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Mechanistic Modeling of Drug Elimination by the Liver using Local Volume Averaging Method

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Abstract— **Local volume averaging method and local mass (drug) equilibrium were used for developing a mathematical model for transient drug transport and elimination in the liver. Taking into account the liver porosity and tortuosity, physio-chemical properties of the drug, the drug effective diffusivity, dispersion, convection, local plasma-hepatocyte equilibrium and hepatocellular drug metabolism, the governing partial differential equation was developed and numerically solved to describe a transient drug transfer and elimination across the liver following intravenous (IV) administration. The predicted values of hepatic clearance and bioavailability had very good agreement with the reported observations for different drugs. Unlike the well-stirred, parallel tube and dispersion models of hepatic clearance, the proposed mechanistic model is able to predict the drug concentration gradient across the liver with time and position in very dynamic conditions associated with drug absorption process in the intestine.**

I. Introduction

LIVER, the largest organ in the body, plays a very important role in the elimination of drugs, toxic substances, and harmful biochemical products produced by the body (i.e. bilirubin, ammonia). The liver is appropriately located in the body so that it directly receives the nutrient rich but poorly oxygenated blood from the intestines via the portal vein and oxygenated blood from the hepatic artery accounting for 75% and 25% of total blood supply, respectively. Both blood supplies perfuse to each polyhedral functional unit called acinus in which portal and arterial blood are mixed in the smallest acini vessels called sinusoids in which mass exchange takes place between blood and hepatic cells (hepatocytes).

The liver's essential role in the regulation of metabolite concentrations as well as drug and toxin elimination in the body demands a detailed understanding of liver function. Mechanistic models that effectively describe liver function can play an important role in understanding and predicting drug concentration and hepatic metabolic performance. Different physiological models have been developed for the liver based on different degrees of simplifications and assumptions. The well-stirred (WS) model and the parallel-tube (PT) model are the two most commonly used models describing drug elimination by the liver [1]. These models are based on idealized situations of blood flow and solute (drug) distribution in the liver. In the well-stirred model, the drug is assumed to be instantaneously and homogeneously mixed with the blood in liver resulting in very uniform drug concentrations across the liver with drug concentration at the liver outlet the same as that within the liver. The parallel tube model assumes that blood containing drug flows through many identical parallel tubes with the same and constant velocities. Mass transfer takes place between the blood and the tube walls (hepatocytes) resulting in an exponential decline in drug concentration across the liver. Bass et al. (1977) and Forker and Luxon (1977) developed a distributed model representing blood flow in parallel tubes where each tube transports a certain fraction of total blood flow as determined by a distribution function [2, 3]. Roberts and Rowland (1986) developed a physiological-based dispersion (DP) model which was based on the residence time distribution of drug in the liver. The distribution of residence times was based on the axial dispersion [4]. Calvetti et al. (2008) used Bayesian flux balance analysis for two compartment spatially lumped liver metabolism to describe flux and transport rates at steady state [5].

The main objective of this study is to develop and validate a local volume averaging (LVA) based mathematical model describing drug hepatic elimination rate, hepatic clearance and bioavailability. Unlike WS, PT and DP models, the proposed mechanistic model considers key structural characteristics of the liver (i.e. porosity and tortuosity) and predicts a drug concentration gradient across the liver with time under very dynamic conditions caused by drug absorption process in the intestine.

II. Theory

A. Local Volume Averaging (LVA) method

A porous medium is a solid matrix consisting of a solid phase and spaces which can be filled with a fluid. As a highly perfused tissue the liver can be treated as a porous medium consisting of a blood phase and a solid matrix of hepatocytes. In porous media when a solid matrix cannot be described within pore size, a representative elementary volume (REV) with a characteristic length of l and volume of V_l is defined to represent the structure of the solid matrix. In the liver, an acinus can be a REV as the smallest differential volume resulting in statistically meaningful average properties of the liver. Averaging properties over the

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REV (V_l) is called local volume averaged properties defined as:

$$\langle \varphi \rangle = \frac{1}{V_l} \int_{V_l} \varphi \, dV \tag{1}$$

where φ is a property of interest and $\langle \varphi \rangle$ is the volume averaged property. The method that uses local volume averaged transport governing equations and properties associated with the REV is called local volume averaging (LVA) method. Considering that a liver approximately consists of one million acini [6], the REV characteristic length of a normal liver with a volume of 1222.76 ± 216.96 cm^3 [7] will be about 600 μm. Since the pore size (sinusoid diameter) of the liver tissue matrix is as small as a few cells (i.e. <60 μm), for a normal liver tissue with a length of ~20 cm, the condition LVA validity can be satisfied as $d_p\ (6\times10^{-5}\ m) < l\ (6\times10^{-4}\ m) << L\ (2\times10^{-1}\ m)$ where d_p and L are the sinusoid and the liver length scales, respectively.

B. Mathematical Modeling

The geometry of the liver was simplified so that a slab with the same thickness and volume as the liver represented the whole organ. Monitoring the mass transfer across a differential element of the simplified geometry, a drug compound is transported into/out of the differential element of the liver by molecular diffusion, radial/axial dispersion, and advection due to the blood flow. While the drug is in local equilibrium with hepatocytes in the element, the drug undergoes hepatocellular metabolism at a metabolism rate described as:

$$\hat{m}_{met} = Cl_{int\_in\ vivo}\, f_{u(B)} \langle C \rangle^P \tag{2}$$

where $\hat{m}_{met}$ is the hepatic metabolism rate ($mgs^{-1}ml^{-1}$), $f_{u(B)}$ is unbound fraction of the drug in the blood, $Cl_{int\text{-}invivo}$ is the average value of *in-vivo* hepatic intrinsic clearance (s^{-1}), and $\langle C \rangle^P$ is the local volume averaged drug concentration in plasma ($mgml^{-1}$). Applying transient mass balance over the differential element of the liver eventually results in the governing equation of drug transport in the liver as:

$$\left(D_\perp + D_{||} + \frac{D_{AB}\,\varepsilon\, f_{u(B)}}{\tau}\right)\frac{\partial^2 \langle C \rangle^P}{\partial x^2} - \bar{u}_B \frac{\partial \langle C \rangle^P}{\partial x} - Cl_{int\_invivo} f_{u(B)} \langle C \rangle^P = \left(f_{u(B)}(1-\varepsilon)K^* + \varepsilon\right)\frac{\partial \langle C \rangle^P}{\partial t} \tag{3}$$

where $D_\perp$ and $D_{||}$ are radial and axial dispersion coefficients (cm^2s^{-1}), D_{AB} is diffusivity of the drug in the blood (cm^2s^{-1}), ε is the liver porosity, τ is the tortuosity of the liver sinusoids, x is the position (cm), K^* is the partition coefficient between the blood and hepatocytes, t is time (s), and $\bar{u}_B$ is the Darcy velocity (cms^{-1}) of the blood in the liver which is obtained as:

$$\bar{u}_B = \frac{Q_h}{A} \tag{4}$$

where Q_h is the hepatic blood perfusion rate (mls^{-1}) and A is the liver cross-sectional area (cm^2) perpendicular to the hepatic blood flow into the liver. The initial and boundary conditions of (3) are defined as:

$$\begin{aligned} &\langle C \rangle^P (x, t=0) = 0 \\ &\langle C \rangle^P (x=0, t) = C_0 \quad where\ D_{||}(x=0,t) = 0 \\ &\left.\frac{\partial \left(f_{u(B)} \langle C \rangle^P\right)}{\partial x}\right|_{x=L,t} = 0 \quad where\ D_{||}(x=L,t) = 0 \end{aligned} \tag{5}$$

Using the predicted unbound drug concentration in the hepatic vein when the drug has been fully distributed in the liver, the hepatic clearance ($Cl_{h\text{-}LVA}$) is calculated as:

$$Cl_{h-LVA} = \frac{Q_h\left(\langle C_u \rangle^P\big|_{x=0} - \langle C_u \rangle^P\big|_{x=L}\right)}{\langle C_u \rangle^P\big|_{x=0}} \tag{6}$$

where $\langle C_u \rangle^P$ is the local volume averaged unbound drug concentration ($mgml^{-1}$), L is the equivalent length of the liver (cm). In order to compare the LVA-based model to other models, the hepatic clearance was calculated in MATLAB at the same input conditions as LVA-based model according to WS, PT and DP models, respectively, as follows [8]:

$$Cl_{h-WS} = \frac{Q_h\, f_{u(B)}\, Cl_{int-invivo} V_t}{Q_h + V_t f_{u(B)}\, Cl_{int}} \tag{7}$$

$$Cl_{h-PT} = Q_h\left(1 - \exp\left(-\frac{f_{u(B)}\, Cl_{int-invivo}}{\frac{Q_h}{V_t}}\right)\right) \tag{8}$$

$$Cl_{h-DP} = Q_h\left(1 - \frac{4a}{(1+a)^2 \exp\left(\frac{(a-1)}{2D_n}\right) - (1-a)^2 \exp\left(\frac{-(a+1)}{2D_n}\right)}\right) \tag{9}$$

where $Cl_{h\text{-}WS}$, $Cl_{h\text{-}PT}$ and $Cl_{h\text{-}DP}$ (s^{-1}) are the hepatic clearance suggested by WS, PT and DP models, and D_n in (9) is 0.14 and a is defined as [9]:

$$a = \sqrt{1 + \frac{4 f_{u(B)} V_t Cl_{int-invivo} D_n}{Q_h}} \quad (10)$$

where V_t is the volume of the liver tissue (ml) and can be calculated as a function of body weight. Having the hepatic clearance (Cl_h) and the hepatic perfusion rate (Q_h), the bioavailability can be calculated as [9]:

$$F_H = 1 - \frac{Cl_h}{Q_h} \quad (11)$$

C. Numerical Solution

Numerical solution of the model required a number of simplifying assumptions as follows: i) extrahepatic clearance of the drug is negligible; ii) compared to the hepatic metabolism, bilary excretion of parent drug is negligible; iii) drug IV administration is followed by a instantaneous distribution in the body so that the inlet plasma drug concentration at the liver can be assumed as the ratio of dose to the volume of distribution of the drug; iv) total blood to the total plasma concentration ratio is unity; v) the unbound fraction of the drug in blood remains constant with time; vi) axial/radial dispersion are negligible compared to the advection.

Equation (3) was solved using implicit finite difference and Gauss-Seidel iterative methods in MATLAB. The grid size was determined based on the sensitivity analysis for the drug concentration gradient across the liver at 100 s versus number of nodes. Time step size was determined based on the analysis of stability, accuracy and the speed of solution.

Simulation was performed for eight drugs at a hepatic perfusion rate of 1500 mlmin^{-1} and liver porosity of 0.12 [11] for a time-course of 200 s following IV administration of the drugs. The input physiological parameters and drug physico-chemical properties to the model were adopted from the literature introduced by Shibata et al. (2002) [10].

III. Results and Discussion

Based on the stability analysis, a mesh size of 0.63 mm and a time step size of 1 s were adopted for the numerical solution. Fig. 1 depicts the LVA model predictions and observations [10] of the hepatic clearance including the uncertainty (error bars) associated with reported data for seven drugs at a perfusion rate of 1500 mlmin^{-1}. A good agreement between predicted and reported values can be observed. Although the LVA-based model underestimates timolol and slightly overestimates caffeine hepatic clearance, the predicted values are within the uncertainties of the observed values with a coefficient of determination (R^2) of 0.91. Table 1 indicates that LVA-based model predictions of hepatic clearance at a dispersion number of 0.17 are consistent with the PT and DP models; however, a larger discrepancy between LVA and WS models can be distinguished due to the significant simplifications

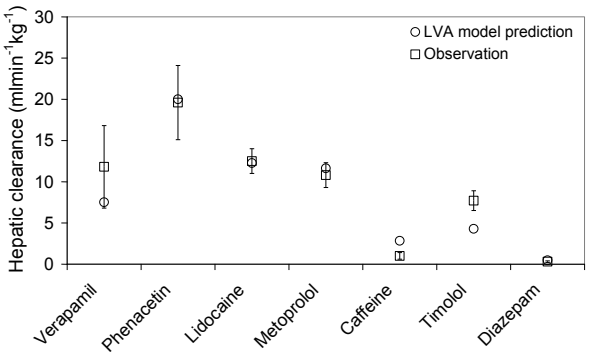

Fig. 1. Predicted values of hepatic clearance from LVA-based model compared to observed values reported by [10] for seven drugs.

TABLE I
Observed Hepatic Clearance (mlmin^{-1}kg^{-1}) and the Predicted Values from LVA, WS, PT and DP Models for Eight Drugs.

Drug	Cl_{h_LVA}	Cl_{h_WS}	Cl_{h_PT}	Cl_{h_DP}	Observed Values[a]
Naloxone	20.34	17.18	21.05	20.20	24.8
Verapamil	7.51	6.18	7.14	6.84	11.8±5.0
Phenacetin	20.00	16.74	20.83	19.83	19.6±4.5
Lidocaine	12.27	9.88	12.32	11.51	12.5±1.5
Metoprolol	11.63	10.14	12.70	11.86	10.8±1.5
Caffeine	2.83	1.05	1.08	1.07	1.0±0.4
Timolol	4.29	3.11	3.11	3.35	7.7±1.2
Diazepam	0.47	0.01	0.01	0.01	0.3±0.1

[a][10]

associated with the WS model. Also, comparing the predicted values to the observed values, Table 1 indicates that the LVA-based model improves predictability for diazepam although the LVA-based model slightly overestimates caffeine hepatic clearance compared to WS, PT and DP models.

Fig. 2 illustrates the LVA model predictions and observations [10] of bioavailability including the error bar of the reported values for seven drugs at a perfusion rate of 1500 mlmin^{-1} for a 70 kg male subject. A relatively good agreement is observed between predicted and observed values although LVA-based model overestimates verapamil,

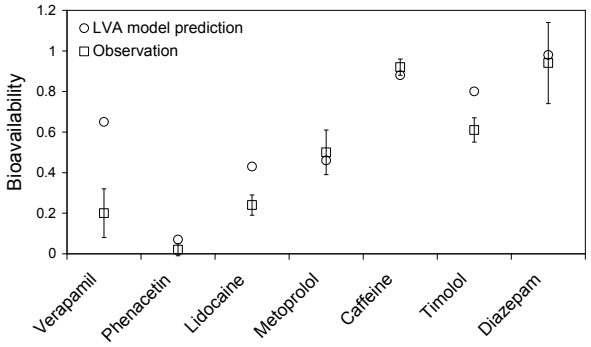

Fig. 2. Predicted values of bioavailability from LVA-based model compared to observed values reported by [10] for seven drugs.

lidocaine and timolol. The error can be attributed to the difference between observed values of oral bioavailability, which includes drug loss across the intestinal wall, and the LVA model predicted values of the hepatic bioavailability.

In addition, the error associated with the predicted hepatic clearance propagates into the predicted values of bioavailability according to (11) causing error accumulation in the predicted bioavailability values. The contribution of hepatic clearance prediction error can be well observed for verapamil where the underestimated hepatic clearance leads to overestimation of bioavailability.

Table 2 indicates that although LVA-based model is consistent with other models, it is mostly consistent with DP model. Table 3 shows mean squared errors (MSE) of the predictions from LVA, WS, PT and DP models for hepatic clearance and bioavailability. It indicates that LVA-based model leads to smaller MSE values of hepatic clearance predictions compared to other models while MSE of bioavailability predictions are the same for LVA, PT and DP models. WS results in larger MSE for hepatic clearance and bioavailability predictions. The higher MSE in the WS model is due to its much less mechanistic nature and oversimplified assumptions for the hepatic elimination process as compared with LVA, PT and DP models.

TABLE II
OBSERVED BIOAVAILABILITY AND THE PREDICTED VALUES FROM LVA, WS, PT AND DP MODELS FOR EIGHT DRUGS.

Drug	F_{H_LVA}	F_{H_WS}	F_{H_PT}	F_{H_DP}	Observed Values[a]
Naloxone	0.05	0.20	0.02	0.06	0.02
Verapamil	0.65	0.71	0.67	0.68	0.20±0.12
Phenacetin	0.07	0.22	0.03	0.07	0.02±0.03
Lidocaine	0.43	0.54	0.43	0.46	0.24±0.05
Metoprolol	0.46	0.58	0.48	0.51	0.50±0.11
Caffeine	0.88	0.95	0.95	0.95	0.92±0.04
Timolol	0.80	0.86	0.84	0.85	0.61±0.06
Diazepam	0.98	0.99	0.99	0.99	0.94±0.2

[a][10]

Fig. 3 illustrates the plasma unbound drug concentration gradient of lidocaine across the liver at different times in the presence and absence of axial dispersion. In the absence of dispersion (D_n=0), only diffusion and advection contributes to drug transport such that the drug distributes along the liver in 20 s (Fig. 3); however, in the presence of dispersion (D_n=0.17) the drug is rapidly distributed in the liver such that the drug compound appears at the hepatic vein in less than 10 s. This indicates that axial dispersion has a significant role in describing the drug distribution in the liver.

TABLE III
MEAN SQUARED PREDICTION ERRORS (MSE) OF HEPATIC CLEARANCE AND BIOAVAILABILITY FOR FOUR MODELS.

Model	MSE of hepatic clearance	MSE of bioavailability
LVA	7.14	0.04
WS	18.41	0.06
PT	8.15	0.04
DP	9.42	0.04

IV. CONCLUSION

A porous media mechanistic model was developed and validated for hepatic drug elimination. Unlike WS, PT and DP models, the LVA model can predict the time-dependent drug concentration at any time and any position across the liver during unsteady/steady state drug distribution in the liver. Also, unlike other models, LVA model can be used for describing the variation of concentration-dependent intrinsic clearance (nonlinear intrinsic clearance) across the liver.

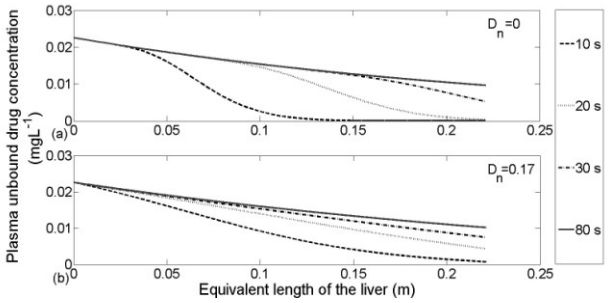

Fig. 3. Unbound drug concentration versus equivalent length of the liver at different times following IV administration of 5 mg lidocaine.

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