The First Human Whole Body Pharmacokinetic Minimal Model for the Liver Specific Contrast Agent Gd-EOB-DTPA

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Introduction: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a commonly used non-invasive diagnostic tool for investigating liver disease. By using hepatocyte specific contrast agents (CA) the functional aspects of the liver tissue can be obtained. Our aim was to derive a physiologically accurate minimal model that can be used to quantitatively evaluate liver function from clinical DCE-MRI examinations.

Materials and Methods: Signal intensity in region of interests placed in the liver (n=7) and spleen (n=3) in T1-weighted DCE images (native, arterial and portal venous phase, 10, 20, 30 and 40 minutes) from 10 healthy volunteers following a bolus injection of Gd-EOB-DTPA (0.025/kg) were converted into change in relaxivity [1] were used to optimize the model. Furthermore blood plasma concentrations following a 10 minutes infusion of Gd-EOB-DTPA from 18 subjects (table 1 in [2]) were also used in the optimization. Our model included a system of ordinary differential equations (ODE'-s) (Eq. 1). Optimization of the parameters was carried out according to Eq. 2. V(p) was also used as test function for a Chi^2 test [3]. Compartment volumes and organ fractions were based on a 70 kg and 20% fat "average human" [4]. The equations used were based on: Michaelis-Menten (MM) kinetics, the model by Tofts [5], renal clearance and flow-dependent transport. The use of ODE'-s implied that all states were assumed to be well stirred compartments with instant and equal mixing of the CA.

$$\dot{x} = f(x, p, u) \quad [1a]$$

$$y = g(x, p, u) \quad [1b]$$

$$\hat{p} = \arg_p \min V(p) \quad [2a]$$

$$V(p) = \sum_{i=t_0}^{t_{last}} \frac{(y_i - \hat{y}_i)^2}{\sigma_i^2} \quad [2b]$$

Results: The model (Fig. 1) was fitted to both DCE-MRI and blood sample data after the distribution of different CA doses (Fig. 2). The parameter vectors used were the extremes of each set of model parameters that were acceptable according to the Chi^2 test. Table 1 shows a sample of extrapolated pharmacokinetic parameters (derived as in [2]) and the K(trans) value from the incorporated model by Tofts for the flux between plasma and extracellular extravascular space (EES) based on the DCE-MRI data. By altering the constants for the input function, the model fitted data independently of the injected amounts of CA, rate or injection time. In addition, the model could describe the flux from the system into the bile and urine compartments in agreement with published excretion fractions [2].

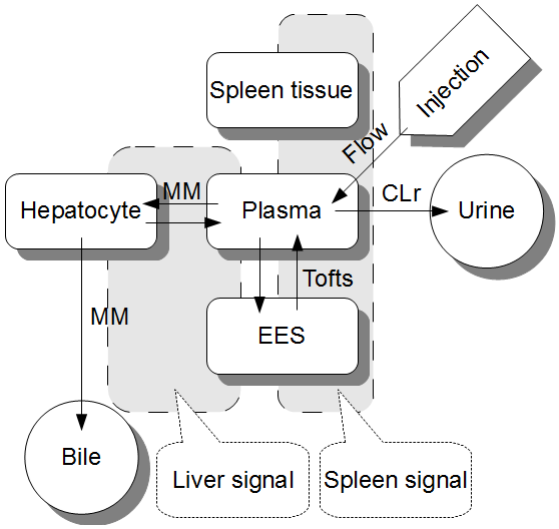

Figure 1 Diagram of the model equations with states (x, rounded rectangles), output (circles), transports with their respective base equations (f, arrows), input function (u, pointed rectangle) and measured MRI signals (y, shaded grey areas).

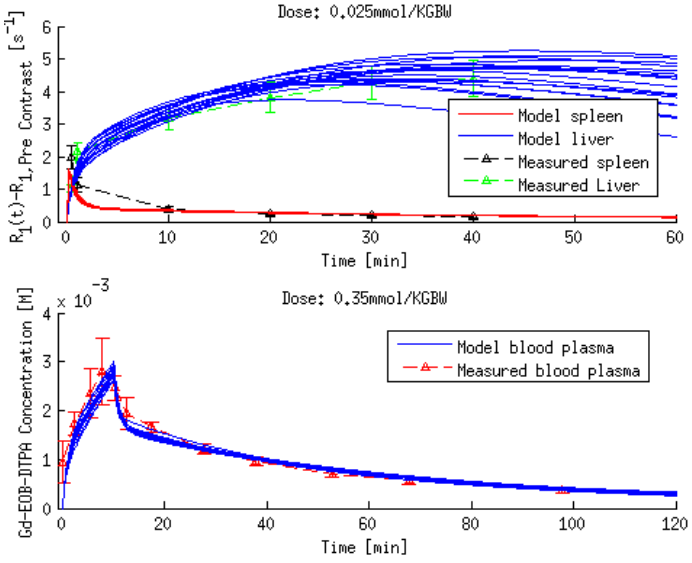

Figure 2 UPPER PANEL: The model fit for liver (red) and spleen (blue) signals (mean ± SE of mean) for healthy subjects. **LOWER PANEL:** The mode fit (same set of parameters) of the mean values ± STD of blood plasma concentrations.

Discussion and Conclusions: The proposed model was constructed by starting with a model that was as simple as possible. It was then expanded until a minimal, but physiologically correct, model with interpretable parameters was achieved. To our knowledge, this is the first complete model of the most important routes of CA flux in the human body that explains data obtained from on DCE-MRI examinations. The minimal model has a significant potential for gaining a better understanding of the CA behavior in the human body. The model is presently tested with mean values obtained from healthy human subjects. However, we believe that by converting the model into a Bayesian modeling framework, it will be possible to derive patient-specific parameters. This will make it possible to provide quantitative information on regional liver function. One can, e.g., derive a range of pharmacokinetic parameters without blood sampling, and it may also be possible to predict the DCE-MRI signals for the liver and spleen for a given CA dose. We believe that other CA'-s such as Gd-BOPTA can also be modeled using this approach.

Table 1 Some pharmacokinetic parameter values based on DCE-MRI data were extracted from the model: K(trans) parameter value range, AUC (0-6 h) area under the simulated blood plasma concentration curve, the total serum clearance (0-6 h) and the fraction of eliminated CA via the kidneys in relation to total elimination (up to ca. 2.12 h).

Ktrans [1/min]	0.13-0.27
AUC (0-6h) [µmol*h/L]	146.6-161.8
Total Serum CL [ml/min/kg]	2.58-2.84
Urine Elimination Fraction [%]	50.2-62.9

References: [1] Dahlqvist Leinhard O 2010 *ISBN: 978-91-7393-390-2*, [2] Schumann-Giampieri G. *et al J Clin Pharmacol* 1997;37:587-596, [3] Cedersund G & Roll J *FEBS Journal* 2009;276;903-922, [4] Levitt D G *BMC Clin Pharmacol* 2003;3:3 [5] Tofts P S *et al J Magn Reson Imaging* 1999;10;223-232