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Sorafenib in Mice – A Pharmacokinetic Study

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Pharmacokinetic models are applied to determine the drug distribution in the organism with respect to a given administration. Models based on body anatomy and physiology can provide an accurate description of drug concentrations reached in specific organs and tissues of mammals. This article proposes a model based on mammalian anatomy and physiology to predict the biodistribution in mice of sorafenib, an anti-cancer drug, with specific attention to the concentration reached in the liver, as that is the action site in case of hepatocellular carcinoma treatment. The model reveals a close correspondence respect to experimental concentration data in the organism and also assesses with good fidelity the enterohepatic circulation, a phenomenon occurring at the liver-intestine level and that strongly characterizes sorafenib distribution.

1. Introduction

The pharmacological effect of drugs is directly related to the concentrations that are reached in blood and tissues of living beings. The assessment of these concentration values results a fundamental aspect in all the scientific areas related to health care. The most common technique to determine the drug concentration requires sampling the reference tissues at specific times and measuring it in laboratory. This practice carries along a large number of drawbacks, as it requires invasive and repeated sampling of tissues, expensive measures and analysis, and a large batch of pharmacokinetic samples. To overcome these limitations, computer programs have become more popular. They are based on mathematical models able to predict the dynamics of drug concentration in the organism.
Mathematical pharmacokinetic models, despite their original simplicity (Wagner, 1993), are now highly detailed and can evaluate the drug concentration in organs and tissues of the target body. These advanced reproductions were christened Physiologically Based Pharmacokinetic (PBPK) models, and even if they were first introduced by Teorell (1937), only recently they have become extensively used and interesting for pharmaceutical companies to submit reports to regulatory agencies (Huang et al., 2013). In order to accurately evaluate the pharmacokinetics, PBPK models are based on the assumption that the body can be described by a certain number of interconnected compartments, each standing for a specific organ or tissue. In order to preserve the consistency with real anatomy and physiology, the compartment connections are based on the real anatomical structure.
The ambitious goal of PBPK modeling is to reduce dramatically the necessity to run experimental pharmacokinetic evaluations and also to be a sophisticated and flexible tool for in silico simulation of the behaviour of new drug molecules in the human body. PBPK models can also facilitate and speed up the research activity of new active principles.
An aspect limiting the extensive use of PBPK models is the necessity of a large amount of detailed information regarding specific properties and features of organs and tissues (e.g., cells membrane permeability, blood volumetric fluxes, drug metabolic reactions, just to mention a few), which can hardly be experimentally measured or theoretically assessed thus resulting often as unknown values.

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Given this background, the final formulation of the PBPK model consists in a system of Ordinary Differential Equations (ODEs) that describes the drug mass balances in every modeled compartment. Figure 1 shows the schematic representation of mammalian body according to its anatomy and physiology. The interconnected compartments represent lumped versions of both organs and tissues and reproduce how the topological structure is interested by the quite complex phenomena involved in the dynamic distribution of drug in the body.

Pharmacokinetic models help understanding better how drugs possibly distribute through, metabolize in, and finally are excreted by the body. Specifically, they are quite promising and interesting as far as anti-cancer drugs are concerned. In fact, during clinical trials it is common practice to administer the studied drug to animals and human volunteers, but this is a critical issue in case of anti-cancer drugs because of the adverse side effects. In addition, the treating of carcinoma is a highly invasive practice, both in case of surgeries and pharmacological treatment.

This article focuses on the cure of Hepatocellular Carcinoma (HCC), which is the most common type of liver cancer and the fifth more frequent malignancy worldwide (Abou-Alfa et al., 2006). The only effective ways to survive this disease are either surgical resection or liver transplantation (Llovet et al., 2000), with the conditio sine qua non for all these cases being the early diagnosis. When the disease is unresectable, the only therapy available is the pharmacological treatment, which may generally allow a life extension of few months.

Sorafenib is a drug for the cure of renal and hepatic carcinoma, approved by both FDA and EMEA, and commercialized as Nexavar®. It acts as a multi-kinase inhibitor that targets tumor growth and angiogenesis (Akaza et al., 2007).

2. State of the art

The mechanistic approach to pharmacokinetic modeling started to be extensively applied with the work of Himmelstein and Lutz (1979); the following decades saw a strong growth of this scientific field. The work by Jain et al. (1981) is surely a milestone as it introduced innovative concepts that are still present in recent publications. That work proposed a complete whole-body PBPK model of the rat composed of 21 compartments originating a system of 38 ODEs and 98 adaptive parameters. Some of those parameters were available in the literature but 37 had to be fitted by a regression routine. The application of such a complex model allows achieving the detailed description of the rat body, but implies some mathematical limitations, manly related to the large number of unknown adaptive parameters. Other PBPK models were proposed in the following years, where it is clear the attempt to reduce the complexity while preserving an extended anatomical and physiological consistency.

Amongst pharmacokinetic (PK) models, it is interesting to highlight the presence of a large number of publications specifically devoted to the description of the oral absorption process. Yu et al. (1996a,b) published a detailed model of the gastrointestinal tract based on ten compartments, which resulted quite detailed. They introduced a system of 10 ODEs based on 18 adaptive parameters. That model, named CAT (from Compartmental Absorption and Transit), showed a good agreement with experimental data of human patients administered with different active principles. A subsequent version of CAT model was implemented in the Gastro Plus commercial software by Simulations Plus. That program is based on the ACAT (Advanced Compartmental Absorption and Transit) model, which features a detailed compartmental description of the gastrointestinal tracts (Agoram et al., 2001).

Del Cont et al. (2014) proposed a comprehensive model that involves the physical processes, which determine the release of drugs from a polymeric matrix and the following intestinal absorption, and implements a complete description of the oral administration process.

The difficulties connected with the model complexity and parameter identification of whole body PBPK simulations induced the implementation of reduced complexity models, which attempt to maintain the core anatomical and physiological consistency. This model reduction activity was mainly based on limiting and lumping together similar compartments so to reduce their total number and as a consequence the number of equations and parameters. Nestorov et al. (1998) and Pilari and Huisinga (2010) provide details about both lumping and model reduction activities.

The work of Di Muria et al. (2010) summarizes some of the concepts reported in the previously cited works. There, a complete mammalian structure is obtained by modeling two lumped compartments, namely the Plasma (i.e., the blood and the largely-perfused organs/tissues) and the Tissues (i.e., blood scarcely-perfused organs/tissues). The PBPK model of Di Muria et al. (2010) considers seven compartments (i.e. gastric lumen, small intestine, large intestine, gastro intestinal circulatory system, liver, plasma, and other tissues). The corresponding mathematical formulation comprises 7 ODEs involving 22 physiological and pharmacokinetic parameters.

For what it concerns the sorafenib PK model, it is worth referring to two literature works. Jain et al. (2011) proposed a one compartment model with additional components to define the gastrointestinal absorption and the enterohepatic circulation. Pawaskar et al. (2013) realized a PBPK model capable to assess drug interactions between sorafenib and everolimus in mice; sorafenib was administered to BALB/c mice and samples were collected from blood and organs/tissues at different time interval.

3. Methods

The proposed model is derived from the original structure of Di Muria et al. (2010), but substantial variations are introduced to describe the gastrointestinal tract, the enterohepatic circulation (EHC), the plasma compartment, and the drug-protein binding properties. Figure 1 shows the model compartmental structure.

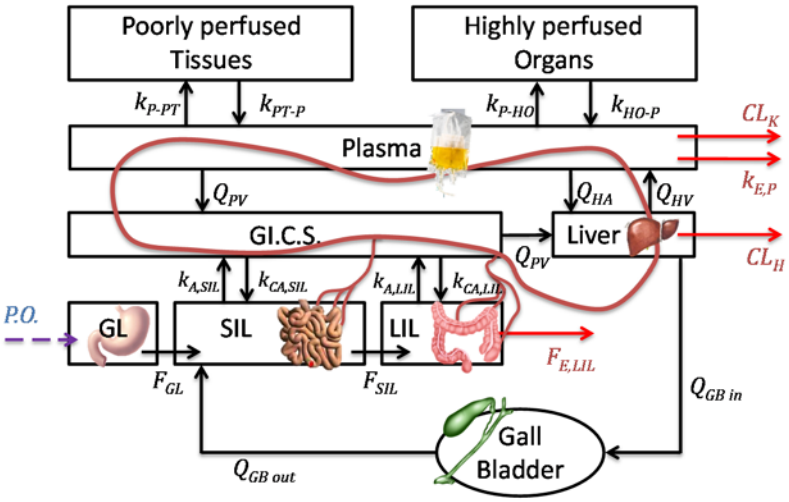

Figure 1: PBPK model compartmental structure.

Sorafenib is administered orally ($P.O.$). In case of mice, it is introduced directly in the stomach through gastric gavage. Then it crosses the two intestine tracts, i.e. small intestine (SIL) and large intestine (LIL). Finally, the residual part is excreted through the faeces ($F_{E,LIL}$). SIL is the main site of absorption of substances from the intestinal lumen into blood circulation. In mathematical terms, this occurs through the application of two mass transfer coefficients: $k_{A,SIL}$ for the absorption into blood, and $k_{CA,SIL}$ for the counter-absorption into SIL. A similar phenomenon characterizes the LIL but with a minor contribution to the global intestinal absorption. Similarly, the related mass transfer coefficients are $k_{A,LIL}$ and $k_{CA,LIL}$.

To provide a consistent mathematical description of the SIL, both time and spatial coordinates of drug concentration in the lumen should be taken into account. This can be achieved by modeling the lumen as a Plug Flow Reactor (PFR), where concentration varies axially. A simplified approach suggests approximating the PFR framework with a sufficiently high number of Continuous Stirred Tank Reactors (CSTRs) in series. The spatial discretization of the longitudinal coordinate allows preserving the ODE structure, thus avoiding any partial derivative equations. Generally speaking, the model is discretized into *NR* CSTRs (in our study we chose *NR*=7 as a suitable compromise between detail and efficiency), where the sum of the volumes of single reactors is equal to the total SIL volume, while the mass transfer phenomena are considered in both directions (i.e. absorption and counter absorption) as discussed above. The parameter values are the same and kept constant for each reactor. The absorbed drug is collected into the so called Gastro-Intestinal Circulatory System ($GI.C.S.$), which represents the blood channels that receive substances from the intestine and deliver them to the liver through the portal vein. Once the drug reaches the liver, it is partially eliminated because of the metabolic activity in the hepatocytes. Mathematically, this is evaluated by the term CL_H standing for hepatic clearance, which is the volume of blood purified from the drug in the unit of time. Blood reaches the liver either through the portal vein (Q_{PV}) or via the hepatic artery (Q_{HA}) and leaves that organ via the venous channel called hepatic vein (Q_{HV}). Finally, a fraction of the drug is excreted from the hepatocytes into the bile. The EHC implies that the bile produced in the liver is collected into the gall bladder, concentrated and introduced at the beginning of the SIL tract. This process occurs cyclically during digestion phases and produces a singular effect on the drug. In fact, the bile carries along a fraction of the drug that, being reemitted in the SIL, goes through a second intestinal absorption. This extends the drug life time in the body.

The drug fraction remaining in the blood flux, reaches the Plasma compartment through the Q_{HV} term. This compartment symbolizes the liquid fraction of the blood and is responsible for the drug transport in the body. The organs and tissues of the body which are not explicitly considered are lumped either in the Highly-perfused-Organs (HO) compartment, or in the Poorly-perfused-Tissues (PT) compartment. The drug mass transfer between plasma and these two compartments is evaluated by means of four mass transfer coefficients (i.e. k_{P-PT} and k_{P-HO} from plasma into the respective compartment, and k_{PT-P} and k_{HO-P} for the back transport of the drug into the plasma). Given this theoretical background, which is strongly based on mammalian anatomy and physiology, the related equations can be inferred naturally as dynamic mass balances describing the drug flow in every compartment. The resulting ODE system is:

$$\frac{dC_{GL}(t)}{dt} = -F_{GL}(t) \tag{1}$$

$$\frac{dC_{SIL,1}(t)}{dt} = -C_{SIL\,1}(t)\cdot k_{A,SIL} + F_{GL}(t)\cdot\frac{V_{GL}}{V_{SIL\,1}} - F_{SIL}(t) + \frac{C_{GICS}(t)}{nSIL}\cdot f_u\cdot k_{CA,SIL}\cdot\frac{V_{GICS}}{V_{SIL\,1}} + C_{GB}\cdot\frac{Q_{GBout}}{V_{SIL\,1}}\cdot ActBile \tag{2}$$

$$\frac{dC_{SIL,n}(t)}{dt} = -C_{SIL\,n}(t)\cdot k_{A,SIL} + F_{SIL\,n-1}(t)\cdot\frac{V_{SIL\,n-1}}{V_{SIL\,n}} - F_{SIL\,n}(t) + \frac{C_{GICS}(t)}{nSIL}\cdot f_u\cdot k_{CA,SIL}\cdot\frac{V_{GICS}}{V_{SIL-n}} \tag{3}$$

$$\frac{dC_{SIL,NR}(t)}{dt} = -C_{SIL,NR}(t)\cdot k_{A,SIL} + F_{SIL,NR-1}(t)\cdot\frac{V_{SIL,NR-1}}{V_{SIL,NR}} - F_{SIL,NR}(t) + \frac{C_{GICS}(t)}{nSIL}\cdot f_u\cdot k_{CA,SIL}\cdot\frac{V_{GICS}}{V_{SIL,NR}} \tag{4}$$

$$\frac{dC_{LIL}(t)}{dt} = -C_{LIL}(t)\cdot k_{A,LIL} + F_{SIL,NR}(t)\cdot\frac{V_{SIL,NR}}{V_{LIL}} - F_{E,LIL}(t) + C_{GICS}(t)\cdot f_u\cdot k_{CA,LIL}\cdot\frac{V_{GICS}}{V_{LIL}} \tag{5}$$

$$\frac{dC_P(t)}{dt} = -C_P(t)\cdot\left(k_{P-PT}\cdot f_u + k_{P-HO}\cdot f_u + \frac{Q_{HA}}{V_P} + \frac{Q_{PV}}{V_P}\right) + C_{PT}(t)\cdot k_{PT-P}\cdot\frac{V_{PT}}{V_P} + \frac{C_L(t)}{k_{lp}}\cdot\frac{Q_{HV}}{V_P} + C_{HO}(t)\cdot k_{HO-P}\cdot\frac{V_{HO}}{V_P} - C_P(t)\cdot f_u\cdot k_{E,P} - C_P(t)\cdot\frac{CL_K}{V_P} \tag{6}$$

$$\frac{dC_{PT}(t)}{dt} = -C_{PT}(t)\cdot k_{PT-P} + C_P(t)\cdot f_u\cdot k_{P-PT}\cdot\frac{V_P}{V_{PT}} \tag{7}$$

$$\frac{dC_{GICS}(t)}{dt} = -C_{GICS}(t)\cdot\left(\frac{Q_{PV}}{k_{pl}\cdot V_{GICS}} + k_{CA,SIL}\cdot f_u + k_{CA,LIL}\cdot f_u\right) + \sum_{n=1}^{NR} C_{SIL\,n}(t)\cdot k_{A,SIL}\cdot\frac{V_{SIL\,n}}{V_{GICS}} + C_{LIL}(t)\cdot k_{A,LIL}\cdot\frac{V_{LIL}}{V_{GICS}} + C_P(t)\cdot\frac{Q_{PV}}{V_{GICS}} \tag{8}$$

$$\frac{dC_L(t)}{dt} = -C_L(t)\cdot\left(\frac{Q_{HV}}{k_{lp}\cdot V_L} + \frac{CL_H}{V_L}\right) - C_L\cdot\frac{Q_{GBin}}{V_L} + C_P(t)\cdot\frac{Q_{HA}}{k_{pl}.V_L} + C_{GICS}(t)\cdot\frac{Q_{PV}}{k_{pl}.V_L} \tag{9}$$

$$\frac{dC_{HO}(t)}{dt} = -C_{HO}(t)\cdot k_{HO-P} + C_P(t)\cdot f_u\cdot k_{P-HO}\cdot\frac{V_P}{V_{HO}} \tag{10}$$

$$\frac{dC_{GB}(t)}{dt} = -C_{GB}(t)\cdot\frac{Q_{GB\ out}}{V_{GB}}\cdot ActBile + C_L(t)\cdot\frac{Q_{GB\ in}}{V_{GB}} \tag{11}$$

Here the differential terms assess the drug accumulation in the specific compartments. On the right hand side of ODEs positives terms enter the compartment while negative ones leave it.
In detail, Eq.s (1-5) describe the transit through the gastrointestinal tract, specifically Eq. (2) refers to the first CSTR discretizing the SIL, Eq. (3) to the generic intermediate CSTR, and Eq. (4) to the last CSTR of the SIL. Eq.s (6-11) refer respectively to Plasma, Poorly perfused Tissues, Gastro-Intestinal Circulatory System, Liver, Highly perfused Organs, and Gall Bladder compartments. Table 1 details the terms characterizing the ODEs system.

Table 1: Model parameters.

Symbol	Units	Description	Value
Eff_H	-	Hepatic efficiency of elimination	0.018
Eff_K	-	Kidneys efficiency of elimination	0.014
$Q_{GB\ in}$	ml/min	Bile volumetric flux to Gall Bladder	0.037
$Q_{GB\ out}$	ml/min	Bile volumetric flux leaving Gall Bladder	0.001
Q_{HA}*	ml/min	Hepatic Artery volumetric flux	0.133
Q_{HV}*	ml/min	Hepatic Vein volumetric flux	1.078
Q_K*	ml/min	Plasma volumetric flux to kidneys	0.605
Q_{PV}*	ml/min	Portal Vein volumetric flux	0.945
V_{GB}*	cm^3	*GB* compartment volume	0.04
V_{GICS}*	cm^3	$GI.C.S.$ compartment volume	0.005
V_{GL}*	cm^3	Gastric Lumen compartment volume	1
V_{HO}*	cm^3	Highly perfused Organs compartment volume	1.48
V_L*	cm^3	Liver compartment volume	1.51
V_{LIL}*	cm^3	LIL compartment volume	0.29
V_P*	ml	Plasma compartment volume	1.28
V_{PT}*	cm^3	Poorly perfused Tissues compartment volume	18.22

Table 2: Model parameters (cont.d).

Symbol	Units	Description	Value
V_{SIL}*	cm^3	SIL compartment volume	0.76
$k_{A,LIL}$*	min^{-1}	LIL to $GI.C.S.$ mass transfer coefficient	0
$k_{A,SIL}$	min^{-1}	SIL to $GI.C.S.$ mass transfer coefficient	0.034
$k_{CA,LIL}$*	min^{-1}	$GI.C.S.$ to LIL counter mass transfer coefficient	0
$k_{CA,SIL}$	min^{-1}	$GI.C.S.$ to SIL counter mass transfer coefficient	0.082
$k_{E,P}$	min^{-1}	Plasma Elimination mass transfer coefficient	0.051
k_{HO-P}	min^{-1}	Highly perfused Organs to Plasma mass transfer coefficient	0.038
k_{P-HO}	min^{-1}	Plasma to Highly perfused Organs mass transfer coefficient	0.215
k_{P-PT}	min^{-1}	Plasma to Poorly perfused Tissues mass transfer coefficient	0.482
k_{PT-P}	min^{-1}	Poorly perfused Tissues to Plasma mass transfer coefficient	0.012
k_{lp}	-	Liver-Plasma partition coefficient	1.9
k_{pl}*	-	Plasma-Liver partition coefficient (k_{lp} reciprocal)	0.52
t_{GL}*	min	GL residence time	100
t_{LIL}*	min	LIL residence time	210
t_{SIL}*	min	SIL residence time	160
$ActBile$*	min	Time corresponding to gall bladder emptying into the SIL	260
f_u	-	Drug fraction unbound to plasma proteins	0.28

*these values were assigned from literature data, other values were estimated via a nonlinear regression procedure respect to experimental data. Here CL_i are defined as $Q_i \cdot Eff_i$, where Q is the plasma flux to the organ i and Eff is related drug removal efficiency. One should observe that $Q_{GB\,in}$ is evidently an overestimation of the real value, but two aspects should be taken into account: (i) the drug concentration in the bile is assumed equal to the one in the liver, while it should be higher as an effect of drug excretion from the liver into the bile; (ii) the bile delivered to the gall bladder is diluted and is concentrated into the gall bladder itself. Unfortunately, at our knowledge more accurate experimental data are not available.

4. Results

The proposed PBPK model was applied to the description of the sorafenib pharmacokinetics in mice. Reference experimental data were the ones published by Pawaskar et al. (2013). In that study 20 mg/kg were administered in a single dose to male BALB/c mice (7 - 8 weeks old, average weight 25 - 30 g).
Figure 2 shows the model outcomes.

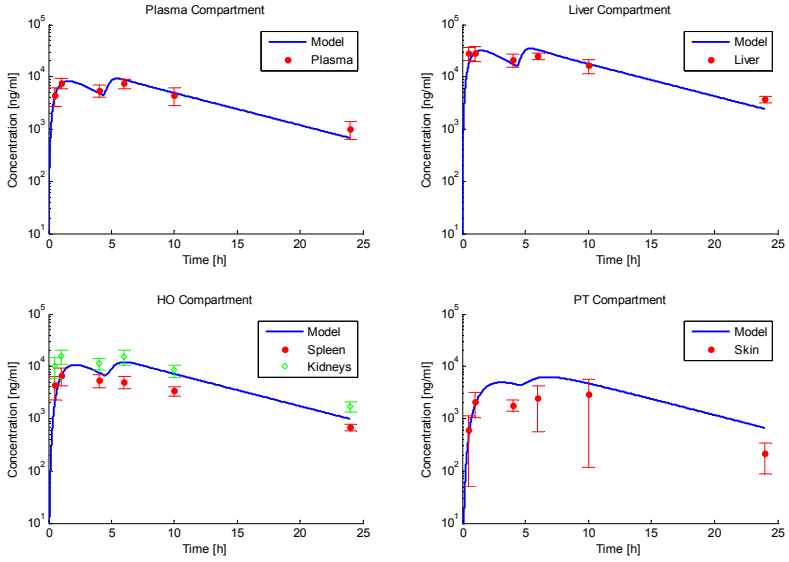

Figure 2: Dynamics of sorafenib concentration in four different representative compartments as predicted by the model (continuous line) respect to experimental data (points with standard deviation).

The model is able to describe the PK behavior of sorafenib in mice. Interestingly, the experimental concentrations are assessed with good fidelity for both organs and tissues. This aspect is of fundamental importance since it valorizes the application of anatomy and physiology to model based PK. Furthermore, the possibility to determine accurately the sorafenib concentration in the liver is fundamental as this drug is intended to act specifically on HCC. Finally, it is worth observing that the apparent overestimation of concentration in the PT compartment, should take into account that experimental values refer exclusively to drug concentration in the skin while PT refers to a larger set of tissues (e.g., muscles) which reasonably account for higher drug concentration respect to skin.

5. Conclusions

A PBPK model capable to describe sorafenib pharmacokinetics in mice was presented and discussed. The model implements some innovative aspects as the description of the EHC, which is responsible for the double peak profile in sorafenib concentration-time diagrams. The similarity of mammalian anatomy and physiology between mice and men is a promising feature that could allow exploiting the predictive features of the proposed model for sorafenib treatments in human patients.

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