individual a priori (individual covariates)	**OK**
	- Individual a posterior (knowing covariates and 1, 2...n measurement results)	To be added
	- Color code for percentiles	**OK**
	- Vanishing importance of remote past results (time function + defaults time + user choice)	To be implemented
	- Taylor and Monte-Carlo should be close	To be checked
	- Full Bayesian percentiles	To be implemented

Item	Specification	Current status
Adjustment proposition	- Reverse calculation from prediction	**OK**
	- Calculation taking into account realistic dose/interval constraints	**OK**
	- Indication of target proximity	
	- On chart	**OK**
	- Numerically	To be implemented
	- Dosage regimen suggestion by the user	**OK**, to be checked
Targets	- Defined at C_{min}, C_{max}, $C_{defined\ t}$ or C_{ss} (equivalent to AUC/τ)	**OK**
	- Possibly t>MIC or AUC/MIC	*Envisaged later*
	- Population values (target + interval)	**OK**
	- Possibly individual values (either affected by covariates or entered for a given individual)	To be implemented
Covariates	- Global: age, sex, bodyweight, height, BMI, BSA, LBM, GFR	**OK**
	- Specific: all other covariates	**OK**
	- Interactive calculation tools for BMI, BSA, LBM, GFR (from creatinine)	To be implemented
	- Flexible operations on PK parameters	**OK**
	- Controlled dictionary	Will be set up manually
Drug dosage	- Easy to introduce	**OK**
	- Easy to modify (missed dose, supplemental dose, change in regimen, end of treatment)	**OK**
Concentration measurements	- Easy to introduce	**OK**
	- Easy to modify (remove)	**OK**
	- Inclusion or not for Bayes individualization (according to forget function + modifiable)	To be implemented
Chart	- Automatic and versatile time axis management (scale, shift, contraction/extension)	**OK**
	- Automatic concentration axis scaling (toggle start from 0 or not)	**OK** (except 0 toggle)
	- Linear/Logarithmic toggle	**OK**
	- Possibility of superposing several curves	**OK**
	- Color code for elements (percentile type, target type)	
	- Percentile type	**OK**
	- Target type	**OK**
	- Cursor, reading of curve values	**OK**
	- Exportation of datapoints	**OK**
	- Unit conversion	**OK**

Item	Specification	Current status
Report generators	- Template-based	To be finalized
	- Output in HTML + CSS	**OK**
	- Conversion into PDF on demand	To be finalized
	- Export into XML, HL7v3	**OK**
	- Export into HL7v2 through Mirth Connect	To be finalized
	- Customised to licensed users (or mentioning no commercial use)	To be implemented
	- Versatile (block selection/deselection)	To be finalized
	- Comment text fields	**OK**
	- Interactivity with data entry (reflexion of corrections and complementations in database)	**OK**
	- Archival	To be implemented
User ID	- Standard fields	**OK**
Patient ID	- Standard fields	**OK**
Physician ID	- Standard fields	**OK**
Internal database	- SQlite, MySQL, SQLserver versatility	**OK**
	- Patient/covariates/dosage/results storage and recall for update	**OK**
	- Protection for sensitive fields	**OK**
	- Users management	**OK**
	- Optional historicization / Audit trail	To be finalized
Data interchange	- Data acquisition from a lab system or a medical record in HL7v3)	**OK**
	- Data acquisition from a lab system or a medical record in HL7v2 trough Mirth connect	To be finalized
	- Exportation of report data	**OK**
Remote database	- Optional send out of usage data to central database	**OK**
	- Advanced protection, no retrieval of sensitive data without user's collaboration	**OK**
	- Coded user ID	**OK**
	- Check with updates in software/drug files	To be finalized
Configuration	- Information on users, license, preferences	To be finalized
	- Verification/security	To be finalized
Users	- Users management	**OK**
	- Accountability, audit trail, security	To be finalized

Item	Specification	Current status
License	- Full functional free version for non-commercial use, tagged as such	To be finalized
	- Individual or institutional licenses for commercial use, with light protection	To be implemented
	- Open-source status for central part of code	**OK**
Validation	- Internal	Underway
	- External, against NONMEM and R	Underway
	- External, against Dose-Me and MW-Pharm on predefined vignettes	**OK**
	- External, during clinical implementation, versus current approaches	*To be done once ready for exploitation*
	- Official by a dedicated organisation	*To be done later*
Alpha-testing	- In PCL Lausanne	*To be done once ready for exploitation*
Beta-testing	- Expert users	*To be done once in beta-phase*
Dissemination	- By EzeCHieL SàRL, to be created	*To be created*
	- Administrative, technical and clinical support	*To be set up*
Website	- Presentation	To be finalized
	- Dissemination of free version	To launch at beta version
	- Documentation (essentials and technical details)	To be revised and finalized
	- FAQ, global support	To be implemented
	- Drug files with comments	To be implemented
	- Users community, blog/wiki	To launch
User Manual	- Quick start guide	To be finalized
	- Comprehensive guide describing all aspects of the program	To be finalized
Regulatory Approval	- EMA and FDA requirements	*To be started once ready for exploitation*

II.2.5. Software validation

Assessment of the predictive performance for concentration predictions

To ensure that EzeCHieL is numerically accurate and precise in terms of concentration prediction, predictive performances [13] are evaluated and graphical inspections are performed. Bias (MPE: mean prediction error) and precision (RMSE: root mean squared error) are calculated by comparing EzeCHieL predicted drug concentrations against those predicted from the non-linear mixed effect modeling software (NONMEM®) considered as the reference method for population analysis and individual prediction, or against measured concentrations if existing.

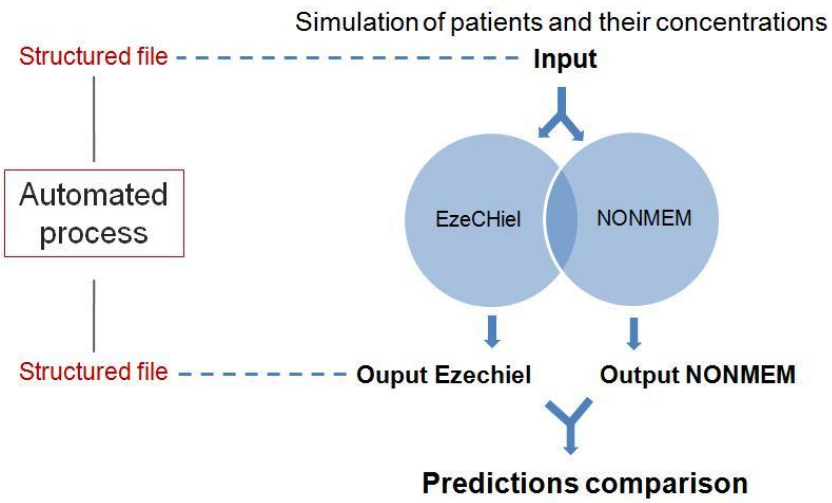

Figure 2.2.5. Scheme of the automated tool for prediction validation against the reference method NONMEM®

An automated tool in order to compare EzeCHieL predictions to the reference method, based on simulated data, as described **figure 2.2.5**, has been developed.

Assessment of dosing regimen recommendation

Further validation test need to be performed in real clinical setting to demonstrate the capacity of the program to suggest suitable dosing regimen recommendation. Predictive performances (bias and precision) will be assessed by predicted drug concentration against those observed after applying dosing recommendation for individualization.

Regulatory approval requirement

Overall, a more general validation process will be performed to meet regulatory requirements for dissemination of such tool. It requires evaluating the testing methodology and the results. European Medicines Agency (EMA) and the Food and Drug Administration (FDA) define criteria to be met for medical devices [14, 15]. A registration dossier also represents one of the next stages of the project.

II.2.6. Discussion

EzeCHieL will offer a powerful resource to support clinicians in therapy individualization based on TDM. It will allow *a priori* and *a posteriori* Bayesian dosing adjustment, based on the knowledge of drug behaviour in the population of interest. This is a fully integrated tool dedicated to the optimal patients care (**figure 2.2.6**). Its main benefits, additionally to its numerical background, will reside in its intuitive user interface and its user-friendliness, mostly suited for non experienced users. The program affords also educational opportunities. Its modular implementation largely based on plugins make it very flexible, able to evolve and readily customizable for any institution.

Alpha testing of EzeCHieL, i.e. an internal testing at the developers' site, is currently ongoing. The release of a beta version is now expected in a short time. This means that the software will be released for a small group of targeted users, outside of the developer's team, for further tests and validation

The software will keep evolving from a user perspective. To ensure the continued existence and the development of the software and its wide use in the future, issues should be fixed and the tool should be able to be modified and improved; addition of novel functionalities should be allowed as well. Support of the software will gently slide towards a semi-private business. Our aim is to set up a flexible structure in order to collect resources for promoting efficiency, development and ensuring financial support, to maintain and disseminate it.

In the future, EzeCHieL will be able to embark into a point-of-care system for bioanalysis of drugs in blood, currently under development [16]. It will also provide the medical doctor with information

on the situation of the patient within the population and accordingly suggest dosing adjustment which in turns could be directly sent back to the patient.

In a World more and more connected and miniaturized, development of an embedded light version of EzeCHieL is also underway, to be used at anytime and anywhere either by the medical doctor or by the patient itself. It could be then synchronised with the standard version of EzeCHieL.

Figure 2.2.6. EzeCHieL: An integrated software for dosage individualization

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CHAPTER III. POPULATION PHARMACOKINETICS

Chapter III in the thesis context

Implementation of a Bayesian approach for TDM requires provision of appropriate PK models. The general concept to support this development is the *non-linear mixed effects modeling*. Because some subpopulation may present specific characteristics in terms of drug disposition, specific models are needed such as for neonates. This chapter handles these two aspects for candidate drugs.

Sepsis continues to be one of the main causes of morbidity and mortality in newborns admitted in a neonatal intensive care unit.

Gentamicin remains one of the most frequently administered antibacterial drugs in the neonates for proven or suspected neonatal infection. A TDM of this drug has been advocated for a long time now as a consequence of a large PK variability as well as well-defined concentration-efficacy and toxicity relationships. The collection of PK and clinical data in a large cohort of premature and term neonates allowed conducting a population PK study of gentamicin, which represents, to the best of our knowledge, the largest study ever done in such population. This study aimed to identify important predictors of drug exposure. Concretely, the study permitted to reassess the necessity of a systematic drug monitoring in the light of shorter treatment duration. Our simulations supported current *a priori* dosage recommendations. Our results were incorporated in EzeCHieL for the development of Bayesian TDM for this drug.

This model was used to re-evaluate the potential association of gentamicin exposure with sensorineural hearing loss (SNHL). Under the supervision of Dr E. Giannoni, that initiates this work, Lara Zimmerman collected and analyzed all demographic, clinical and therapeutic data (including aminoglycoside treatment course) to conduct a case-control study. A brief overview of our contribution in this work is given after the model description.

In contrast, imipenem is administered in complex and critical situations, often in very premature neonates. Our institution offers a TDM for this drug. Standard recommended dosage seems leading

to sub-therapeutic exposure in many of those patients in this subpopulation. Only one population PK study has been published in neonates so far (Yoshizawa et al. Pediatr Infect Dis J. 2013). This study has the advantage to present blood and urinary data, but with only a limited number of covariates of importance retained for such population (body weight, age). Once again, this study aimed to identify important predictors of drug exposure, and to quantify their impact. Simulation will provide dosage recommendation that should further be validated in a real clinic care setting. Our result will be incorporated in EzeCHieL.

Own contribution:

For both population PK analysis (gentamicin and imipenem): Protocol elaboration. Collection and assembly of all the data. Population pharmacokinetics modeling, analysis and interpretation of the data. Drafting of the article. Publication process for gentamicin. Regarding imipenem, the work is still ongoing. Dosing regimen simulations will be provided in a near future.

For the case control-study regarding gentamicin exposure and SNHL: Collection and assembly of gentamicin dosing history. Individual pharmacokinetics parameters of gentamicin exposure estimation. Logistic regression analysis.

III.1. POPULATION PHARMACOKINETIC STUDY OF GENTAMICIN IN A LARGE COHORT OF PREMATURE AND TERM NEONATES

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ABSTRACT

Aim: This study aims to investigate the clinical and demographic factors influencing gentamicin pharmacokinetics in a large cohort of unselected premature and term newborns and to evaluate optimal regimens in this population.

Method: All gentamicin concentration data, along with clinical and demographic characteristics, were retrieved from medical charts in a Neonatal Intensive Care Unit over 5 years within the frame of a routine therapeutic drug monitoring programme. Data were described using non-linear mixed-effects regression analysis (NONMEM®).

Results: A total of 3039 gentamicin concentrations collected in 994 preterm and 455 term newborns were included in the analysis. A two compartment model best characterized gentamicin disposition. The average parameter estimates, for a median body weight of 2170 g, were clearance (CL) 0.089 l h−1 (CV 28%), central volume of distribution (*V*c) 0.908 l (CV 18%), intercompartmental clearance (Q) 0.157 l h−1 and peripheral volume of distribution (*V*p) 0.560 l. Body weight, gestational age and post-natal age positively influenced CL. Dopamine co-administration had a significant negative effect on CL, whereas the influence of indomethacin and furosemide was not significant. Both body weight and gestational age significantly influenced *V*c. Model-based simulations confirmed that, compared with term neonates, preterm infants need higher doses, superior to 4mg kg−1, at extended intervals to achieve adequate concentrations.

Conclusion: This observational study conducted in a large cohort of newborns confirms the importance of body weight and gestational age for dosage adjustment. The model will serve to set up dosing recommendations and elaborate a Bayesian tool for dosage individualization based on concentration monitoring.

III.1.1. Introduction

The use of aminoglycosides is limited by their potential ototoxicity and nephrotoxicity, consequent to drug accumulation in the inner ear and kidney [1-5]. Despite their toxicity, aminoglycosides are widely used in clinical practice. In recent guidelines, gentamicin remains the first line of treatment for suspected early-onset neonatal sepsis [6, 7]. Pharmacodynamic investigations have shown a concentration-dependent activity, mainly related to the ratio of peak plasma concentration over minimum inhibitory concentration (*C*max : MIC), which should exceed 8 to 10 for optimal efficacy [8]. Gentamicin is essentially eliminated by renal excretion through glomerular filtration and binds to only a limited extent to plasma proteins (between 0–15% [9, 10], and up to 30% according to some authors [11]). The majority of nephrons are formed in the third trimester of pregnancy and nephrogenesis is complete between 32 to 36 weeks of gestation [12, 13]. In the last decade, preterm births (below 37 weeks of gestation) have constituted about 10% of total births worldwide [12] and the survival rates of these extremely preterm infants have particularly increased. Infants born at 25 weeks of gestation now have up to 80% chance of survival [14]. In this subpopulation, the glomerular filtration rate (GFR) is quite low at birth, but this is also typical in term newborns. During the first weeks of life, there is a progressive rise in GFR resulting from an acute increase in cardiac output and renal blood flow induced by birth and a decrease in renal vascular resistance [15]. Thus, renal elimination of gentamicin in neonates is largely linked to both gestational age and post-natal (PNA) age. It is worth noting that, as creatinine crosses the placental barrier, blood creatinine concentrations are not a reliable indicator of renal function in the first days of life as they reflects maternal rather than neonate concentrations [13]. Gentamicin is a polar molecule and is distributed predominantly in extracellular fluid, which varies inversely with gestational age [16, 17]. The large amount of extracellular body water in neonates and young infants results in lower plasma concentrations compared with adults for a given body weight-adjusted dosage regimen [18]. Therefore, because of age-associated changes in organ function and body composition,

gentamicin treatment regimens must be individualized appropriately to reflect maturation (increase in age) and growth (increase in size). Therapeutic drug monitoring (TDM), involving a close monitoring of the exposure of drug plasma concentrations so as to prevent toxicity and lack of efficacy, is the standard of care to optimize the dosage of aminoglycosides. A Bayesian forecasting approach for estimation of individual pharmacokinetic (PK) parameters currently represents the gold-standard approach for TDM [19]. It is becoming increasingly advocated for treatment individualization in neonates [20, 21]. The purpose of this study was to characterize the population PK parameters of gentamicin in a large cohort of preterm and term neonates and to investigate the influence of clinical, physiological and environmental factors on the disposition of the drug. The second objective was to evaluate the achievement of target concentrations according to dosage regimen recommendations based on simulations. These recommendations will retrospectively be compared with a dosing regimen based on a two point adjustment approach performed routinely in our hospital within the framework of TDM. The results should ultimately serve to build up gentamicin Bayesian-inspired TDM tools for dosage individualization in patients who need monitoring [22].

III.1.2. Method

Study population

All neonates admitted in the Service of Neonatology of the Lausanne University Hospital between December 2006 and October 2011 and receiving gentamicin were eligible for the study. This retrospective study was approved by the local ethics committee of the Lausanne University Hospital. Initially, 3168 gentamicin concentration measurements collected from 1500 subjects, were retrieved using the clinical information system (MetaVision, iMDsoft, Massachussetts, USA) and the routine TDM database. Of these, 129 samples were excluded from analysis for the following reasons: missing information on drug administration or sampling times, inconsistencies in dosing interval or administered dose or unclear dosing schedules. The following characteristics were

systematically collected: gender, body weight (BW) at the time of blood sampling, gestational age (GA), PNA, concomitant treatment with furosemide, dopamine and non-steroidal anti-inflammatory drugs (ibuprofen and indomethacin), presence of a patent ductus arterious (PDA) and concomitant respiratory support with invasive or non-invasive ventilation.

Drug administration and serum concentrations

Gentamicin (Garamycin®, Hexal, Holzkirchen, Germany) was administered intravenously over a 30 min infusion, most of the time in association with amoxicillin. The conventional initial dose was 3mg kg–1 from December 2006 until April 2011, followed by 4mg kg–1 from May 2011 to October 2011 according to a change in local guidelines. Within the framework of a routine TDM programme in our hospital, plasma drug concentrations were drawn twice, 1 h and 12 h after the first gentamicin dose, in order to individualize the dosage regimen based on a classical two point approach linear regression [23]. Further concentration measurements could be requested by the physician if the treatment was prolonged.

Analytical assay

Serum concentrations were determined by fluorescent polarization immunoassay (Cobas Integra 400 Plus, Roche Diagnostics, Rotkreuz, Switzerland). Lower limits of detection and quantification were, respectively, 0.04 and 0.5 mg l^{-1}. Coefficients of variation (CV) for imprecision were ≤2.5% at 0.9 and 7.8 mg l^{-1} within run and ≤3.1% at 1.5, 4.4 and 7.0 mg l–1 between runs.

Model-based pharmacokinetic analysis

Base model: The population PK analysis was performed using a non-linear mixed-effect modelling approach with NONMEM® (version 7.1.0, ICON Development Solutions, Ellicott City, MD, USA), using first order conditional estimation with interaction (FOCEI). A stepwise procedure was used to identify the model that best fitted the data comparing one and two compartment open models. Exponential errors were used for the description of the between subject variability (BSV) of PK

parameters. Proportional, additive and mixed error models were compared which describe the residual variability.

Covariate model: At first, the graphical exploration of continuous covariates (BW, GA, PNA, postmenstrual age (PMA) defined as the sum of PNA and GA) and categorical covariates (gender, co-treatment with furosemide, dopamine and indomethacin, PDA, invasive and non-invasive ventilation) effects were carried out to visualize the relationship between the PK parameters and the covariates. Potentially influencing covariates were then included in the model following a sequential forward selection and backward elimination. Ibuprofen and vancomycin, which can affect renal function, were not administered in this population and their influence could thus not be investigated. The influence of body weight on gentamicin PK parameters was used as a first covariate characterized using allometric scaling [24].

$$\theta = \theta_1 . \left(\frac{BW}{BW_{median}}\right)^{PWR} \quad (1)$$

Other continuous covariates were implemented in the model using a linear (2), allometric (3) or exponential equation (4). Continuous variables were centred on the median:

$$\theta = \theta_1 . \left(1 + \theta_2 . \left(\frac{COV - COV_{median}}{COV_{median}}\right)\right) \quad (2)$$

$$\theta = \theta_1 . \left(\frac{COV}{COV_{median}}\right)^{\theta_2} \quad (3)$$

$$\theta = \theta_1 . \exp\left(\theta_2 . \left(\frac{COV - COV_{median}}{COV_{median}}\right)\right) \quad (4)$$

Categorical covariates were implemented in the model according to the following equation:

$$\theta = \theta_1 . (1 + \theta_2 . COV) \quad (5)$$

Since PMA represents the sum of GA and PNA, PNA or GA were not considered if PMA was already included in the model and *vice versa*.

Parameter estimation and model selection: Difference in objective function value (ΔOF), NONMEM® goodness-of-fit statistics, along with diagnostic goodness-of-fit plots, were used for model comparison. Since ΔOF between any two hierarchical models approximates a $\chi 2$ distribution, it was considered statistically significant if it exceeded 3.8 ($P < 0.05$) and 6.6 ($P < 0.01$) points respectively, for one additional parameter during model building and backward deletion procedures. Akaike's information criterion (AIC) was used for non-hierarchical models. Shrinkage was also examined. When more than one covariate describing the same effect (GA, PNA and PMA) was found significant, the covariate causing the largest drop in objective function was preferred. A sensitivity analysis was performed for patients with absolute values for conditional weighted residuals (CWRES) greater than 5 to test for potential bias in parameter estimation and in covariate exploration. It concerned eight data points for six patients. Four observations were excluded for suspected error in administered dose, one observation for suspected error in time recording and one observation for suspected sampling bias. No obvious reason could plain high CWRES (6.3 and 5.8) associated with the two remaining observations and they were thus kept in the analysis. The sensitivity analysis showed that none of these concentration values affected the PK estimates (data not shown). Parameters estimates, when scaled on BW, are reported for the median BW, i.e. 2170 g.

Model validation and simulation: The final model stability was assessed by the bootstrap method using the PsNToolkit [25] (version 3.5.3, Uppsala, Sweden). Mean parameter values with their 95% confidence interval (95% CI) estimated from 2000 re-sampled data sets were compared with the original model estimations. In addition, prediction-corrected visual predictive checks (pcVPC) [26] were performed with PsN-Toolkit and Xpose4 [27] (version 4.3.5, Uppsala, Sweden) by simulations based on the final PK estimates using 1000 individuals. Mean prediction corrected concentrations

with their 95% percentile interval (95% PI) at each time point were retrieved. Eventually, an independent set of 71 premature and term newborns recruited through TDM between January 2013 and April 2013 was employed for external model validation. From this external dataset, two individuals were excluded for an inconsistent dosing record. Population and individual *post hoc* concentrations were derived from the final model to assess the accuracy and the precision by means of the mean prediction error (MPE) and the root mean squared error (RMSE) [28], using log-transformed concentrations. Goodness-of-fit plots of population and individual predictions obtained in the final model *vs*. the observations were generated using R (version 2.15.1, R Development Core Team, Foundation for Statistical Computing, Vienna, Austria). Finally, observed and simulated concentrations were also compared by the normalized prediction distribution error (NPDE) method where each observation was simulated 3000 times (supporting information **Figure 3.SI**). Average concentration–time profiles, with their 90% prediction interval (90% PI), were simulated for five representative patients (with a GA of 26, 30, 34, 37 and 40 weeks and a BW of 890, 1080, 2120, 2950 and 3580 g respectively, chosen as illustrative from the original dataset) using different dosage regimens, without dopamine co-administration. Dosage regimens evaluated were any combination of 4mg kg^{-1}, 4.5 mg kg^{-1} or 5mg kg^{-1} any 24 h, 36 h or 48 h.

Comparison of dosage adjustment methods

The achievement of target concentrations was evaluated by comparing (i) dosing regimen recommendations based on the previously presented simulations and (ii) by TDM using the classical linear regression [23]. The external validation dataset was used for the comparison between both approaches. Peak and trough concentrations were predicted based on our final model (i) with dosing regimens adjusted for GA and BW according to our recommendations and (ii) based on individual dosage regimens derived from the linear regression method in the frame of TDM. Each set of patients was simulated 1000 times per method. For each set of patients simulated,

the proportion of subjects meeting concentration targets at steady-state was retrieved. The mean with the 95% CI of the proportions were calculated.

III.1.3. Results

Gentamicin concentration data were collected from 1449 neonates, including 994 preterm (median gestational age 32 2/7 weeks, range 24 2/7–36 5/7 weeks) and 455 term newborns, representing a total of 1449 neonates who provided 3039 concentration measurements. A summary of the patients' characteristics for the model building and validation datasets is presented in **Table 3.1.1.** Peak concentrations represented 42% of samples (measured between 0.5 and 1.5 h after the start of infusion), while 40% were sampled about 12 h after the first dose (between 11.5 and 12.5 h after the start of infusion). Most drug measurements (86%) were performed after the first gentamicin dose and only 3% of concentrations were sampled beyond 72 h of treatment. The majority of the measurements (98%) were performed within the first week of life. Gentamicin concentration measurements ranged between 0.5 and 22.1 mg l^{-1} (one subject had a concentration of 29 mg l^{-1} because he received accidentally 10 times the usual prescribed dose).

Table 3.1.1. Characteristics of the patients at treatment initiation

	Model-building set *N = 1449*		**External validation set** *N = 69*	
BW (g)	2170	(440-5510)	2060	(600-4200)
GA (wk)	34	(24-42)	34	(24-42)
PNA (d)	1	(0-94)	1	(0-34)
PMA (wk)	34.4	(24.2-42.4)	34.2	(24.2-42.1)
Male	834	(57.5%)	38	(53.5%)
IV	301	(20.8%)	21	(30.4%)
NIV	861	(59.4%)	51	(73.9%)
PDA	153	(10.6%)	9	(13.0%)
Furosemide	5	(0.3%)	0	(0%)
Dopamine	136	(9.4%)	1	(1.4%)
Indomethacin	27	(1.9%)	2	(2.7%)
Amikacin	2	(0.1%)	0	(0%)

Median (range) or count (percent). **BW** = Body Weight; **GA** = Gestational Age; **PNA** = Postnatal Age; **PMA =** Postmenstrual Age; **IV** = Invasive Ventilation; **NIV** = Non Invasive Ventilation; **PDA** = Patent Ductus Arteriosus

Base model

A two compartment model parameterized in terms of clearance (CL), inter-compartmental CL (Q), volume of distribution of the central compartment (*V*c) and peripheral volume of distribution (*V*p) best described the data (ΔOF from the one compartment model was −280.0, $P < 0.001$). In addition to CL, an improvement of the fit was observed while including BSV on *V*c (ΔOF = −252.8, $P < 0.001$) and a correlation of 87% was estimated between CL and *V*c (ΔOF = −186.8, $P < 0.001$). Intrapatient variability was best described by a combined additive and proportional residual error model. The final base population parameters with their BSV were a CL of 0.087 l h^{-1} (CV 65%), a *V*c of 0.825 l (CV 45%), a Q of 0.185 l h^{-1} and a *V*p of 0.714 l. Additive and proportional residual error were 0.89 mg l^{-1} and 18%, respectively.

Covariate model

Figure 3.1.1 summarizes the model-building steps performed for the covariate analysis. The assignment of BW on CL, *V*c, Q and *V*p, following an allometric equation with a power of 0.75 on CL and Q and 1 on the volume parameters, markedly improved the description of the data (ΔOF = −3391.5, $P < 0.001$). The comparison of a one compartment allometric with a two compartment allometric model for BW showed that the latter provided a better fit of the data (supporting information **Table 3.SI**). The use of a power function of 0.66 for BW on CL parameters was also investigated [29] but was significantly worse than the model with a power of 0.75 (ΔOF = 99.8, $P < 0.001$). Estimates of CL and Q increased by 68% whilst *V*c and *V*p on BW doubling increased by 100 %. This explained 45% of the intervariability in CL and 55% in *V*c. Owing to the very large effect of BW on these parameters, this variable was kept in the model for further covariates searches. The sequential addition of GA, PNA and PMA using a linear function on CL and *V*c resulted in a better description of the data. PMA was the most important covariate on CL (ΔOF = −658.1, $P < 0.001$) and on *V*c (ΔOF = −214.6, $P < 0.001$). Since PMA is the sum of GA and PNA, we searched which combination of these latter variables provided the best description of the data. Comparing PMA

with GA + PNA on CL showed a significant drop in the OF value (ΔOF = −750.8 $P < 0.001$) in favour of the model with the two distinct covariates GA and PNA. PMA was slightly more significant than GA on *Vc* (ΔOF = −206.1 for PMA compared with ΔOF = −201.8 for GA, $P < 0.001$ with the AIC difference between the two models 4.3 points in favour of PMA). However, PNA did not show any influence on *Vc* in the univariate analysis (ΔOF = −1.9, $P = 0.16$). Following the parsimony principle, GA alone was preferred to PMA as a covariate on *Vc*. Eventually, PMA was also retested in the final model in replacement of GA, confirming that it was not a better predictor than GA (ΔOF = 0.14, $P = 0.70$, and AIC was 1964 for both models). CL was reduced by 12% and 18% by co-administration of dopamine (ΔOF = −11.3, $P < 0.001$) and indomethacin (ΔOF = −7.8, $P = 0.005$), respectively. Although not statistically significant, furosemide co-administration reduced CL by 34% (ΔOF=−6.3, $P = 0.012$). No other covariates showed any significant effect on gentamicin disposition (ΔOF > −6.1, $P > 0.01$).

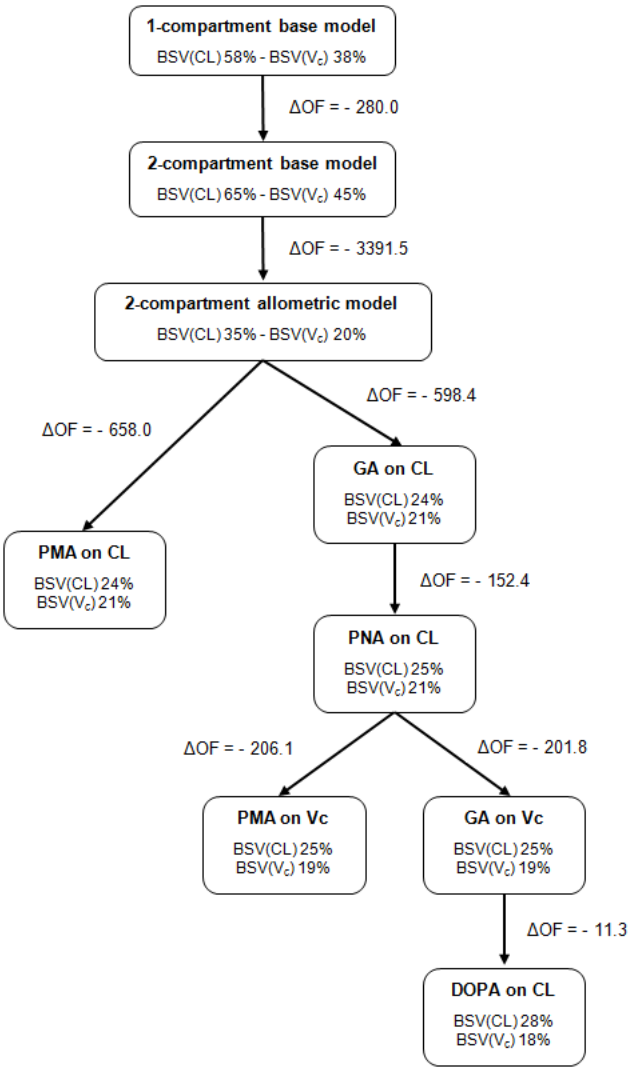


Figure 3.1.1. Major steps of model building

Model validation and simulation

The parameter estimates of the final population PK model, except for indomethacin, remained within the bootstrap 95% CI and differed by less than 9% from the median parameters obtained with the bootstrap analysis, suggesting that the model was acceptable. Since the indomethacin

coefficient 95% CI included 0, it was omitted from the final model. It appeared that it did not affect the model as the relative difference in parameter estimates between the model with and without indomethacin was less than 3% (data not shown). The structural and the final model parameter estimates as well as the bootstrap are presented in **Table 3.1.2**. The results of pcVPC supported the predictive performance of the model and are presented in **Figure 3.1.2.** Goodness-of-fit plots are presented in **Figure 3.1.3**. The external validation showed a small bias of −3% (95% CI −1, −4%) in the individual predictions, with an imprecision of 12% (supporting information **Figure 3.SII**). A similar bias of −6% (95% CI −3, −9%) was calculated for population predictions, with an imprecision of 22%. Only one patient received dopamine among the newborns of the validation dataset. Average concentration−time profiles for the different GAs and dosing schedules are presented in **Figure 3.1.4**. These results confirm that higher doses and longer dosage intervals are needed in very preterm newborns compared with term infants to reach target concentrations (Cmin ≤ 1mg l^{-1} and Cmax ≈ 8mg l^{-1}). The dosing recommendations that came forth from these simulations were identical to those proposed by reference drug guidelines used in neonatology, namely 5mg kg^{-1} every 48 h for GA ≤ 29 weeks, 4.5 mg kg−1 every 36 h for 30 ≤ GA ≤ 34 and 4mg kg^{-1} every 24 h in the first days of life [30].

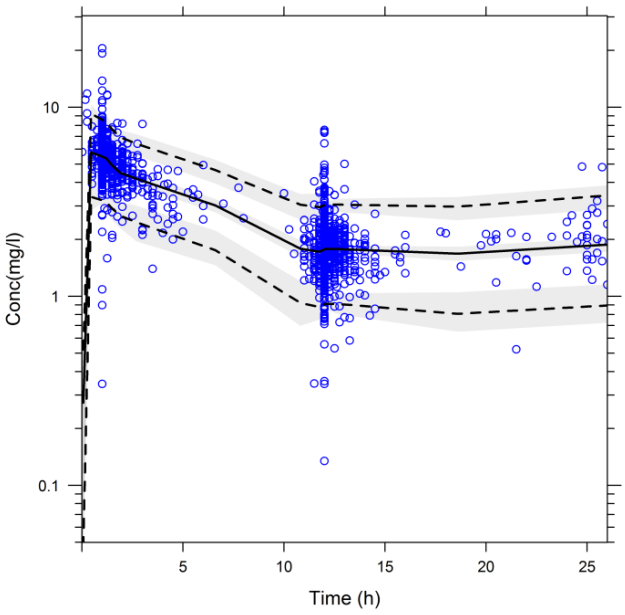


Figure 3.1.2. Prediction-corrected visual predictive check of the final model with gentamicin prediction-corrected concentrations (circles) and population prediction (solid line) with the corresponding 95% prediction interval (dotted lines). Semi-transparent grey fields represent the model-based percentile confidence interval

Table 3.1.2. Parameter estimation of structural and final pharmacokinetic models, with final model associated bootstraps

	Structural model		Final model		Final model bootstrap (n=2000 samples)		
Parameters	**Estimates**	**SE (%)**	**Estimates****	**SE (%)**	**Estimates****	**CI (2.5%)**	**CI (97.5%)**
CL (L/h)	0.087	1 [a]	0.089	1 [a]	0.089	0.084	0.098
θ_{CLBW}			0.75	-	0.75	-	-
θ_{CLGA}			1.870	3 [a]	1.879	1.638	2.010
θ_{CLPNA}			0.054	6 [a]	0.054	0.024	0.082
θ_{CLDOPA}			-0.120	22 [a]	-0.118	-0.198	-0.034
V_c (L)	0.825	1 [a]	0.908	2 [a]	0.895	0.481	0.950
θ_{VcBW}			1	-	1	-	-
θ_{VcGA}			-0.922	8 [a]	-0.940	-2.276	-0.816
Q (L/h)	0.185	9 [a]	0.157	7 [a]	0.172	0.108	0.737
θ_{QBW}			0.75	-	0.75	-	-
V_p (L)	0.714	16 [a]	0.560	4 [a]	0.580	0.472	0.678
θ_{VpBW}			1	-	1	-	-
BSV CL (%)	65	5 [b]	28	3 [b]	28	22	30
BSV V_c (%)	45	5 [b]	18	1 [b]	19	12	39
Correlation CL-V_c (%)			87	3*	86	54	111
Additive residual error (mg/L)	0.89	14	0.10	24 [a]	0.10	0.03	0.19
Proportional residual error (%)	18	11	18	1 [a]	18	16	19

[a] Standard errors of the estimates (SE),defined as SE/estimate and expressed as percentages. [b] Standard errors of the coefficient of variation, taken as $SE/(Estimates \times 2)$ and expressed as percentage. * Standard error of the correlation estimate directly retrieved from the NONMEM® output file and expressed as percentages. **CL** = Clearance; **V_c** = Central volume of distribution; **BW** = Body weight; **GA** = Gestational age; **PNA** = Postnatal; **DOPA** = Dopamine; **Q** = Intercompartmental clearance; **V_p** = Peripheral volume of distribution; **BSV** = Between subject variability

$$TVCL = \theta_{CL} \times \left(\frac{BW}{2170}\right)^{0.75} \times \left[1 + \theta_{CLGA} \times \left(\frac{GA-34}{34}\right)\right] \times \left[1 + \theta_{CLPNA} \times \left(\frac{PNA-1}{1}\right)\right] \times (1 + \theta_{CLDOPA})$$

$$TVV_c = \theta_{V_c} \times \left(\frac{BW}{2170}\right)^{1} \times \left[1 + \theta_{V_cGA} \times \left(\frac{GA-34}{34}\right)\right]$$

** Value estimates for the median body weight 2.170 kg from the current study

Comparison of dosage adjustment methods

Table 3.1.3 presents the proportion of subjects reaching target trough and peak concentrations at steady state, according to both methods (i.e. the guidelines and the two point linear regression). One subject was excluded because the $C12h$ concentration was missing and the dosage adjustment using the two points approach could not be performed. A broader range of target concentrations was also considered in this comparison to account for different thresholds proposed in the

literature (trough concentration <2mg l–1 and peak concentration between 5–12 mg l^{-1} [31, 32]). This analysis reveals that the application of guidelines would lead to similar, if not better results in terms of target achievement of peak and trough concentrations than the linear regression based on a systematic TDM.

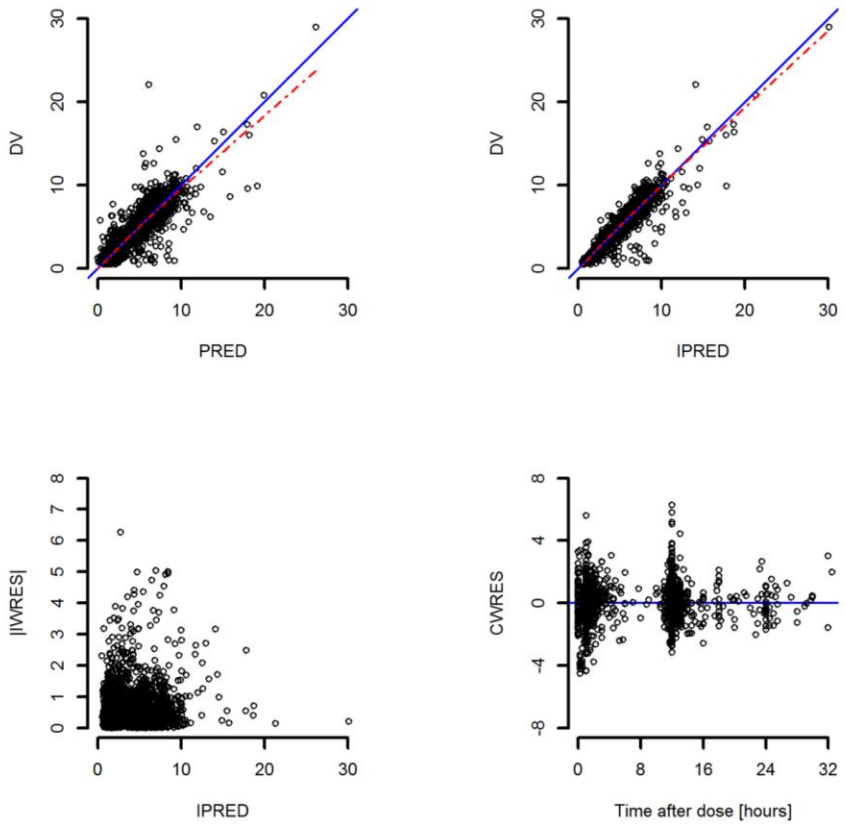


Figure 3.1.3. Goodness-of-fit plots of observations (DV) versus the population (PRED, left up panel) and individual predictions (IPRED, right up panel), absolute individual weighted residuals (|IWRES|) versus

Table 3.1.3. Model-based simulated proportion of patients reaching target concentration according to dosing adjustment method *

GA (weeks)	BW (g)	< 1 mg/l (% [CI95%])		< 2 mg/l (% [CI95%])		> 6 mg/l (% [CI95%])		> 8 mg/l (% [CI95%])		> 10 mg/l (% [CI95%])	
		Guidelines	Linear regression	Guidelines	Linear regression	Guidelines	Linear regression	Guidelines	Linear regression	Guidelines	Linear regression
24-42	600-4200	64	42	94	82	93	83	69	55	37	28
n=68		[52-73]	[32-52]	[89-99]	[73-89]	[86-99]	[75-91]	[58-79]	[45-65]	[26-49]	[18-38]

GA = Gestational age; **BW** = Body weight

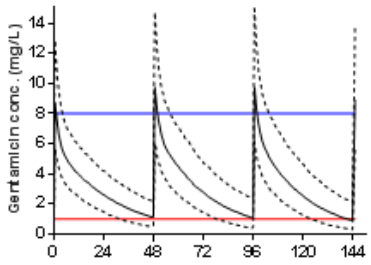
* Guidelines were as follows:

GA ≤ 29 weeks	5 mg/kg	every 48 hours
30 ≤ GA ≤ 34 weeks	4.5 mg/kg	every 36 hours
GA ≥ 35 weeks	4 mg/kg	every 24 hours

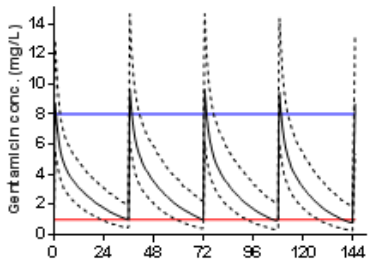
* Linear regression provides an individualized dosing regimen based on a two-points method

Results are based on a small group of 68 patients that were simulated 1000 times each according to both methods of dosing adjustment

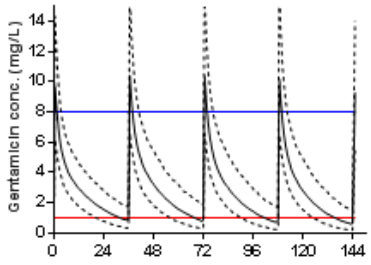
GA	26 weeks
BW	890 g
Dose	5 mg/kg
Interval	48 hours



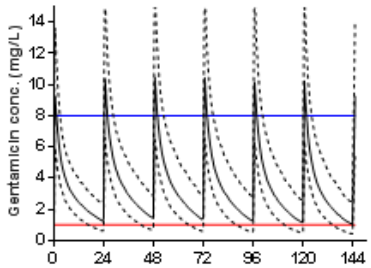
GA	30 weeks
BW	1080 g
Dose	4.5 mg/kg
Interval	36 hours



GA	34 weeks
BW	2120 g
Dose	4.5 mg/kg
Interval	36 hours



GA	37 weeks
BW	2950 g
Dose	4 mg/kg
Interval	24 hours



GA	40 weeks
BW	3580 g
Dose	4 mg/kg
Interval	24 hours

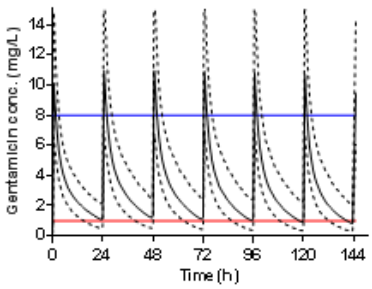


Figure 4. Model-based predicted concentration-time profiles (solid line) and the 90% prediction interval (dotted lines) for five gestational ages and body weights using the dosage regimen allowing target concentration to be reached ($C_{min} \leq 1$ mg/l and $C_{max} \approx 8$mg/l). **GA** = Gestational Age, **BW** = Body Weight

III.1.4. Discussion

To our knowledge, this is the largest study evaluating the population PK of gentamicin in a cohort of unselected neonates covering a wide range of body weight and gestational age. The PK of gentamicin has been previously described using one [33-46] two [47-50] and three [51, 52] exponential disposition terms, which probably illustrate the deep compartments and tissue accumulation of gentamicin. Our PK estimates of CL and *V*c are in good accordance with previously published studies in a similar population [34, 35, 37, 38, 43, 46]. The half-life of the terminal phase was estimated to be 12.5 h, much lower than the values derived by others based on three compartment models (87 to 173 h [48], 27 to 693 h [49], 94 h [51] in adults and 425 h [52] in neonates). This discrepancy is most probably related to differences in study design, with short treatment courses and lack of gentamicin concentration measurements beyond 72 h, preventing adequate characterization of the slowest distribution component of the drug in peripheral tissues and thus, of a third exponential term. Description of gentamicin PK confirmed that the primary factors influencing newborns' exposure are size and age (BW, GA and PNA) [53]. Gentamicin is a hydrophilic drug that is rapidly and predominantly distributed into extracellular fluid. Extracellular fluid represents approximately 65% of BW at 35 weeks of gestation and falls to 40% at term [16]. At the same time, fat mass and intracellular water increase. Decrease in body water also continues after birth and extracellular fluid becomes closely related to BW [54], supporting our observations of an effect of body weight on *V*c. Gentamicin CL increases with age. Because renal maturation progresses before birth [18], it was advocated that PMA would be a better predictor than PNA [53, 55, 56]. In the present study, PMA was found to be a good predictor of gentamicin CL, but the use of GA and PNA described gentamicin disposition better than PMA alone. Our results are in excellent agreement with the study of Nielsen *et al*. [52], who found an influence of both GA and PNA on CL and GA on *V*c. Dopamine was found to be a relevant factor associated with a 12% decrease in CL. The impact of dopamine on GFR in neonates is not well documented [57-59] and, has never been observed for gentamicin in others studies. Only a few patients were treated with dopamine (9%). Its influence on gentamicin elimination appears small and of limited clinical significance in this

analysis. It might principally reflect cardiovascular instability in critically ill newborns. Several studies have shown the potential effect of ibuprofen and indomethacin on glomerular filtration reflected by a reduction of renal excretion of drugs such as aminoglycosides [15, 42, 60-62]. Our results also suggest an influence of indomethacin on gentamicin CL, although this effect was not validated. The small number of patients (n = 27) might have limited the power to detect true effect. It is also possible that confounding factors were reflected this way, since those newborns had a very low body weight, (mean 852 g, range 440–1390 g), as well as haemodynamically significant PDA, which is associated with poor renal perfusion [63]. Even so, PDA had no significant impact on CL *per se* in this analysis. Furosemide was not found to significantly reduce gentamicin CL, as opposed to one study which suggested an increase in gentamicin concentrations as a result of furosemide co-administration [64]. Only five patients received it, four of whom were on concomitant dopamine treatment. This might have limited the possibility to detect an independent effect of furosemide. In addition, some studies found a relation between respiratory disorders or invasive and non-invasive ventilation with gentamicin CL or V [34, 65, 66]. No influence of respiratory support on gentamicin kinetics was observed in our study. Several limitations of this analysis should be acknowledged, in particular the use of routine TDM data involving for the most part only two concentration measurements collected after the first dose, thus limiting the possibility to characterize deep compartment kinetics. In addition, due to the retrospective design, errors coming from inaccurate times or dosage recording could not be systematically traced and corrected. Model-based simulations suggest that most infants born at a GA above 34 weeks are expected to reach target concentrations (peak above 8mg l^{-1} and Cmin below 1mg l^{-1} [67, 68]) with a standard dosage of 4mg kg^{-1} once daily. Preterm neonates require longer dosing intervals, up to 48 h and extremely preterm neonates (below 28 weeks of GA) will also require higher doses of 5mg kg–1. These observations are in accordance with dosing recommendations issued since the mid-1990s [30, 69] that advocate high doses and extended intervals to reach sufficient peak concentrations whilst minimizing toxicity. Proposed dosing regimens were designed assuming fixed values of concentration thresholds for effect and toxicity, in accordance with numerous studies

demonstrating the importance of a high ratio *C*max: MIC for aminoglycosides. One study suggested that the area under the curve (AUC) might be of clinical importance for extreme preterm newborns [70]. Target concentrations can also be challenged, as adaptive resistance can arise within the first hours of therapy, probably through a down regulation of the active transport of gentamicin into the bacteria. The use of extended interval dosing seems thus preferable to improve clinical efficacy, as it allows adaptive resistance to resolve while taking advantage of the post-antibiotic effect [31, 70, 71]. Considering that *a priori* dosage regimen recommendations [30] appear appropriate to ensure effective and safe concentration exposure, and that most gentamicin treatments will be stopped after 48 h, TDM has a limited role at treatment initiation in this population. However, the use of TDM to optimize target achievement will still be needed for some patients, since a large variability in drug exposure remains after adjustment for age and body weight, and a proportion of patients will still fail to reach adequate PK targets. This should be particularly considered for those patients receiving prolonged treatment. In conclusion gentamicin kinetics in newborns are very variable and mostly dependent on growth status (represented by BW) and maturation (represented by GA and PNA). The influence of comedications, such as dopamine, as direct or indirect factors influencing renal function should be confirmed. Recent dosing recommendations showed a benefit in terms of target concentration achievement and reduction of TDM need at treatment initiation. Our model will serve to elaborate a Bayesian tool for dosage individualization based on a single measurement [72], that could be ideally suited for dosage individualization of neonates at particular risk of sub-optimal dosing during prolonged therapy.

This work was supported by the Swiss National Science Foundation through the Nano-Tera initiative. The corresponding project (ISyPeM) involves the implementation of software for Bayesian therapeutic drug monitoring. The authors thank Jocelyne Urfer and David Jenny for data management. The authors are also thankful to Sonja Roetlisberger for the careful reading of the manuscript.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare our institution has support from the Swiss National Science Foundation through the Nano-Tera initiative (the corresponding project, ISyPeM, involves the implementation of software for Bayesian therapeutic drug monitoring) for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

Supplementary Material 1

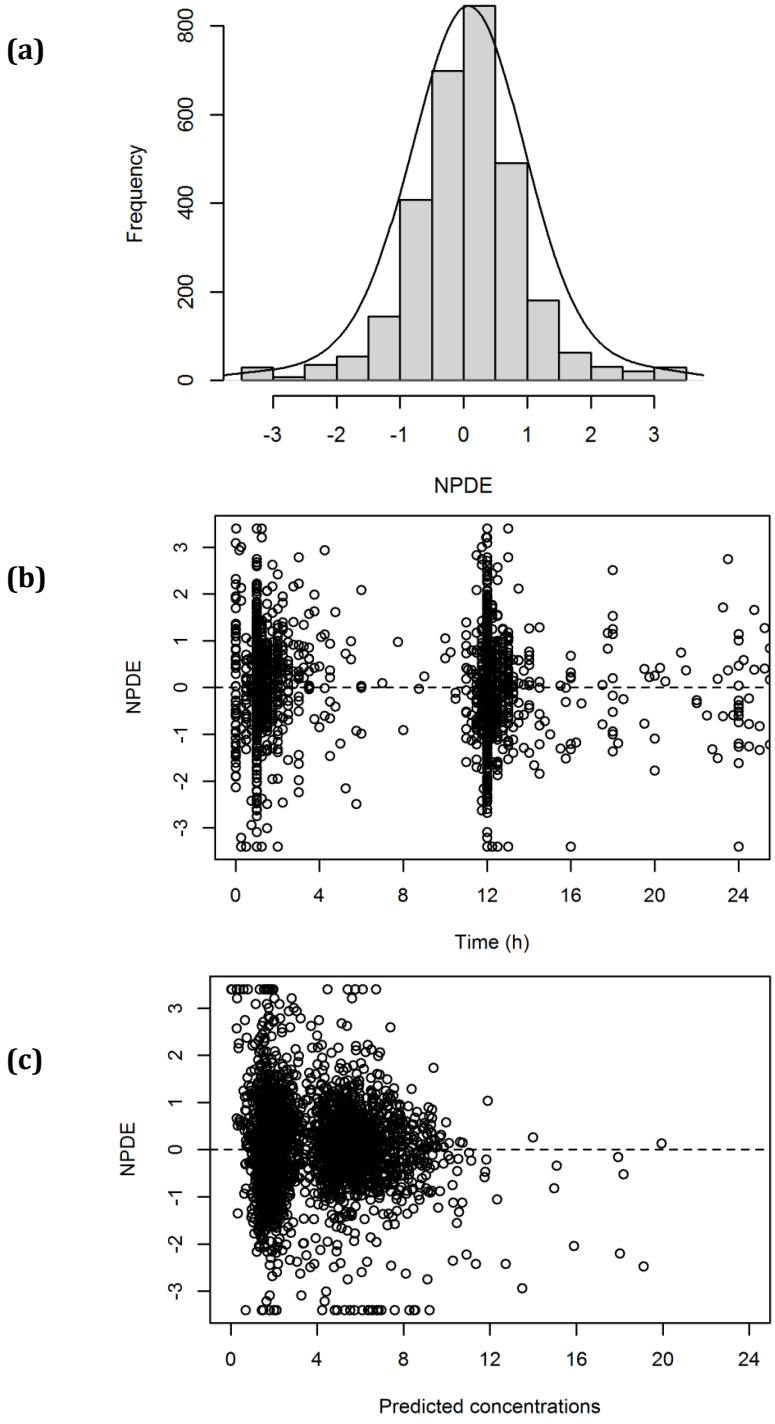


Figure 3.SI. Distribution of the normalized prediction distribution error (NPDE) method. (a) Histograms of the distribution of the NPDE and the solid line representing the normal distribution. Distribution of the NPDE (b) versus time and (c) versus predicted concentrations.

Supplementary Material 2

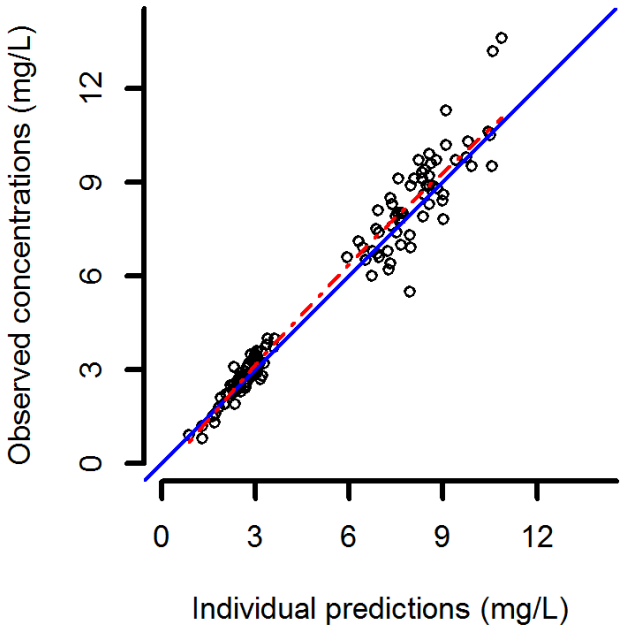


Figure 3.SII. Individual gentamicin predicted concentrations versus observed concentrations (circles) with the smoothed relationship (dotted line) from the final model from the external validation dataset.

Supplementary Material 3

Table 3.SI. Parameter estimation of one-compartment allometric model and two-compartment allometric model

	One-compartment allometric model		Two-compartment allometric model	
Parameters	**Estimates ****	**SE (%)**	**Estimates ****	**SE (%)**
CL (L/h)	0.100	1 [a]	0.089	1 [a]
θ_{CLBW}	0.75	-	0.75	-
V_c (L)	1.041	1 [a]	0.547	2 [a]
θ_{VcBW}	1	-	1	-
Q (L/h)			0.216	11 [a]
θ_{QBW}	0.75	-	0.75	-
V_p (L)			0.635	8 [a]
θ_{VpBW}	1	-	1	-
BSV CL (%)	25	8 [b]	28	4 [b]
BSV V_c (%)	12	15 [b]	11	24 [b]
Additive residual error (mg/L)	0.52	19 [a]	0.26	16 [a]
Proportional residual error (%)	17	7 [a]	19	5 [a]

[a] Standard errors of the estimates (SE),defined as SE/estimate and expressed as percentages. [b] Standard errors of the coefficient of variation, taken as $SE/(Estimates \times 2)$ and expressed as percentage. **CL** = Clearance; **V_c** = Central volume of distribution; **BW** = Body weight; **Q** = Intercompartmental clearance; **V_p** = Peripheral volume of distribution; **IIV** = Interindividual variability. ** Value estimates for the median body weight 2.170 kg from the current study

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III.2. GENTAMICIN EXPOSURE SENSORINEURAL HEARING LOSS IN PRETERM INFANTS

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Under preparation

III.2.1. Objective

The association between gentamicin treatment and development of sensorineural hearing loss (SNHL) is controversial in newborns. Early studies have found an association between aminoglycoside treatment and SNHL in newborn infants [1, 2]. However, since the early 1990s, a number of studies have suggested that gentamicin administered in controlled therapeutic doses is not associated with ototoxicity in newborn infants [3-9]. Gentamicin is still a first-line treatment for infection suspicion: for instance, about 3000 newborns received it between 2000 and 2010 in the service of neonatology of Lausanne. A systematic Therapeutic Drug Monitoring (TDM) was performed after first dose administration. Safety use appears as a public health issue. Our main contribution was to evaluate the role of gentamicin exposure in SNHL in preterm neonates.

III.2.2. Method

Infants that presented a SNHL during the first 5 years of life, born between 1993 and 2010 at a gestational age < 32 weeks and/or with a birth weight < 1500g and hospitalized at Lausanne University Hospital during their neonatal period were identified. For each case, two controls matched for gender, gestational age, birth weight, and date of birth were retrieved.

Gentamicin administration and TDM measurements were recovered from medical records. Different parameters reflecting gentamicin exposure were determined. Cumulative dose, cumulative dose per kg were then calculated. Based on the previously described population pharmacokinetic (PK) model, gentamicin individual PK parameters were retrieved by maximum a posteriori Bayesian estimation. Calculated parameters were: cumulative area under the curve (AUC), maximum predicted trough concentration (C_{trough}) during treatment, clearance per kg with:

$$AUC = \int Concentration \,.\, dt$$

Additionally, weighted AUC for a saturable accumulation in the inner ear was also calculated, according to Michaelis constant (K_M) defined as 0.5, 1 and 2 mg/l, as follow:

$$AUC_{ear} = \int \frac{K_M \times Concentration}{Concentration + K_M} . dt$$

Possible contribution of gentamicin exposure was analysed by logistic regression. Odds ratio and p-value were generated based on the *z* score.

III.2.3. Results

Twenty-five infants diagnosed with a SNHL were identified for the period of search. The proportion of patient treated with gentamicin was 76% in the study group and 70% in the control group. Patients' characteristics are shown in **table 3.2.1**. Individual concentrations predicted by the population PK model were consistent with observations as shown in **figure 3.2.1**.

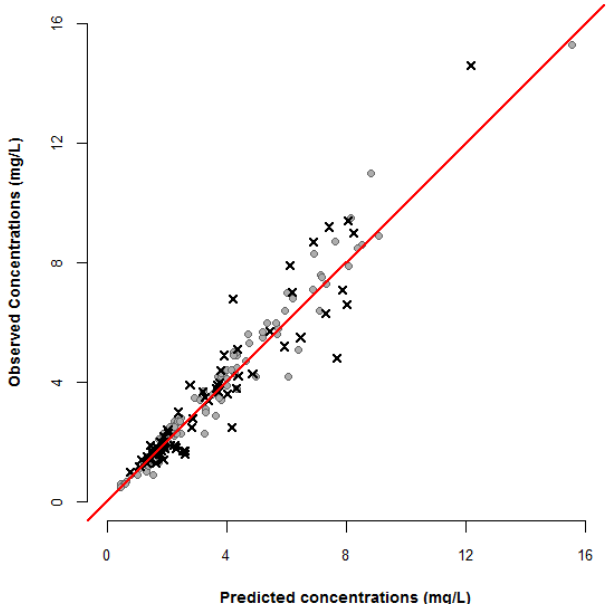

Figure 3.2.1. Observed concentrations versus predicted concentrations. Points: control group, cross: study group

Table 3.2.1. Patients characteristics

	Study group	Control group	*p* value
Total patients			
Count (n)	25	50	*NS*
Female/Male, n (%)	12 (48) / 13 (52)	24 (48) / 26 (52)	*NS*
Median gestational age, weeks [range]	28 [24-32]	28 [25-33]	*NS*
Median birth weight, grams [range]	780 [475 - 2030]	835 [510 - 2060]	*NS*
Patients that received gentamicin			
Count (n) (%)	19 (76)	35 (70)	*NS*
Female/Male, n (%)	11 (56) / 8 (44)	13 (56) / 22 (44)	*NS*
Median gestational age, weeks [range]	28 [24-32]	27 [25-31]	*NS*
Median birth weight, grams [range]	780 [550-1670]	750 [510 - 1670]	*NS*

Cumulative doses and individual pharmacokinetic parameters are presented in **Table 3.2.2**, and a visual comparison per group is proposed in **figure 3.2.2**.

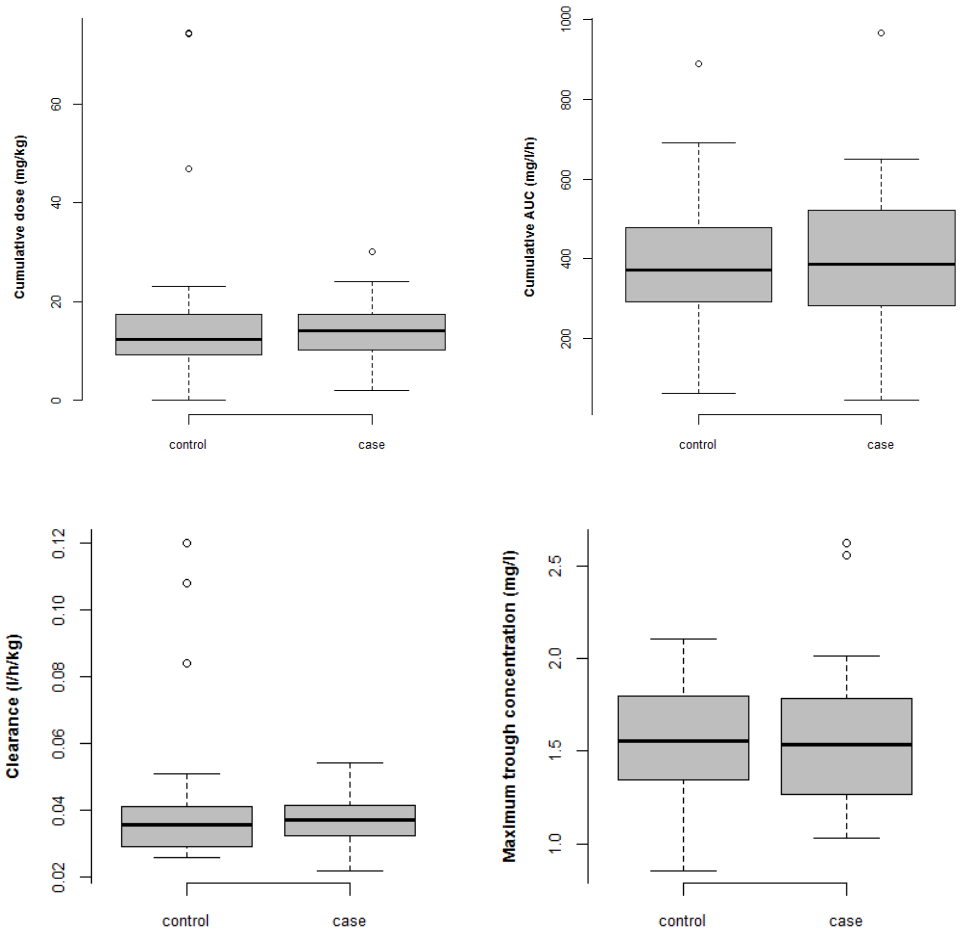

Figure 3.2.2. Boxplots of cumulative dose and derived PK parameters of gentamicin exposure per group

The univariate analysis did not show any significant difference between two groups, neither in cumulative dose nor in the derived PK parameters. Finally, effect of a saturable accumulation in the inner ear at a concentration of 0.5 mg/l ($AUC_{0.5}$), 1 mg/l (AUC_1) and 2 mg/l (AUC_2) did not show any difference between the two groups. Statistics are presented in **table 3.2.2**.

Table 3.2.2. Descriptors of gentamicin exposure

Parameters	Study group	Control group	Odds ratio	*p* value
Cumulative dose (mg)	10 [0 - 33]	8 [0 - 118]	0.99	0.6
Cumulative dose per kg (mg/kg)	12 [0 - 30]	10 [0 – 74]	<0.01	0.7
Cumulative AUC (mg/l.h)	386 [45 - 966]	373 [63 - 888]	1.00	0.8
Clearance per kg (l/h/kg)	0.037 [0.022 – 0.054]	0.036 [0.026 – 0.120]	<0.01	0.4
Maximum trough concentration (mg/l)	1.5 [1 – 2.6]	1.6 [0.9 – 2.1]	2.36	0.2
Cumulative $AUC_{0.5}$ (mg/l.h)	57 [13 - 154]	59 [17 - 121]	1.00	0.9
Cumulative AUC_1 (mg/l.h)	95 [19 - 255]	98 [25 -201]	1.00	0.9
Cumulative AUC_2 (mg/l.h)	148 [25 - 391]	151 [35 - 314]	1.00	0.9

One may notice two higher cumulative doses in the control group due to two patients that received a second subsequent treatment of gentamicin. Analysis was also performed ignoring these two individuals to assess if they could have influenced our results. Again, no statistical difference was observed between the two groups (data not shown). Consequently, no further analyses were undertaken.

III.2.4. Conclusion

While multiple risk factors have been identified in SNHL [10-18], the association with gentamicin exposure was not confirmed in our study.

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III.3. POPULATION PHARMACOKINETIC STUDY TO EVALUATE DOSING STRATEGIES OF IMIPENEM IN NEONATES AND INFANTS

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Under preparation

ABSTRACT

Imipenem is administered to critically ill neonates with severe infections after failure of first lines antibiotic treatments. The objectives of our study was to evaluate imipenem pharmacokinetic (PK) in a cohort of neonates treated in the Neonatal Intensive Care Unit of the Lausanne University Hospital in order to characterize the relationship between imipenem disposition and patients' characteristics. PK data were analyzed using non linear mixed-effect modeling. Infants who had at least one imipenem concentration measurement between 2002 and 2013 were retrieved. A total of 144 plasma samples from 68 neonates was collected. Infants were predominantly preterm newborns, with a median gestational age of 27 weeks (range: 24 – 41 weeks) and a median postnatal age of 21 days (range: 2 – 153 days). A two-compartment model best characterized imipenem disposition Population PK parameters estimates for clearance, central volume of distribution, intercompartmental clearance, peripheral volume of distribution were 0.27 L/h/kg$^{0.75}$, 0.57 L/h, 0.05 L/h/kg$^{0.75}$, 0.18 L/h. Actual body weight exhibited the greatest impact on PK parameters, followed by age (gestational age and postnatal age) and serum creatinine on clearance. It explains 19%, 9%, 14% and 9% of the interindividual variability in clearance respectively. The elimination half-life was estimated to 3.3 hours for a typical patient.

Imipenem is characterized by an important variability, and dosage adjustment according to body weight and age is recommended in premature and septic neonates. Further work will assess adequate imipenem dosing regimen for this population.

III.3.1. Introduction

Imipenem is a broad-spectrum carbapenem antibiotic, active against a wide range of Gram-positive, Gram negative and anaerobic organisms. Carbapenems are used in severe and complicated bacterial infections that are encountered in neonatal intensive care units [1-4]. The drug is distributed into tissues compartment [1, 5] and protein binding is only about 20%. [6, 7]. Imipenem is mostly eliminated by renal pathway, essentially by glomerular filtration and to some extent by tubular secretion. About 25% of a dose is eliminated by non renal pathway. Because imipenem is rapidly hydrolysed by a brush border dehydropeptidase I of the renal proximal tube, it is administered in combination with cilastatin, a dehydropeptidase I inhibitor, to increase urinary recovery and plasma concentration [8, 9].

It has been well described that developmental physiology, related to age and size dependant factors, [10, 11] have an impact on drug absorption, disposition, metabolism and excretion in neonates and children. Such considerations are important for the safe and effective management of imipenem. Seizure, a serious side effect of imipenem, has been previously associated with inadequate dosing adjustment in adult patients with renal impairment and pre-existing neurological disorder [12, 13]. A correlation between high imipenem concentration and seizure apparition has also been suggested in a case report of an adult patient with mild renal dysfunction [14]. In terms of efficacy, beta-lactam antibiotics, including carbapenems, requires that free-drug concentrations stay above the minimum inhibitory concentration (MIC) for at least 40% of the dosing interval [1, 3, 15], but 50 – 60% is sometimes preferred in neonates due to the immaturity of their immunity [16]. Although imipenem dosing is well established in adults, in patients with impaired renal function, in geriatric patients and in infants ≥ 3 months of age [17], only few studies have evaluated the pharmacokinetics (PK) of imipenem in neonates [18-23]. In the present work, we aimed at characterizing imipenem PK in a larger cohort of neonates and to define clinical and

demographic factors that might influence the disposition of this drug in this fragile population of premature and severely ill infants.

III.3.2. Method

Study population

All neonates admitted in the Service of Neonatology of the Lausanne University Hospital that had at least one imipenem concentration measurement within the framework of a routine therapeutic drug monitoring (TDM) program were retrieved between 2002 and 2013 from the laboratory and medical charts. Imipenem co-formulated with cilastatin (Tienam®, MSD Merck Sharp & Dohme AG, Kenilworth, USA) was administered intravenously over a 30 min infusion. The conventional initial dosing regimen was 15 to 20 mg/kg every 8 to 24 hours according to birth weight and postnatal age. Individualized dosage regimen could be applied for maintenance dose, according to imipenem concentration measurements.

For each patient, time of sampling, time of last dose preceding blood sampling and dosing history was collected. Blood samples were collected at peak (29%) with sampling made between 1 and 2 hours after the start of infusion and at trough (71%) between 5 to 24 hours after the start of infusion. The median number of samples per patient was 2 (range 1 - 8) for a median number of occasion of 1 (range 1 - 4). One patient was removed because of missing information on dosing time and two concentrations were discarded due to suspected sampling bias. The following clinical and demographic characteristics were collected: sex, birth body weight (bBW), body weight at the time of blood sampling (BW), birth height (bHT), height at the time of blood sampling (HT), gestational age (GA), postnatal age (PNA), creatininemia (CRT), concomitant treatment with furosemide, spironolactone, hydrochlorothiazide, vancomycine, metronidazole and erythromycin. If CRT or HT were not available on the day of sampling, they were calculated by linear interpolation between two closest known adjacent values of PK sampling. For 3 patients, interpolation was not possible

and the CRT value of the previous day was used. For 7 patients, interpolation was not possible to obtain HT. Since BW and HT were highly correlated (R^2 = 0.88), we derived HT based on the linear regression model of BW and HT. This retrospective study was approved by the ethics committee of the Faculty of Biology and Medicine of the University of Lausanne.

Bioanalytical Assays

From 2002 until March 2010, free fraction of imipenem plasma concentrations was determined by high-performance liquid chromatography (HPLC). The calibration curves were linear in the range of 0.25 to 200 mg/L and coefficient of variation (CV) was < 5%. After March 2010, total plasma imipenem concentrations were determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). The calibration curve was linear in the range of 0.1 to 100 mg/L and the method was precise (inter-day CV < 7%) and accurate (biais <12%).

Plasma creatinine measurements were performed using the modified Jaffe reaction on a Cobas 8000 analyser (Roche Diagnostics, Rotkreuz, Switzerland). The LOQ was 15 µmol/L and the CV was 3.0%.

Pharmacokinetic modeling

Base model

The population PK analysis was performed using a nonlinear mixed effect modeling approach with NONMEM® (version 7.1.0, ICON Development Solutions, Ellicott City, MD, USA). Free and total plasma imipenem concentration were analysed together considering that imipenem is little bound to proteins, that total serum concentration protein is low and binding affinity is reduced in neonates [24] and from the observation that free and total plasma concentrations were within the same range. Analytical method was also evaluated as covariate in the model. Additionally stepwise procedure was used to identify the model that best fitted the data. One-, two- and three-compartment model were tested with linear and nonlinear elimination. Inter-individual variability

was modeled on the PK parameters assuming exponential errors following a log-normal distribution. Additive, proportional and combined proportional and additive error model were tested to describe the intra-individual (residual) variability.

Covariate model

The correlation between individual PK parameter estimates and the available covariates was first explored graphically. Potentially influencing covariates were then included in the model. The rationale for covariate modeling was elaborated based on developmental pharmacokinetics [24, 25] and include size, age in the initial model developments.

Since BW is obtained more reliably and easily than HT [26, 27], and considering the good correlation between both parameters, BW was used as a proxy of HT. Its influence on the PK parameters was quantified using an allometric power model defined as $P = \theta_1 . BW^{PWR}$, where θ_1 is the typical value of the parameter P, and PWR was set to 0.75 for clearance parameters (clearance and intercompartmental clearance) and 1 for volume parameters (central and peripheral volume of distributions). Other covariates: GA, PNA, postmenstrual age (PMA) defined as GA plus PNA in weeks, CRT, concomitant treatment (furosemide, spironolactone, hydrochlorothiazide, vancomycine, metronidazole and erythromycin), gender and analytical method were included in the model following a sequential forward selection and backward elimination. Continuous covariates were tested for potential relationship using linear, exponential and power model, except for CRT for which only a power function of CRT was used to quantify its influence on clearance (CL). Postnatal age was also tested using a piece-wise function on clearance CL and PMA was tested as well using a Hill equation [28, 29]. When more than one covariate describing totally or partially the same age effect was included (GA and PNA versus PMA), the second age variable was not investigated. Concomitant treatment, gender and analytical method were evaluated using a categorical model.

Parameter Estimation and Model Selection

Model estimation was performed using the first-order conditional estimation with interaction (FOCE-I). Imipenem concentration measurements below the LOQ were handled with the M3 likelihood based approach described by Ahn *et al* [30]. As a goodness-of-fit statistic, NONMEM® uses an objective function. The likelihood ratio test, based on the difference in objective function value (ΔOF) was used to compare two models. Since -2 log likelihood, approximate $\chi 2$ distribution, it was considered statistically significant if it exceeded 3.8 ($p<0.05$) and 6.6 ($p<0.01$) points, for one additional parameter during model-building and backward deletion procedures, respectively. Model assessment was also based on goodness-of-fit plots along with precision of the PK parameters estimations, and the reduction of inter- and intra- individual variability of the population PK parameters. Apart from BW and age that were initially introduced in the model, covariates were retained if they were judged clinically significant based on an effect of at least 20% and on the importance of the reduction in inter-individual and/or residual variability. Besides, shrinkage was examined. A sensitivity analysis was performed for patients with absolute values for conditional weighted residuals (CWRES) greater than 3 to test for potential bias in parameter estimation and in covariate exploration. Because creatinine often reflects maternal creatinine during the first days of life, another sensitivity analysis was performed ignoring patients that had imipenem concentration measurements during the first 3 days after birth [31].

Evaluation method

The final model stability was assessed by the bootstrap method using the PsN-Toolkit [32] (version 3.5.3, Uppsala, Sweden). The median and the 95% confidence interval (CI95%) estimated from 2000 re-sampled data sets were compared to the original model estimations. In addition, prediction-corrected visual predictive checks (pcVPC) [33] were performed with PsN-Toolkit and Xpose4 [34] (version 4.3.5, Uppsala, Sweden) by simulations based on the final pharmacokinetic estimates using 2000 individuals. To perform the pcVPC, imipenem below the LOQ were recorded

as half of the LOQ. Mean prediction-corrected concentrations with their 95% percentile interval (PI95%) at each time point were retrieved. Plot was generated using R (version 2.15.1, R Development Core Team, Foundation for Statistical Computing, Vienna, Austria).

III.3.3. Results

Study data

A total of 144 imipenem plasma concentrations were obtained from 68 babies of whom 59 (87%) were preterm babies (median gestational age 26.7 weeks, range 24.3 – 35.6 weeks; median birth body weight 800 g, range 500 – 2500 g) and 9 (13%) were term newborns (median gestational age 38.7 weeks, range 37.1 – 41.4 weeks; median birth body weight 3540 g, range 2300 – 3720 g). Plasma concentrations were comprised between 0.1 and 57.9 ng/mL. Data below the LOQ constituted 15% of the samples. Most patients were critically ill and previously treated with various other antibiotics before switching to imipenem and therefore mean postnatal age at first concentration measurement was 21 days. Characteristics of the study data are presented in **Table 3.3.1**.

Base model

The data were best described by a two-compartment open model parameterized in terms of clearance (CL), inter-compartmental clearance (Q), volume of distribution of the central compartment (V_c) and peripheral volume of distribution (V_p) (ΔOF from the one-compartment model was -38.0, $p<0.001$). An interindividual variability was assigned to CL and no further variability on any other parameters could be detected (ΔOF<-0.9, $p>0.3$). Intrapatient variability was best described by a proportional residual error model. The final base population parameters with interindividual variability (CV%) were a CL of 0.311 L/h (43%), a Vc of 0.519 L, a Q of 0.077 L/h and a Vp of 0.427 L. Residual unexplained variability was 47%.

Table 3.3.1. Characteristics of patient at first concentration measurement and of imipenem concentration

Patients	**Median (range) or count (%)**
Total	68
Gender (male / female)	32 (47%) / 36 (53%)
Gestational Age (weeks)	27.3 (24.3 – 41.4)
Postnatal Age (days)	21 (2 – 153)
Postmenstrual Age (weeks) *	31.6 (29.6 – 48.3)
Body Weight (g)	1195 (500 – 4120)
Height (centimeters)	38 (30 – 54)
Plasma creatinine (µmol/l)	46 (9 - 243)
Concentrations	
Total	144
Below the limit of quantification	22 (15%)
Trough (count / value (mg/l)) †	102 (71%) / 1.2 (0.1 – 8.2)
Peak (count / value (mg/l))	42 (29%) / 21.1 (7 – 57.9)
Per patient	2 (1 - 4)
Dose before concentration (mg/kg)	20 (12 - 30)
Medications††	
Furosemide	16 (24%)
Spironolactone	5 (7%)
Hydrochlorothiazide	5 (7%)
Vancomycine	41 (60%)
Metronidazole	12 (18%)
Erythromycine	3 (4%)

* Postmenstrual Age (weeks) is defined as the sum of gestational age and postnatal age
† Trough concentration values without taking into account data below the limit of quantification
†† Only relevant medication have been searched; count on total concentration measurements

Covariate model

The incorporation of BW on all parameters following an allometric model markedly improved the description of the data (ΔOF=-55.3, $p<0.001$). It explains 19% of the interindividual variability on CL. Among age parameters tested, significant linear relationships were observed between PNA (ΔOF=-21.0, $p<0.001$) and GA and CL (ΔOF=-22.1, $p<0.001$) that provided a further improvement of the model fit. GA was centred on 40 weeks, representing the full term GA. PMA also showed a significant linear relationship with CL, providing the same parameters estimation with the same drop of objective function as PNA and GA. The model integrating PMA according to the Hill equation did not converge. Separating the influence of each age component was rather preferred, and PMA

was thus discarded from the model. Addition of age-dependant covariates explains 23% of the interindividual variability on CL. Creatininemia was a significant covariate on CL (ΔOF=-9.1, p=0.002), explaining 9 % of the remaining interpatient variability. An additional improvement of the data description was observed by introducing vancomycin coadministration in the model (ΔOF = -9.2, p=0.002). However, its effect was of limited clinical relevance, since the reduction CL was only of 14%, with almost no impact on reducing the inter-individual or residual unexplained variability. It was thus no kept in the final model. No other covariates showed any significant effect on imipenem disposition, including different analytical methods over time. Extend of η-shrinkage was low (11% in the final model, which was the highest value observed during model-building). The model described the observed data well, as indicated by the goodness-of-fit plots in **Figure 3.3.1**. A summary of the major step during covariate building is given in **Table 3.3.2**. According to the model, a term neonate (GA 40 weeks, PNA 3 weeks, BW 3.1 kg, CRT=46 µmol/l) would have a clearance of 0.76 L/h, while a very preterm neonate (GA 24 weeks, PNA 3 weeks, BW 0.520 kg, CRT=46 µmol/l) would have a clearance of 0.14 L/h (81% reduction). The half-lives of the disposition phase and of the terminal phase for a typical individual (GA 27 weeks, PNA 3 weeks, BW 1.2 kg, CRT=46 µmol/l) are 1.1 and 3.3 hours, based on an estimated clearance of 0.28 L/h. Renal failure in a typical patient, with CRT=200 µmol/l, would decrease clearance to 0.21 L/h (20 % reduction).

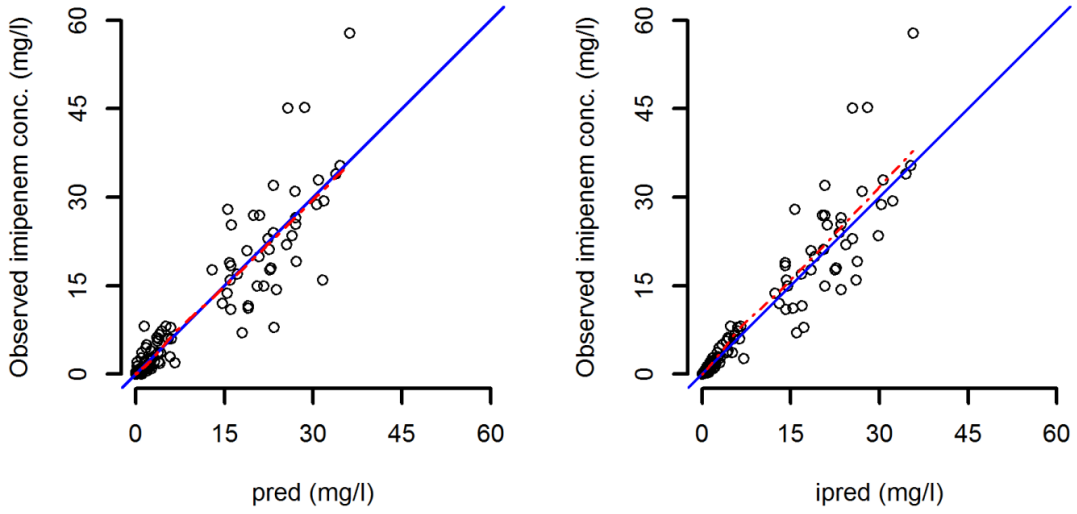

Figure 3.3.1. Goodness-of-fit plots of observed imipenem, concentrations versus the population model-predicted (pred, left) and individual model-predicted (ipred, right) concentrations from the original dataset.

Table 3.3.2. Significant step in imipenem population PK model building

Model	Equation of CL	ΔOF	IIV CL(%)	Proportional residual error (%)
Base model	$CL = \theta_{CL}$		43	47
Allometric model	$CL = \theta_{CL} \times BW^{0.75}$	-55.3	35	39
PNA on CL	$CL = \theta_{CL} \times BW^{0.75} \times (1 + \theta_{PNA} \times PNA)$	-21.0	31	36
GA on CL	$CL = \theta_{CL} \times BW^{0.75} \times (1 + \theta_{PNA} \times PNA) \times (1 + \theta_{GA} \times (GA - 40))$	-22.1	25	36
CRT on CL†	$CL = \theta_{CL} \times BW^{0.75} \times (1 + \theta_{PNA} \times PNA) \times (1 + \theta_{GA} \times (GA - 40)) \times CRT^{\theta_{CRT}}$	-8.9	21	37
VANCO on CL*	$CL = \theta_{CL} \times BW^{0.75} \times (1 + \theta_{PNA} \times PNA) \times (1 + \theta_{GA} \times (GA - 40)) \times \left({CRT}/{50}\right)^{\theta_{CRT}} \times (1 + \theta_{VANCO})$	-8.6	20	37

CL = Total clearance; **BW** = Actual body weight (kg); **PNA** = Postnatal age (weeks)**; GA** = Gestational age (weeks); **CRT** = plasma creatinine (μmol/l); **VANCO** = coadministration of vancomycin; **IIV** = inter-individual variability

The change in OF is relative to prior model

† Final model

*Effect of vancomycine coadministration was not kept in the final model

Model Evaluation

The median parameter estimates obtained with the bootstraps with the 95% CI are presented in **Table 3.3.3**. Median parameters differed in less than 1% from those obtained with the original dataset. The parameter estimates of the final population pharmacokinetic model lied within the 95% CI of the bootstrap results suggesting that the model was acceptable. The sensitivity analysis concerned 2 data points. It showed that none of these concentration values affected the pharmacokinetic estimates with a maximum difference in parameter estimates of 14% for creatinine factor (data not shown). Impact of the 4 patients that received treatment during the first 3 days of life was of little importance. A maximum difference of 21% was observed on Q estimate when they were removed. The results of pcVPC supported the predictive performance of the model and are presented in **Figure 3.3.2**.

Table 3.3.3. Estimated population pharmacokinetic parameters and bootstrap 95% confidence interval

Parameters (units)	Parameters	Base parameter estimates (SE)		Final parameter estimates (SE)		Bootstrap model estimates (95% CI)	
CL (L/h/kg$^{0.75}$/µmol.l$^{-0.2}$)	θ_1	0.31	(35.0%)	0.27	(10.1%)	0.27	(0.22 , 0.33)
Effect of BW on CL	θ_5			0.75		0.75	
Effect of PNA on CL	θ_9			0.07	(31.8%)	0.07	(0.03 , 0.13)
Effect of GA on CL	θ_{10}			0.02	(22.7%)	0.02	(0.01 , 0.03)
Effect of CRT on CL	θ_{11}			-0.20	(39.4%)	-0.20	(-0.33 , -0.03)
Vc (L/kg)	θ_2	0.52	(46.2%)	0.57	(7.8%)	0.57	(0.46 , 0.68)
Effect of weight on Vc	θ_6			1		1	
Q (L/h/ kg$^{0.75}$)	θ_3	0.08	(26.5%)	0.05	(39.0%)	0.05	(0.01 , 1)
Effect of BW on Q	θ_7			0.75		0.75	
Vp(L/kg)	θ_4	0.43	(59.0%)	0.18	(27.6%)	0.18	(0.09 , 0.28)
Effect of weight on Vp	θ_8			1		1	
Residual error (% CV)	θ_{12}	47	(7.0%)	37	(6.3%)	37	(31 , 41)
IIV CL (% CV)	η_1	43	(5.0%)	21	(13.8%)	21	(14 , 26)

CL = Total clearance: **BW** = Actual body weight (kg); **PNA** = Postnatal age (weeks) **; GA** = Gestational age (weeks); **CRT** = plasma creatinine (µmol/l); **Vc** = central volume of distribution; **Q** = intercompartmental clearance; **Vp** = peripheral volume of distribution; **IIV** = inter-individual variability

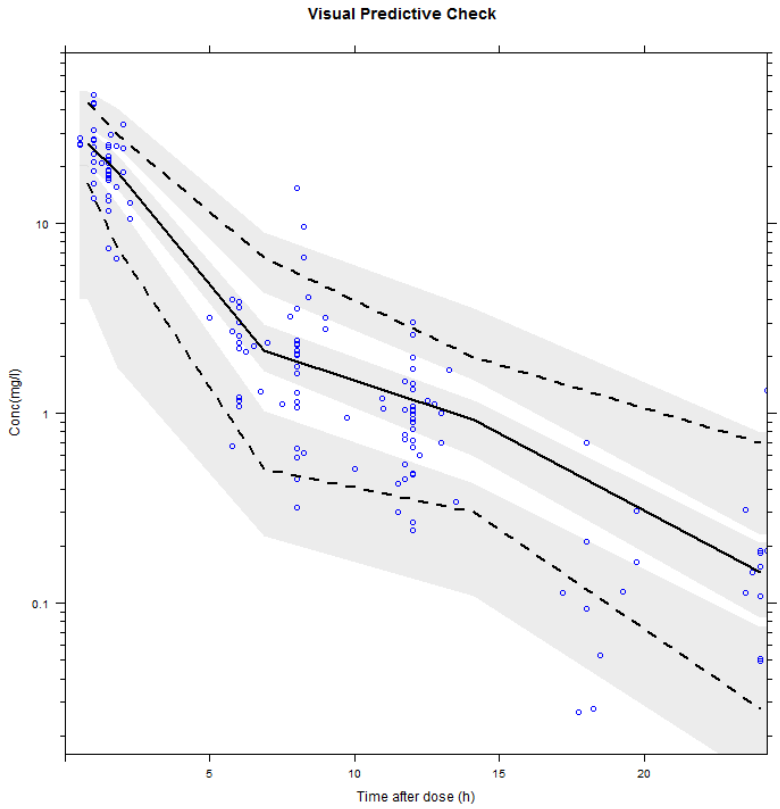

Figure 3.3.2. Prediction-corrected visual predictive check of the final model with imipenem prediction-corrected concentrations (circles) and median observation (solid line) with the corresponding 95% observation interval (dotted lines). Semi-transparent grey fields represent the model-based percentile confidence interval.

III.3.4. Discussion

This study is the first population pharmacokinetic study of imipenem performed in a cohort of mostly very preterm neonates suffering from severe clinical conditions. It allows identification of key pathophysiological factors, BW, age, and renal function status, which showed clinically important influence on imipenem disposition in this fragile population. This is of major importance in order to define adequate dosage regimen for neonates, which have been little studied.

The primary factor influencing imipenem PK was BW, which explained an important percentage of the interpatient variability in drug concentrations. An allometric model described the effect of BW

at best, accounting for the gradual increase in imipenem distribution and elimination with body weight and thus size [35, 36]. Since neonates have an immature organ system and nephrogenesis is incomplete in preterm newborns below 36 weeks [37], renal function is expected to influence imipenem elimination. Although quite low at birth, renal function changes rapidly after birth, even in preterm neonates [38, 39]. Inclusion of age descriptors (GA and PNA) allowed accounting for this maturation process starting before birth, apart from size effect. It showed that both GA and PNA are good predictors of concentrations and that they both should be used for initial dosage adjustment. Eventually, creatininemia seems to have an additional impact on imipenem elimination. Although CRT is generally a good predictor of GFR in adults, it is not considered a good predictor in very preterm neonates due to differences in muscle, age, or size compared to older infants [40, 41]. The use of GFR estimators such as Schwartz formulae was thus not possible in our study population. Nevertheless, creatininemia seemed to influence imipenem PK in addition to growth and maturation components, offering further description of the effect of acute renal failure on imipenem elimination in neonates with high CRT levels.

None of the other covariates tested had a relevant impact on drug disposition. No difference was found according to the analytical methods used, confirming the very low protein binding of imipenem. Finally a small effect of vancomycin could be observed based on statistical criterion that was considered marginal once other covariates were included in the model.

To our knowledge, only one population analysis of imipenem PK has been published in term neonates so far [23]. Our results suggest a reduction by about half of imipenem elimination in premature neonates (1.5 h vs 3.3 hours) compared to term neonates, which is mostly related to a larger volume of distribution (0.466 L/kg vs 0.75 L/kg for a typical patient: GA 27 weeks, PNA 3 weeks, BW 1.2 kg). The volume of distribution is also larger than in older children (0.46 L/kg for a mean age of 3 years old [42] or 0.260 L/kg for a mean age of 9 years old [23] and in adult patients (about 0.22 L/kg) [43-47]. Changes in the ratio between total body water and fat tissue occurs

during gestation and continues after birth. Since imipenem is a polar drug that is predominantly distributed in the intra- and extra- vascular fluid, the larger volume of distribution might thus the be the consequence of the larger extracellular fluid in neonates [9]. In addition, the high prevalence of sepsis can explain the larger distribution due to increased capillary permeability during the inflammatory response, fluid flow to the extracellular compartment and third spacing [48]. Compared to adult and children for which imipenem half-life range from 1 to 3 hours [43-47, 49-52] and from 0.5 to 1.2 hours, respectively [23, 53]. Our study shows that elimination is lower in our population of neonates, which seems to be explained by the immaturity and small size of elimination organs and to a larger volume of distribution in preterm infants.

The main limitation of our results is the retrospective design, fostering errors in the recollection of information. In addition, concentration samples were measured within the routine clinical setting and few samples per patient and on very limited occasion were available, thus limiting the power to differentiate inter from intra-individual variability. Finally, cilastatin concentration was measured only since 2012, and its influence could not be evaluated.

In conclusion, the present study described the disposition of imipenem in a cohort of predominantly premature neonates. The large variability in its concentrations could be explained by physiologic and pathologic variables, including body weight, gestational age, post-natal age and organ capacity based on creatininemia. This model will serve to simulate concentration-time profiles for various dosage regimens in order to provide a priori dosing recommendations to reach predefined target concentration, with respect to relationship with the MIC of the most often organism encountered in nosocomial infections and sepsis. The results will be implemented in EzeCHieL, a Bayesian computer tool for dosage individualization based on a single measurement.

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CHAPTER IV. ADHERENCE

Chapter IV in the thesis context

The benefits of a Bayesian TDM approach rely on accurate popPK models. Most of popPK models use data gathered during routine TDM, and assume steady-state and full adherence. However, non-adherence might be common, particularly in chronic diseases, and thus represent an additional cause of unexplained variability.

In the other side, interpretation of a single patient concentration may also suffer from ignoring adherence issues.

Only a limited number of studies have investigated the pharmacokinetics in relation to adherence data, in particular the influence of poor adherence on population model elaboration or its impact on TDM measurement interpretation. In our institution, patient at risk of non-adherence for their antiretroviral therapy are addressed to the adherence-enhancing program of the Outpatient Medical Clinic, which recourse to electronic monitoring. TDM along with electronic monitoring offer a unique opportunity to evaluate impact of the precise drug dosing history on population model development and thus its reliability for concentration forecasting. It also gives the possibility to assess its impact on sample interpretation against patient self-reported data.

Own contribution: Protocol elaboration. Assembly of data. Population pharmacokinetic and statistical analysis. Interpretation of the data. Drafting of the article.

IV. IMPACT OF MEDICATION ADHERENCE MEASUREMENT ON LOPINAVIR, ATAZANAVIR, EFAVIRENZ, AND ETRAVIRINE PHARMACOKINETICS: A RETROSPECTIVE STUDY

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Under preparation

ABSTRACT

Non-adherence is common during chronic diseases, such as HIV infection. Therapeutic drug monitoring is one way of monitoring antiretroviral therapy that usually relies on steady-state and full adherence assumptions, while neglecting non- or partial medication adherence. This study evaluates the impact of adherence measurement by electronic monitoring, which allows recording of longitudinal adherence data. Precise dosing history was compared with patient self-reported information on the estimation of lopinavir, atazanavir, efavirenz and etravirine population pharmacokinetic parameters. Influence of "pocket-doses" escaping electronic monitoring was also searched. In addition, the study evaluates the impact of adherence issues on clinical interpretation of individual drug levels. Population pharmacokinetic modeling, based on previously published studies, was performed with NONMEM® on paired datasets i.e. dosing times based on steady-state with full adherence assumption versus electronic dosing history, from 140 HIV-patients taking part in a medication-adherence enhancing program, providing 384 drug concentrations. Clearance estimates and likewise predicted concentrations did not markedly differ between approaches. Self-reported last dose intake appears to be reliable enough for concentration prediction in most patients. However, specific patterns of non-adherence lead to suboptimal exposure that will escape to TDM interpretation.

IV.1. Introduction

Non-adherence is a common issue in the treatment of chronic diseases: up to 40% of patients who begin a long-term treatment stop it during the first year [1, 2]. In HIV infection management, medication adherence is crucial to control the viral load, to limit the emergence of resistant strains and to prevent the dissemination of the virus throughout the community [3-6]. Poor adherence is a significant problem in this population with 40% patients, who do not achieve 90% adherence worldwide[7]. Indeed, this often stigmatized population has to cope with a lifelong and sometimes complex treatment, associating several pills with up to two daily administrations. The actual clinical consequences of insufficient adherence vary depending on drug regimens and non-adherence patterns [8-10].

Although no gold standard method is universally established for the assessment of adherence, electronic monitoring of medication events is considered among the most reliable approaches. It records pill bottle openings, assumed to correspond to the times of dose intake by the patient. However, electronic monitoring may still underestimate adherence [11]. Actually, a not infrequent misuse of this system consists in the removal of more than one dose per opening for later use, called *pocket-doses* (PDs). Therefore, a combination of several adherence measurement methods probably represents the best option to assess the patient's medication behaviour [12-15].

To support patient adherence to treatment, the Community Pharmacy of the Department of Ambulatory Care & Community Medicine in Lausanne (Switzerland) has implemented an adherence-enhancing program, as previously described [16, 17]. Briefly, it combines (*i*) electronic recording of bottle openings with a Medication Event Monitoring System (MEMS™, Aardex, MWV Healthcare, Switzerland), (*ii*) manual pill count, (*iii*) regular motivational interviews and (*iv*) feed-back to physicians and nurses. Eligible patients are referred to the program by their physician; all drugs prescribed in their combined antiretroviral therapy are monitored individually, which allows the collection of medication adherence data for each single molecule. At each interview and before showing the adherence electronic report to the patient, this latter is asked about the time usually elapsing between electronic monitor opening and medication

swallowing, whether any PDs were taken during the last period, and if so when they were actually swallowed.

The use of therapeutic drug monitoring (TDM) has been advised and incorporated into guidelines to watch over and possibly optimize antiretroviral therapy (ART). Actually, consistent concentration-efficacy and -toxicity relationships have been shown for both protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [18, 19], while their pharmacokinetics (PK) are characterised by large inter-individual variability for PIs and in a less extend for NNRTIs. Although evidence to support routine TDM use is still debated, particularly in ART-naive patients, it is generally admitted that individual patients can benefit from this intervention in specific clinical situations [20, 21], to ensure desired drug exposure and response. The Laboratory of Clinical Pharmacology in Lausanne offers the determination of numerous antiretrovirals including ritonavir boosted-PIs (e.g. lopinavir and atazanavir) and NNRTIs (e.g. efavirenz and etravirine). This service is complemented with the interpretation of concentration measurements with a Bayesian-inspired approach based on population pharmacokinetic (popPK) models, applicable to concentrations measured at random sampling times [22].

Population pharmacokinetic modeling has been largely applied to ART, mostly to relate treatment outcomes with pharmacokinetic variations [23]. Among other advantages, popPK approaches can handle sparse data, such as those collected from TDM interventions. However, this requires reliable information about the time of last dose intake. Moreover, it generally assumes full adherence in patients under steady-state regimen. Thus, knowing in particular that a frequent reason for TDM request is uncertain adherence, popPK models built up on TDM data may be flawed due to inaccurate dosing history [23-25]. Biases due to adherence issues may thus occur both during the elaboration of reference information for TDM interpretation, and during the specific interpretation of a single patient sample.

Therefore, we aimed to evaluate whether electronic measurement of adherence would influence popPK parameter estimation, compared with the mere assumption of steady-state with full adherence. We also wanted to determine to what extent neglecting PDs might impact on parameter estimation that

incorporates electronic adherence data. Our second objective was to assess the importance of adherence measurement in terms of individual concentration prediction, as it is usually performed during TDM interpretation.

IV.2. Method

Study and subjects

This retrospective observational study included all naïve or experienced patients enrolled in the Swiss HIV Cohort Study (SHCS, www.shcs.ch) and referred to the above mentioned adherence-enhancing program between 2004 (establishment of the program) and 2011, who had at least one TDM measurement for any of the following antiretroviral agent: Lopinavir (LPV) co-formulated with ritonavir, Atazanavir (ATV) co-prescribed with ritonavir, Efavirenz (EFV) and Etravirine (ETV). It received approval from the local Ethics Committee for clinical research number 25/14.

Analytical method

Blood samples (5ml) were collected into lithium-heparinate or potassium-EDTA syringes (Monovette®, Sarstedt, Nümbrecht, Germany). Plasma was isolated by centrifugation, virus inactivated in a 60°C water bath for 60 min, and stored at -20°C until analysis. Total plasma drug concentrations were determined by liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) according to validated methods [26-29]. Calibration curves are linear up to 20 µg/ml for LPV, up to 10 µg/ml for ATV and EFV, and up to 4 µg/ml for ETV.

Dosing data

Patient self-reported last drug intake before TDM was recorded on the day of blood sampling. In parallel, electronic monitor data were retrieved on a period of 5 literature half-lives before each blood sample[25], a sufficient time to assume steady-state in case of full adherence, i.e. 10 days for LPV, ATV and ETV and 15 days for EFV. This period thus always included a weekend, when drug intake is known to be less accurate [30, 31]. Electronic data were reconciled with interview notes and pill count according to an operational

manual. PDs identified during the reconciliation process were added into electronic monitor dosing history. We thus obtained three paired datasets for each molecule considered: (*A*) a first one assuming steady-state with full adherence, with the time of last dose intake before drug level measurements as reported by the patient, and (*B*) a second one built up with the detailed history of drug intake over the last 10 to 15 days, reconciled from electronic monitor records and patients' allegations. The last dataset (C) was built up , incorporating exclusively the raw electronic monitor information on dosing history but disregarding patients' information on PDs.

Data analysis

Time differences between self-reported and electronic monitor recorded times of last dose intake before blood sampling for TDM were evaluated by calculating:

Time interval difference (Δt) = Patient self-reported time – electronic monitor recorded time

Population PK model parameters were estimated by nonlinear mixed effect modeling with NONMEM® (version 7.3.0, ICON Development Solutions, Ellicott City, MD, USA), using first-order conditional estimation with interaction (FOCEI). PopPK models were chosen based on previously published studies [32-35], without consideration for covariates.

Shortly, all molecules were described according to a one compartment-model parameterized in terms of clearance (CL) and distribution volume (V_d). Absorption was described by a first order-process (constant Ka), except for ETV assumed to follow a zero-order process (constant D_1). A lag time (ALAG) was defined for ATV. Residual variability was deemed proportional for EFV and ETV, while a mixed error model (combining proportional and additive residual variability) was used for LPV and ATV. Inter-individual variability on PK parameters was described with exponential errors.

To evaluate the influence of *pocket-doses* (PDs) on PK parameter estimation, the use of PDs if any by patients was entered in the model as an index or dummy variable (Q1) as follow:

$$\theta = \theta_1 . (1 + \theta_2 . Q1)$$

where θ_1 is the typical value of the PK parameter θ, θ_2 is the fractional change in parameter θ associated with PDs use, and Q1 is equal to either 0 or 1. Different criteria were tried sequentially for coding PDs use with Q1 = 1:

(*i*) when PDs were identified at anytime during the recovered dosing history;

(*ii*) when PDs were identified in the two days preceding TDM;

(*iii*) when identified PDs represented at least 50% of recovered dosing history.

From the retained model, popPK estimation was compared between two types of datasets: (*A*) steady-state and full adherence assumption with self-reported last dosing time, versus (*B*) reconciliated adherence data from electronic monitors and patient interviews. A third, considering raw electronic data (*C*) was also analyzed, neglecting all PDs recovered from interviews and considering them merely as missed doses. The 95% confidence intervals ($CI_{95\%}$) for parameters were estimated using the bootstrap method on 2000 re-sampled data sets. Model-based population concentration profiles with their 95% prediction interval ($PI_{95\%}$) were generated as well from 2000 simulations for each drug, for the 3 types of datasets described above.

Differences in *post hoc* Bayesian individual parameter estimates between dataset types A and B, and between dataset type A and C, were evaluated by Wilcoxon signed-rank tests for paired observations. Individual predicted concentrations (C_{ipred}) based on both dataset types were compared with actual observations, and relative predictions errors (PE_i) were computed as the difference of both these prediction errors. Relative bias was computed as the mean relative prediction error (MPE), and relative imprecision was calculated from the difference in mean squared error (MSE), expressed as root mean squared error (RMSE) [36]:

$$PE_{i,A} = C_{ipred_{A,i}} - C_{obs}$$

$$PE_{i,B} = C_{ipred_{B,i}} - C_{obs}$$

$$PE_i = PE_{i,A} - PE_{i,B}$$

$$MPE = \frac{1}{n}\sum_{i=1}^{n}(PE_i)$$

$$MSE_A = \frac{1}{n}\sum_{i=1}^{n}(PE_{i,A})^2$$

$$MSE_B = \frac{1}{n}\sum_{i=1}^{n}(PE_{i,B})^2$$

$$\Delta MSE = MSE_A - MSE_B$$

$$\Delta RMSE = \sqrt{|\Delta MSE|}$$

where subscript A refers to the steady-state and full adherence assumption dataset, whereas subscript B refers to the reconciled electronic data, C_{obs} is the observed concentration, C_{ipred} is the individual predicted concentration by the corresponding model, n is the number of concentration values. Similar comparisons were calculated as well between datasets A and C, replacing subscript B by C.

Finally, individual patients' exposure profiles were simulated from their *post hoc* Bayesian individual PK parameters using parameter values obtained with datasets A and B or C. The minimum concentration (C_{trough}) predicted at the end of the dosing interval was calculated for each patient according to both parameter sets.

IV.3. Results

A total of 384 blood samples were collected in 140 patients. Data by drug are detailed in **Table 4.1**. The number of missed doses was higher for PIs than for NNRTIs but globally low, below 5% for all drugs. Time interval differences between both dosing data collection methods was almost centred around 0 and symmetrically distributed for all drugs, with a mean and standard deviation for LPV: -0.6 ± 4.7 hours, for ATV: 0.3 ± 7.9 hours, for EFV: 0.4 ± 3.4 hours, for ETV: -1.1 ± 5.7 hours. Histogram plots of time interval differences are depicted in **Figure 4.1**. The time interval difference was greater than ± 3 hours for 48 blood samples (LPV: 22 (17%); ATV: 13 (14%); EFV: 5 (9%) and ETV: 8 (28%)).

Table 4.1. Summary of study data

	Boosted-PIs		NNRTIs	
	LPV	**ATV**	**EFV**	**ETV**
Patients (n)	65	40	55	28
Samples (n)	129	92	107	56
Concentrations range (ng/ml)	0-24390	0-4976	535-12680	147-840
Visits per patient (n) (median)	2	2	1	1.5
[Range]	[1-10]	[1-9]	[1-7]	[1-9]
Pocket-doses (n)	50	26	44	11
Patients (n) (%)	11 (17%)	8 (20%)	13 (23%)	5 (18%)
% of total doses	2.0 %	2.9%	2.6%	1.1%
Missed doses (%)†	4.9%	4.3%	1.7%	1.5%
Before concentration (%)	34.9%	22.8%	16.8%	19.6%
Patients (%)	46.1%	37.5%	25.4%	25.0%
Standard dosage	400 mg b.i.d.	300 mg q.d.	600 mg q.d.	200 mg b.i.d. or 400 mg q.d.
Half-life (h) ††	5-6	12	56-72	30-40

† Based on reconciled electronic monitor records

†† Based on the summary of product characteristics

LPV = Lopinavir; ATV = Atazanavir; EFV = Efavirenz; ETV = Etravirine

The data were fitted with the popPK models selected for each drug using both (*A*) the patient self-reported dosing information with steady-state and full adherence assumption, and (*B*) the full electronic monitorreconciled dosing history and (C) neglecting all PDs recovered from interviews . Inter-individual variability was estimated solely for CL, which ensured model convergence for all drugs. The identification of

PDs did not affect significantly the estimation of parameters for all drugs, irrespective of the way it was taken into account, and the corresponding term was thus not kept in the models.

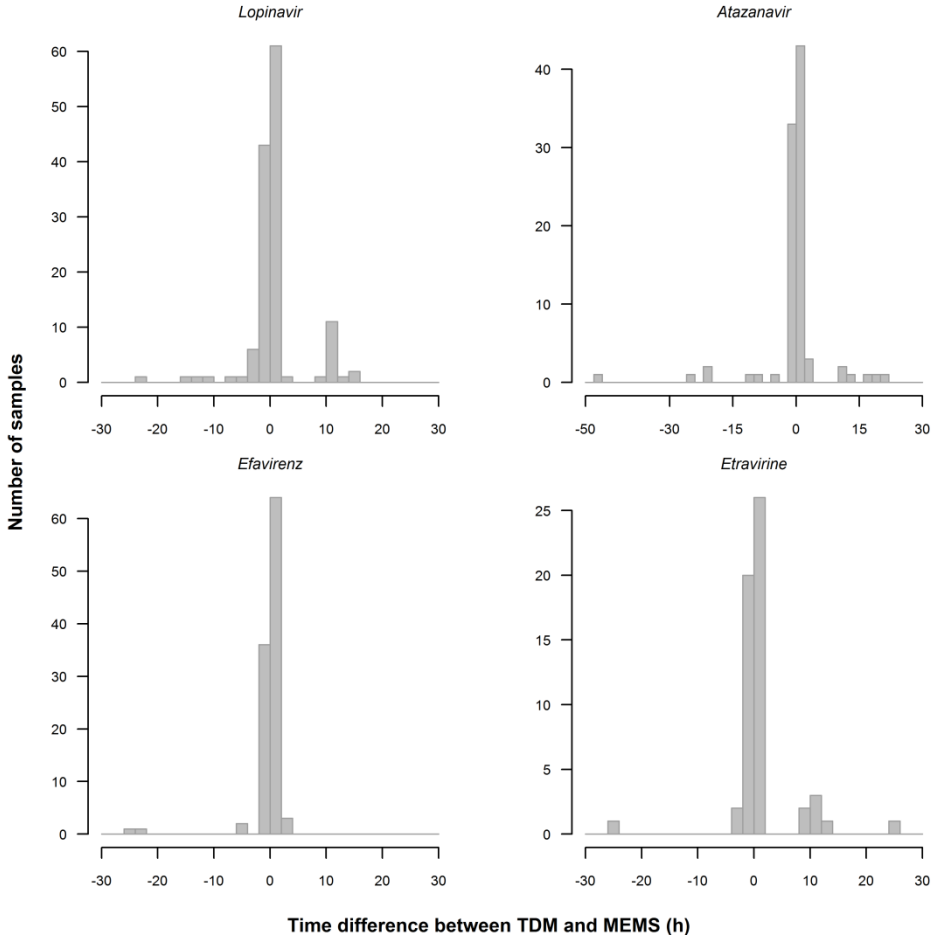

Figure 4.1. Histogram plot of the distribution of time interval differences between self-reported and electronic dose intake data

Population PK parameters estimates with their $CI_{95\%}$ are presented in **Table 4.2**. Comparing the results from self-reported data and steady-state full adherence assumption with those from reconciled electronic data, population clearance (CL) was similar no matter the dosing history input, with a maximum difference of 4% for ETV. Conversely, population volume of distribution (Vd) could differ largely according to the dosing history input (discrepancy for LPV: 39%, for EFV: 47% and for ETV: 87%), which was also the case for absorption constant (discrepancy for LPV: 48% and for ETV: 24%). Only ATV retained similar population volume of distribution (relative difference of 3%), while its absorption parameters were fixed.

For all other population parameters, estimation was essentially similar whatever the dosing input (relative differences <20%), except for inter-individual variability on CL for ATV (difference of 80%). When the raw electronic monitor data were considered, without addition of the doses identified during the reconciliation procedure, LPV parameters where particularly affected regarding Vd, absorption constant and above all, residual error. By contrast, estimates did not vary so drastically for the other drugs.

Table 4.2. Parameter estimates with their 95% confidence interval, according to dosage history input method

	Boosted Protease Inhibitors					
	Lopinavir			**Atazanavir**		
	Steady-state and patient self-reporting	Reconciled electronic records	Raw electronic records	Steady-state and patient self-reporting	Reconciled electronic records	Raw electronic records
CL (L/h)	4.4 [4.0-4.8]	4.5 [4.0-5.0]	4.3 [3.8-4.9]	8.3 [7.4-9.5]	8.2 [7.3-9.4]	8.1 [7.2-9.4]
V_d (L)	62 [23-173]	38 [22-55]	29 [18-56]	103 [77-134]	106 [81-155]	101 [77-184]
Ka (h^{-1})	0.420 [0.167-2.498]	0.217 [0.111-0.342]	0.156 [0.103-0.301]	0.405 FIXED	0.405 FIXED	0.405 FIXED
ALAG (h)	-	-	-	0.88 FIXED	0.88 FIXED	0.88 FIXED
ω_{CL} (%)	31 [21-39]	30 [21-37]	29 [18-37]	10 [3-23]	18 [5-32]	21 [6-36]
ω_V (%)	-	-	-	-	-	-
ω_{Ka} (%)	-	-	-	122 FIXED	122 FIXED	122 FIXED
ω_{ALAG} (%)	-	-	-	-	-	-
σ_{prop} (%)	35 [24-44]	33 [16-40]	24 [8-40]	46 [14-58]	42 [23-60]	43 [0-63]
σ_{add} (ng/mL)	1095 [383-1934]	907 [337-1931]	2370 [337-3195]	444 [31 – 787]	445 [24-666]	452 [-62-706]
	Non-Nucleoside Reverse Transcriptase Inhibitors					
	Efavirenz			**Etravirine**		
	Steady-state and patient self-reporting	Reconciled electronic records	Raw electronic records	Steady-state and patient self-reporting	Reconciled electronic records	Raw electronic records
CL (L/h)	8.5 [7.2-9.8]	8.5 [7.1-10.0]	8.2 [6.8-9.7]	32.6 [27.1-39.5]	33.9 [28.2-41.3]	33.5 [27.5-40.7]
V_d (L)	240 [137 -1131]	352 [215-649]	370 [210-654]	705 [425-1275]	1315 [493-2885]	1320 [481-2914]
Ka (h^{-1})	0.62 FIXED	0.62 FIXED	0.62 FIXED	-	-	-
D_1 (h)	-	-	-	3.4 [2.7-4.4]	2.6 [2.0-9.4]	2.6 [2.1-9.8]
ω_{CL} (%)	55 [43-64]	57 [45-72]	59 [46-76]	41 [22-52]	41 [21-61]	41 [20-64]
ω_V (%)	-	-	-	-	-	-
ω_{Ka} (%)	-	-	-	-	-	-
ω_{D1} (%)	-	-	-	-	-	-
σ_{prop} (%)	24 [19-28]	25 [19-29]	25 [20-30]	28 [20-33]	31 [23-36]	31 [23-35]

95% confidence interval were calculated by bootstraps with 2000 datasets
CL = Clearance; **V_d** = Volume of distribution; **Ka** = absorption constant, first-order; **D_1** = absorption constant, zero-order; **ALAG** = lag time; **ω** = interindividual variability; **σ_{add}** = additive residual error; **σ_{prop}** = proportional residual error; FIXED = fixed value from the original publication.

Based on the final models estimated from each dosing history input, concentration profiles were simulated according to each scenario (see **Figure 4.2**). It shows essentially similar PK profiles and concentration ranges, independently of the method used to record the dosing history.

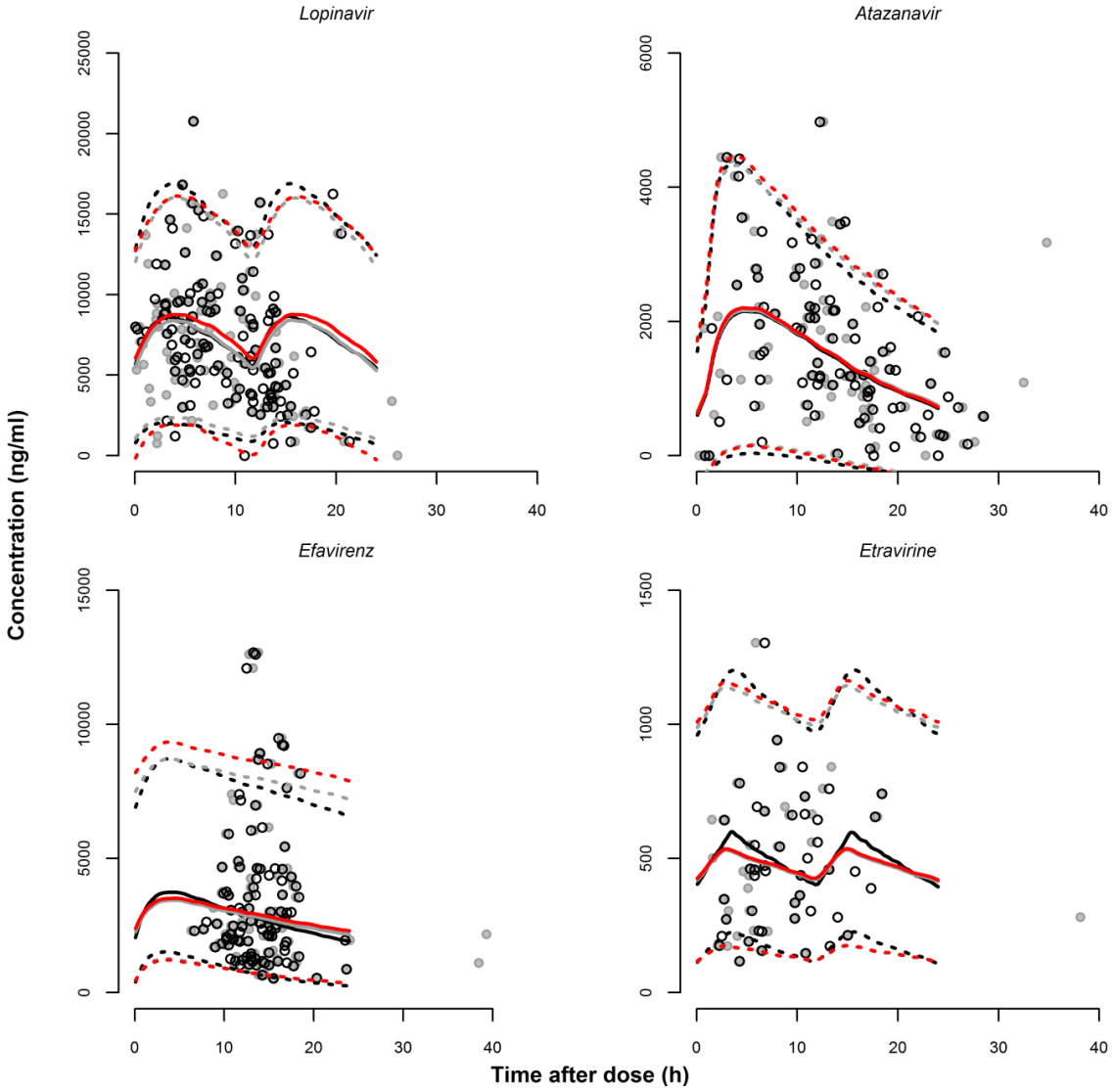

Figure 4.2. Concentration versus time for self-reported (white circle) and electronic monitor recorded data (grey circle). Population predictions (solid line) with their 95% prediction intervals (dotted line) are represented for steady-state data (black), reconciled electronic data (grey) and raw electronic monitor data (red). Concentrations are normalized for the standard dosage

Since the differences in paired individual CL estimates between the dose recording methods presented atypical values, a non parametric test was preferred for comparison. Differences in individual clearance

estimates did not reach statistical significance for LPV and ATV (median ΔCL= 0.0 L/h, P=0.06 and median ΔCL= 0.1 L/h, P=0.07 respectively), while they did so for EFV and ETV (median ΔCL= - 0.1 L/h and -1.1 L/h respectively, P=0.02 for both drugs) if a level α=5% is considered. Using the raw electronic data, with all PDs considered as missed doses, only LPV showed a difference in individual clearance estimation (median ΔCL = 0.1 L/h, P=0.001).

A summary of the MPE between predictors calculated under steady-state full adherence assumption and reconciled electronic data is presented **Table 4.3**. All $CI_{95\%}$ included 0, indicating no systematic differences of prediction between both approaches, neither did predictions with the raw electronic data. The comparison of MSE shows that reconciled electronic data produced more precise predictions than patient self-reporting for LPV, ATV and ETV, and particularly LPV. Only EFV predictions were slightly better with patient self-reported data. Predictions for all drugs based on raw electronic monitor data remained slightly more precise than those based on patient self-reporting.

Table 4.3. Relative bias and precision of self-reported last dosing time against electronic monitor data dosing history

	LPV	ATV	EFV	ETV
Self-reported *vs* reconciled electronic data				
MPE (ng/ml)	-33.5	15.2	12.7	4.23
[$CI_{95\%}$]	[-275.9;208.9]	[-60.4;90.7]	[-43.4;-68.9]	[-14.6;23.1]
Range PE_i (ng/ml)	[-3675.1;8972.7]	[-1096.3;1588.0]	[-1237.1;2043.1]	[-186.3;367.8]
ΔMSE (ng^2/ml^2)	1475748.2	73758.4	-15968.1	766.7
ΔRMSE (ng/ml)	1214.8	271.6	126.4	27.7
Worst case scenario: self-reported *vs* electronic data without PDs				
MPE (ng/ml)	-131.5	18.5	6.6	4.3
[$CI_{95\%}$]	[-422.2;159.2]	[-61.5;98.4]	[-68.0;81.3]	[-14.5;23.1]
Range PE_i (ng/ml)	[-3405.2;9610.6]	[-1084.4;1619.7]	[-1509.6;2069.5]	[-184.9;366.9]
ΔMSE (ng^2/ml^2)	610360.6	66396.1	14486.8	821.1
ΔRMSE (ng/ml)	781.3	257.7	120.4	28.6
reconciled electronic data *vs* electronic data without PDs				
MPE (ng/ml)	-96.5	2.34	6.1	0.1
[$CI_{95\%}$]	[-270.7;77.6]	[-20.9;25.6]	[-62.2;49.9]	[-2.2;2.3]
Range PE_i (ng/ml)	[-1319.0;8654.8]	[-303.2;738.2]	[-1717.8;1398.1]	[-26.5;34.7]
ΔMSE (ng^2/ml^2)	-868087.2	-9247.8	30454.9	54.4
ΔRMSE (ng/ml)	931.71	96.2	174.5	7.4

MPE = mean relative prediction error; **MSE** = mean squared error; **RMSE** = root mean squared error

Even though predictions appear globally similar between the different methods used to record dosing histories in our datasets, they may significantly differ for specific patients according to their adherence patterns. To illustrate this issue, representative patient profiles, taken from the dataset used for this analysis, for LPV (patients 1, 2 and 3) and EFV (patients 4, 5 and 6) are depicted in **Figure 4.3**.

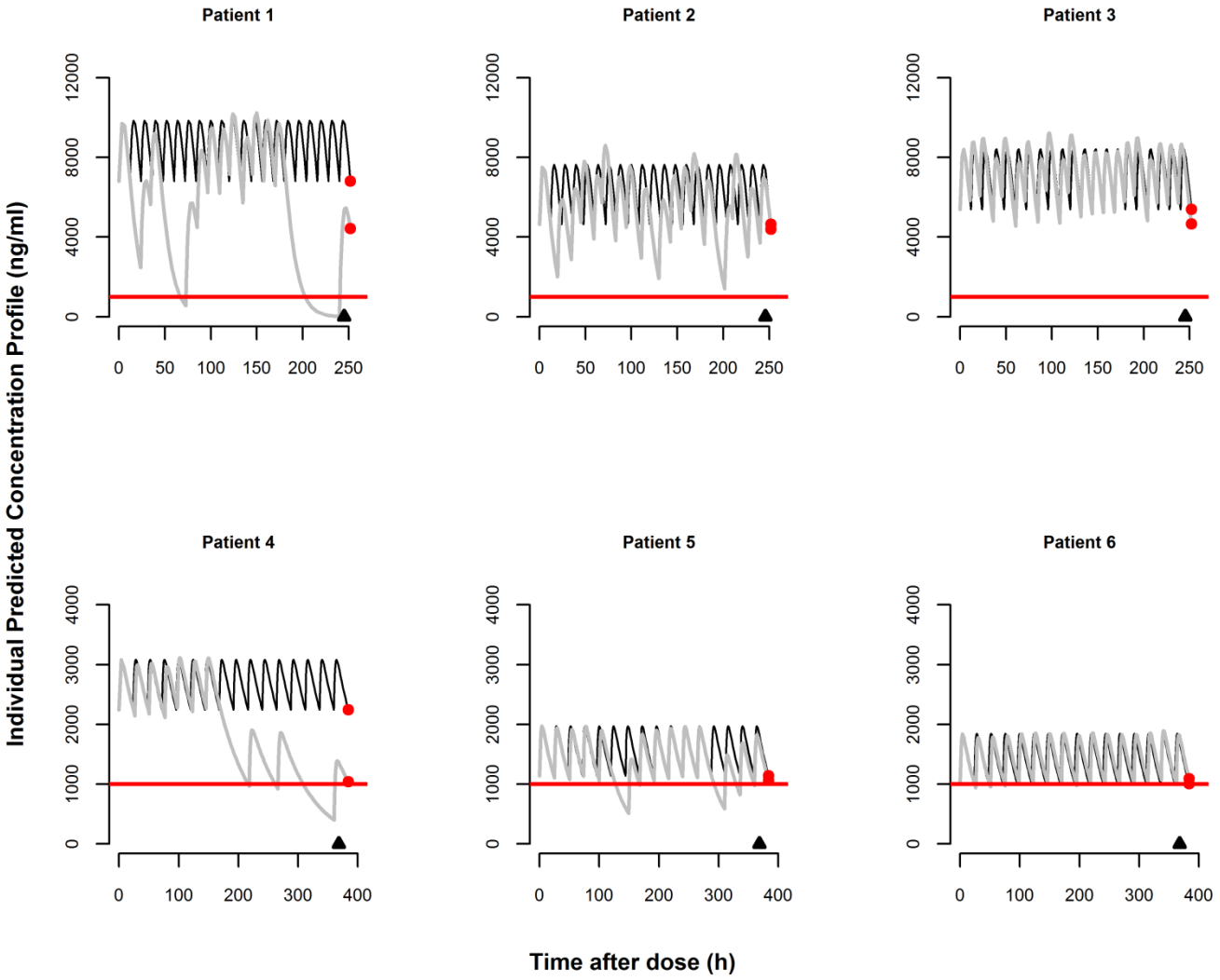

Figure 4.3. Individual concentration exposure profile for efavirenz (upper panel) and lopinavir (down panel) based on steady-state assumption (black) or reconciled electronic monitoring record (grey). Suggested target trough concentration by the FDA, in patients with HIV-1 (red line). Visit to the physician (triangle). Predicted C_{trough} (red points).

In the case of a large number of doses consecutively missed few days before the visit (patient 1and patient 4), despite similar time interval with respect to last dose intake according to self-report and electronic record, the predicted C_{trough} vary greatly between the steady-state with full adherence assumption and the reconciled electronic monitor record. This is in accordance with individual CL estimation: for patient 1, the difference in predicted trough concentration (ΔC_{trough}) was 2380 ng/ml and a difference in individual CL was 0.74 L/h, while patient 4 showed ΔC_{trough} of 1202 ng/ml and a difference in individual CL of 1.12 L/h. If a sparser pattern of missed dose is examined (one missed dose at a time), the differences in predicted trough concentration become much smaller: patient 2 and 5 had respectively a ΔC_{trough} of 242 ng/ml and ΔC of 77 ng/ml. However, even one missed dose can show a drastic though transient drop in drug exposure. The last examples illustrate patients well adherent, taking all their doses regularly, but the time interval between dosing and sampling reported by the patient differ from the value recorded by the electronic monitor by more than 2 hours. The resulting differences on predicted C_{trough} were of little importance for LPV and insignificant for EFV: patient 3 and patient 6 had a ΔC_{trough} of 727 ng/ml and ΔC_{trough} of 84 ng/ml, respectively. Difference in individual CL between both approaches for patients 3, 4, 5 and 6 were always smaller than 0.28 L/h.

IV.4. Discussion

In this observational study, popPK models based on dosing data either assuming steady-state with perfect adherence or using precise electronic monitor dosing records resulted in very similar estimations of population CL, which is the most important pharmacokinetic parameter determining average concentration exposure. Conversely, the type of dosing data tended to affect the population Vd as well as absorption parameters, known to correlate with one another. This was not the case for EFV and ATV, whose absorption constants were fixed according to the referred publication in order to achieve convergence. In contrast, for LPV, electronic monitor records revealed several measurements occurring in the first hours after the last dose intake, which were not reported by the patients. This probably explains the noticeable changes in absorption parameters and Vd estimation. Within-patient variability was said to be highly sensitive to

variable adherence [24]. In this study though, intra-individual variability seemed not affected by the type of dosing input. However, we had only few patients with several samplings. A study design that could collect several samples per patients would be of interest to evaluate this issue.

The procedure of reconciliation of electronic monitor records with patients' allegations, set up in the frame of our adherence program, made it possible to capture the majority of the PDs made by the patients, compared to raw electronic monitor data. This gives a more realistic picture of the patients' adherence in routine care. In our observations however, only lopinavir popPK parameters estimation would have been largely affected by missing patient information about dosing history, even though the frequency of PDs was in the same range for the other drugs (see **Table 4.1**). Neglecting PDs and merely treating them as missing doses for popPK analysis is expected to overestimate inter-individual variability and to bias PK parameters. The underestimation of adherence by electronic monitor might be of importance for certain drugs, particularly those with a shorter half-life. Thus, as LPV typically exhibits a rather short half-life even with ritonavir boost, a thorough estimation of adherence taking PDs into account is of importance. The concept of forgivingness was invoked to account for viral suppression despite incomplete adherence under combined antiretroviral treatments. While an adherence rate of at least 95% was formerly advocated to achieve sustained viral suppression and to prevent the emergence of resistance mutations [37, 38], the advent of ritonavir-boosted PI regimens as well as more potent NNRTIs might alleviate this constraint to some extent [39-41]. Improved potency and longer half-lives of boosted-PIs and NNRTIs are indeed among the reasons for improved forgiveness [42], as these agents produce exposure levels much higher than HIV replication inhibiting concentrations (IC_{90}), less likely to drop down to subtherapeutic levels with infrequent missed doses. Yet despite these considerations, any increase in the degree of adherence increases the probability of viral suppression [39, 43].

TDM is one tool among others that can support physicians in patient's care, to prevent therapeutic failure due to insufficient drug exposure or limited adherence. The pre-dose concentration C_{trough} is the classical

parameter to optimize by TDM interventions for PIs and NNRTIs. Target trough concentrations have indeed been proposed for most anti-HIV drugs in the control of wild-type HIV-1 infection [44]. Others predictors of efficacy have been promoted, such as maximal concentration (C_{max}) or area under the curve (AUC)[45]. The inhibitory quotient (IQ), derived from the ratio of C_{trough} over virological sensitivity (IC_{90}), probably represents a promising alternative [19].

Measuring true trough concentrations may be impractical in outpatients, hence the interest of Bayesian prediction of C_{trough} based on popPK models. Still the interpretation of a concentration measurement requires a precise knowledge of the times of sample collection and of last dose intake. As expected, a small variation in the dosing to sampling interval showed no significant impact on concentration prediction. Conversely, some specific patterns of poor adherence may have an important impact on the estimation of individual PK parameters and thus on prediction, as shown by patients 1 and 4 in our examples. In general, TDM is not ideally suited as a measure of adherence, as it essentially reflects the intake of one or a few previous doses. The monitoring of pharmacokinetic as well as pharmacodynamic (viral load and CD4 count) markers may increase health literacy and patient adherence by impacting on patient's motivation and management of treatment if such data are discussed emphatically with patients[46]. It has also been said that pharmacodynamic markers might benefit from more accurate recording of dosing history [47].

A major limitation of our study was the limited amount of data available, which prevented extensive modeling of the results. Still our analysis shows that, even though electronic monitor records are usually assumed to provide more reliable information on adherence than other methods, this information should be interpreted with caution, as it relies on uncertain assumptions: e.g. that each opening corresponds to a removed and directly ingested dose; or that the dose removed corresponds to the nominal dose prescribed (for instance, a nominal prescription of 400 mg of lopinavir q.d. means to remove and to ingest 2 pills of 200 mg from the electronic monitor bottle). Thus, the approach of reconciling electronic monitor data with patients' allegations should be privileged in such studies.

Another limitation was possibly that the study subpopulation did not reflect the overall population receiving ART. Patients referred to the adherence enhancing program have different characteristics than the entire HIV population: for example, besides problematic adherence, they were more often women with lower CD4 count [48]. The program showed successful results with 87% of persistence and 88% of execution [16].

Patient non-adherence issues are tackled during the medication adherence program to ensure adherence and success of treatment. Therefore, monitored patient adherence is quite high with restrained deviation from prescription and few nonadherent patients, which is probably closer from the behaviour of the population under ART.

In conclusion, this observational study showed that popPK analysis assuming steady-state with full adherence produced results similar to those based on precise electronic monitor recorded dosing history reconciled with patients' allegations. This reconciliation is important to identify PDs and correct the raw electronic monitor data according to a standardized procedure. Some drugs, less forgivable, may specially suffer from unrecorded PDs. Self-reported last dose intake appears to be reliable enough for concentration prediction in most patients. However, specific patterns of non-adherence lead to suboptimal exposure that will escape to TDM interpretation. Thus, especially in problematic patients, it is probably a combination of monitoring methods that best captures the complementary aspects of patients' exposure to therapeutic agents in routine care: longitudinal follow up of medication behaviour through electronic monitoring and actual quantitative measurement through TDM.

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Competing Interests

Authors declare no conflict of interest that could appear to have influenced the submitted work.

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CHAPTER V. DISCUSSION AND PERSPECTIVES

V.1. Discussion

Therapeutic Drug Monitoring relying on population PK/PD currently represents the state-of-the-art of drug dosage individualization. Concentration measurement without clinical interpretation is of poor value. Because of limited data availability (one concentration marred by uncertainty) and difficulties to obtain exact C_{trough} in clinical practice, PK interpretation largely benefits from Bayesian approach. Whereas, Bayesian forecasting can be mathematically demanding, we present the development of a new tool, EzeCHieL, to be used in clinical routine dedicated to this task. EzeCHieL provides essential information about expectedness and suitability of blood drug concentrations and gives dosage adjustment suggestion if needed. It offers a simple solution to develop patient tailored dosage regimen based on Bayesian feedback, which represents the gold-standard currently. In the emerging field of personalized medicine, it allows maximising therapeutic benefits for patient being treated with drugs candidate for TDM.

Implementation of Bayesian methods has also some limitations. It requires the right definition of the model, accurate and precise estimates of the PK model parameters, appropriate parameters distribution assumption, no change in individual PK parameters over time to trust *a posteriori* information, as well as quality of dosage. Finally, estimates should be obtained from data arising from the specific patient population, except if modeling and simulation allows extrapolating [1, 2].

Regarding special subpopulation, extrapolation cannot be performed for patients in early stage of life. There are also ethical and practical constraints related to the investigation of the fate of the drugs in this population. Therefore, dosing requirement and pharmacotherapy management continue to be a challenge in neonates. We present two population studies performed with data generated during routine clinical practice, providing in-house models to overcome those problems since it permits to characterise the PK of drugs and factors influencing drug exposure in this subpopulation. Their implementation in EzeCHieL allows Bayesian forecasting and drug dosage

regimen suggestion. Such quantitative pharmacological approaches have been recognised as a concept to enhance drugs development and appropriate routine use of drugs. In the last decade, regulatory agencies have recognized the role of modeling and simulations. In paediatrics, drug development programs have been growing and a number of initiatives have been undertaken [3, 4].

The reliability of the population models used along with adherence has been investigated in this thesis. In our study, Bayesian forecasting supported the use of population PK model and implementation in EzeCHieL. Since population PK models implemented in the software and simulations enable to derive expected concentration range (percentiles), it also allows evaluating some issues such as drug-interaction, specific individual PK characteristics or adherence.

Practice of TDM relies on the correlation between plasma drug concentration and therapeutic outcomes. An important limitation of this work was the lack of pharmacodynamics (PD) data. Thus, the association between plasma concentration and therapeutic endpoints was not investigated. In the scope of anti-infective agents or other drugs, this following hypothesis is accepted, but not yet supported, that target concentration is the same in infants, children and adults [5]. Reason to not support entirely this theory yet is the lack of adequate PD studies in paediatric population (the MIC are often determined *in vitro* or in adults), the stage of development that can alter PK (absorption, elimination, protein binding, etc.) and response to drug, as well as differences in organ penetration of the drug.

A number of issues arise from the development of new technologies in medicine. Acceptance among clinicians, in large and small facilities, has encountered considerable resistance [6]. Moreover, concerns for ethics and patient privacy are often raised [7, 8]. From the economic point of view, setting up Health Information Technology (HIT) would cause massive expenditure but it is believed that it would be compensate with the net saving awarded. So far, cost effectiveness has however not been demonstrated [9]. Use of new technologies should be adapted to literacy skills of the potential

users, and creating an intuitive interface appears to be critical. Ultimately, there is currently a lack of appropriate infrastructure and connectivity for a successful implementation [7, 10]. During the conception of EzeCHieL, we keep in mind those issues and as its development is performed in the scope of a multidisciplinary project, we attempt to address them at different levels (acceptance, privacy, user-friendliness, appropriate implementation in the existing structure, cost).

V.2. Perspectives

Since 1950, rate of drug introduction on the market remains constant, but drug industry is progressively less innovative [11] and more and more drugs are administered on long term. This largely fosters current TDM expansion. Monitoring of existing or new critical therapies and dosage individualization will transform clinical practice and patients care. There is a cultural change occurring. Particularly with the progress of embedded, miniaturized devices able to measure drug concentration of biomarkers directly on hand of the clinician and the availability of novel computing tools to support interpretation, drug monitoring will spread out.

However, there are still room for improvements in monitoring drug therapy for practical care management of patients. Many monitoring strategies have been set up without critical assessment. There is a need for prospective controlled clinical trial [12]. Clinical research has not yet devoted sufficient attention to evaluate monitoring procedure. Improvement of concentration monitoring strategy will gain in increasing the aggregation of concentration and effect data at large scale and by redirecting PK/PD modeling towards monitoring question compared to sole clinical trial purpose. Such data should be aggregated in systematic reviews to retrieve the more information possible [13]. It would support better definition of necessary criteria for monitoring and rationalise the procedure. Central coordination and repositories should allow dissemination and facilitate clinical use. Efficient monitoring tool, such as EzeCHieL, will ensure wide access to monitoring procedure and to conceptual criteria of TDM application [14]. At the current stage, EzeCHieL is almost fully

developed software that will be under beta testing shortly. Larger diffusion is expected and support via a semi-private structure will ensure continuous evolution. Later, it will be embedded, to point-of-care system currently under development in the frame of ISyPeM project.

This work focus mostly on neonates, but in the other side, the population is aging and this trend is accelerating in the world. Elderly people are often neglected during drug development. Variability in drug response is increased at both sides of these age spectrum and that may warrant precise dosing modification also in older adults. Older adults also undergo age-specific change in physiological parameters that influence their pharmacokinetic profile. Frail geriatric patients are associated with polymorbidity and multiple treatments. There is no appropriate model using scaled parameters to describe the non linearity observed in this population as well. Modeling can provide the link necessary for developing safe and efficient treatments to those patients. Further studies should thus also focus on elderly [15, 16].

Current practice uses dosage regimen defined for population target intervals. However there is a lack of PD studies to define rational dosing, as, for example, for those subpopulation described above. PK variability is recognised as an important source of variability in drug response, but the inter-individual differences in PD aspects of drug response need also to be considered. Thus, the following step is to take into account individual PD sensitivity rather than the expected population response and the use of individual target along with individual TDM observation represents another move in the personalized medicine [17]. The concept of target concentration could be defined as the optimal concentration for achieving efficacy with the lower possible toxicity for an individual. This more active approach is already advocated and has been named Target Concentration Intervention (TCI) [18].

Thus, progress in many facets of drug monitoring is ongoing and represents a desired extension of drug development. In that context, the outcomes represent possible solutions to improve TDM.

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