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Definition and validation of a patient-individualized physiologically-based pharmacokinetic model

Roberto Andrea Abbiati [a], Gaetano Lamberti [b], Mario Grassi [c], Francesco Trotta [d], Davide Manca [a,*]

[a] PSE-Lab, Process Systems Engineering Laboratory, Dipartimento di Chimica, Materiali e Ingegneria Chimica "Giulio Natta", Politecnico di Milano, Piazza Leonardo da Vinci 32, 20133 Milano, Italy
[b] Dipartimento di Ingegneria Industriale, Università degli studi di Salerno, Via Giovanni Paolo II 132, 84084 Fisciano Salerno, Italy
[c] Dipartimento di Ingegneria ed Architettura, Università di Trieste, Via Alfonso Valerio 6/A, 34127 Trieste, Italy
[d] UO Chirurgia Generale e Toracica, Ospedale Maggiore di Lodi, Via Fissiraga 15, 26900 Lodi, Italy

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ABSTRACT

Pharmacokinetic modeling based on a mechanistic approach is a promising tool for drug concentration prediction in living beings. The development of a reduced physiologically-based pharmacokinetic model (PBPK model), is performed by lumping organs and tissues with comparable characteristics respect to drug distribution phenomena. The proposed reduced model comprises eight differential equations and 18 adaptive parameters. To improve the quality of the PBPK model these adaptive parameters are alternatively: (i) individualized according to literature correlations on the physiological features of each patient; (ii) assigned as constants based on the features of either human body or drug properties; (iii) regressed respect to experimental data.

The model predictive capability is validated with experimental blood concentrations of remifentanil, an analgesic drug, administered *via* bolus injection with four doses (2, 5, 15, 30 μg/kg) to mixed groups of patients. Concentration profiles for the four simulated doses reveal a rather good consistency with experimental data.

1. Introduction

The administration of drugs to patients is one of the main activities involving physicians and this practice is matter of great attention. The discrimination among similar drugs to determine the most suitable one for a specific treatment and a given patient is rather challenging. Furthermore, the dose selection to achieve a desired effect is critical as an excessive quantity may cause toxic effects in patients whilst a moderate dose does not produce any benefits.

Dose appraisal related to the administration of anesthetics and analgesics during surgeries results particularly difficult. The anesthetist has to maintain the drug concentration in the blood amidst a well-defined range, called therapeutic window, to keep the patient sedated.

An important support to pharmaceutical companies during new-drug-development phases and to physicians in their daily activities can be provided by the application of mathematical models capable of describing the drug administration and biodistribution in the organism.

Pharmacokinetic (PK) modeling has been already applied to the pharmaceutical field and it allows scientists to determine the dynamics of blood drug concentration. Compartmental pharmacokinetic modeling can also be used to determine the drug PK parameters, such as the area under the curve (*AUC*), the terminal half-life time ($t_{1/2}$), and the clearance (*CL*) which support the physicians in administering the drug to patients properly.

In their native conception, classical compartmental pharmacokinetic (CCPK) models assumed that the human body could be depicted as a single volume, or compartment, to which the drug is administered and from which is eliminated. Those models were obtained by fitting exponential functions that depended on some parameters that did not have any physiological affinity to the human body and were only meant to minimize the error respect to experimental data (see Wagner, 1981 for a review on the history of early PK modeling).

More recently, CCPK models were characterized by preserving a rather simplified approach, although the number of compartments

* Corresponding author. Tel.: +39 02 23993271.
E-mail address: davide.manca@polimi.it (D. Manca).

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Notation

Abbreviations

ACAT	advanced compartmental absorption and transit
ADME	absorption distribution metabolism excretion
AUC	area under the curve
BM	body mass (kg)
BSA	body surface area (m^2)
CAT	compartmental absorption and transit
CCPK	classical compartmental pharmacokinetics
CPU	central process unit
GICS	gastrointestinal circulatory system
GL	gastric lumen
IVIVC	*in vivo*/*in vitro* correlation
LIL	large intestinal lumen
mPBPK	minimal-PBPK
ODE	ordinary differential equation
PBPK	physiologically based pharmacokinetics
PDE	partial differential equation
PK	pharmacokinetic
SD	standard deviation
SIL	small intestinal lumen

Symbols

B	blood flow to different organs (ml/min)
C	drug concentration (ng/ml)
CL	clearance (ml/min)
CO	cardiac output (l/min)
Eff	efficiency
F	material flow (ng/(ml min))
IV	intravenous (ng/min)
j	mass transfer coefficient (min^{-1})
k	reaction rate constant (metabolism) (min^{-1})
M	mass (ng)
PO	drug orally administered (*per os*) (ng/min)
Q	plasma flow to different organs (ml/min)
R	drug bound to protein (expressed as fraction)
t	time (min)
V	volume (cm^3 or ml)
w	mass fraction

Subscripts

½	terminal plasma half-life
A	absorption
CA	counter absorption
E	elimination
$HO\text{-}P$	from Highly perfused Organs to Plasma
MAX	value of the drug peak concentration
$P\text{-}HO$	from Plasma to Highly perfused Organs
$P\text{-}PT$	from Plasma to Poorly perfused Tissues
$PT\text{-}P$	from Poorly perfused Tissues to Plasma

Superscripts

GICS	gastrointestinal circulatory system
GL	gastric lumen
H	hepatic
HA	hepatic artery
HO	Highly perfused Organs
HV	hepatic vein
K	kidneys
L	liver
LIL	large intestinal lumen
P	plasma
PT	Poorly perfused Tissues
PV	portal vein
SIL	small intestinal lumen

Greek letters

Δ	difference
ρ	density (g/ml)

increased (generally to two or three), and took into account, at different levels of detail, the connections among compartments (Wagner, 1993). These CCPK models carried along a series of drawbacks, the most important being the extreme simplicity of the model structure that hindered any direct correlation to real living systems. Therefore, every CCPK parameter had to be determined mathematically for every specific drug by a fitting procedure (*i.e.* (non)linear regression) respect to experimental data. As a consequence, CCPK models require conducting extended and differentiated studies on either humans or animals. These tests are expensive and ethical issues are always a matter of great concern. In addition, it is often challenging to scale up to humans the experimental activity conducted on animals (Mordenti, 1986; Jones and Rowland-Yeo, 2013).

Recently, a contribution to the use of CCPK models was provided by Laínez-Aguirre et al. (2014), who proposed a model having a flexible structure. Based on an experimental data set, the model can reshape itself mathematically to produce a more suitable structure for the description of the specific pharmacokinetics under study.

A modern and alternative approach to pharmacokinetic modeling is based on the attempt to increase the mechanistic foundations by referring to and reproducing the real anatomy and physiology of mammalian systems. This is achieved by implementing an extended system of interconnected compartments. Here a compartment is an element that stands for either an organ or a tissue of the human/mammalian body, and which is mathematically described by a dynamic mass balance. By doing so, it is possible to quantify the concentration of the drug in blood, and in different organs and tissues. These mathematical *mockups* of mammalian body are named Physiologically Based Pharmacokinetic (PBPK) models.

The transition from CCPK to PBPK models is justified by a number of advantages. In fact, the possibility to have a complete and detailed model of the human body to run *in silico* simulations of drug's ADME processes (*i.e.* absorption, distribution, metabolism, excretion) allows speeding up the development of new drugs by saving large amounts of money, shortening pre-clinical and clinical tests, and reducing the number of experiments on both animals and humans. The implementation of these models is not only important for pharmaceutical companies but also for physicians in several therapies and for patients' treatment (Egan, 2003).

This approach is favorably seen and progressively encouraged by pharmaceutical companies that start considering and referring to PBPK models in dossiers submitted to the regulatory agencies (Zhao et al., 2012; Huang et al., 2013).

1.1. ADME phenomena

The theoretical bases of physiological approach to PK modeling point to the mathematical reproduction of ADME processes. Drugs are administered to the organism *via* several routes (*e.g.*, enteral, parenteral, inhalation, topical). Each of these paths carries along a series of advantages and drawbacks. For instance, amongst the parenteral routes, the endovenous infusion is of common use. It guaranties an immediate introduction of the drug into the systemic circulation and the entire dose administered is available