A population pharmacokinetic model for Gd-DTPA in small animal DCE-MRI

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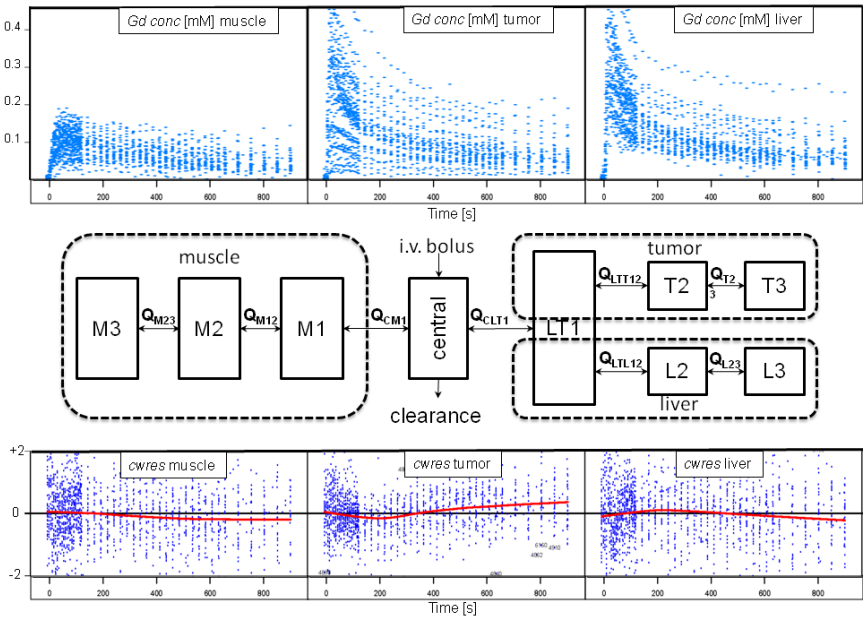
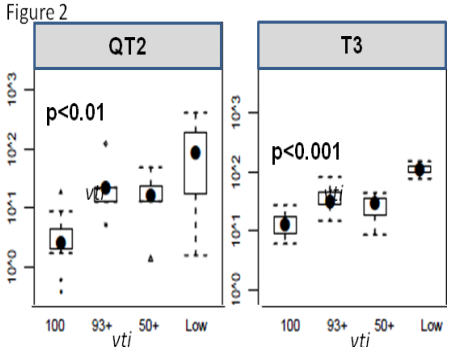
Introduction: In quantitative DCE-MRI applying low molecular contrast agents, 2-compartment models, consisting of a plasma and tissue compartment (1,2), are most often used to quantify parameters such as the plasma-tissue transfer constant K^{trans} (K_{12}) and relative plasma v_p and interstitial v_i distribution volumes. The calculation of these parameters relies on either the knowledge of the arterial input function (AIF model) or a simultaneously acquired reference tissue concentration curve with known tissue K^{trans} or ve values (RR model) (3,4). These models fall short of the multiple effective compartments present in normal tissue and especially in tumor physiology. The integration of several simultaneously acquired individual tissue concentration curves within a study population could allow for the development of more complex multiple compartment models. Based on population nonlinear mixed effects (popPK) modeling, this study was aimed at developing and evaluating a robust multi-compartment popPK model for Gd-DTPA in rat hepatocellular carcinoma (HCC).

Figure 1



Methods: The DCE-MRI and treatment experiment is described in (4). 34 animal data sets (pre and post treatment) with concentration curves of tumor, muscle and liver (figure 1 top) were included for popPK modeling. Based on histological analysis, tumors were classified into four groups of different amounts of remaining vital tissue (*vti*), i.e. 100%, 100-93% (93+), 50-93% (50+) and <50% (Low). All popPK analyses were performed by means of the full Markov Chain Monte Carlo (MCMC) Bayesian analysis method using the NONMEM® 7 program (ICON, Dublin, Ireland) preceded by stochastic approximation expectation maximization (SAEM) method for fast initial parameter estimation. Model building and selection was based on standard numerical criteria (conditional weighted residuals (*cwres*), objective function value (*OFV*), caterpillar plots (*cps*), standard errors (SE) of parameters and inter-individual variability, matrix condition number (*mcn*) and supported by anatomical (i.e. tumor location within the liver), physiological (specifics of liver blood supply) and histological (estimated size of extravascular space, tumor necrosis area) considerations. The selected final model with best and robust numerical outcomes consisted of 9 compartments, and is displayed together with the *cwres* in figure 1 middle and bottom. The subsequent model evaluation was performed by successive deletion of single or multiple tissue compartments and numerical criteria were compared to the final model. A multiple linear regression model was used for the post-hoc analysis of the impact of vti on model parameters.

Figure 2



SE model parameters [%]			
V_c	10	Cl	0
V_{M1}	2	Q_{CM1}	7
V_{M2}	7	Q_{M12}	9
V_{M3}	3	Q_{M23}	288
V_{LT1}	3	Q_{CLT1}	4
V_{T2}	7	Q_{LTT12}	25
V_{T3}	4	Q_{T23}	10
V_{L2}	2	Q_{LTL12}	7
V_{L3}	5	Q_{L23}	21

Transfer constants [s^{-1}]			
$K = Cl/V_c$	0.01		
$K^{cm1}=Q_{CM1}/V_c$	2.98	$K^{m1c}=Q_{CM1}/V_{M1}$	0.01
$K^{m1m2}=Q_{M12}/V_{M1}$	1.67	$K^{m2m1}=Q_{M12}/V_{M2}$	116.16
$K^{m2m3}=Q_{M23}/V_{M2}$	0.44	$K^{m3m2}=Q_{M23}/V_{M3}$	0.01
$K^{clt1}=Q_{CLT1}/V_c$	29.94	$K^{lt1c}=Q_{CLT1}/V_{LT1}$	0.66
$K^{lt1t2}=Q_{LTT12}/V_{LT1}$	0.04	$K^{t2lt1}=Q_{LTT12}/V_2$	0.92
$K^{t2t3}=Q_{T23}/V_{T2}$	33.70	$K^{t3t2}=Q_{T23}/V_{T3}$	0.83
$K^{lt1l2}=Q_{LTL12}/V_{LT1}$	0.00	$K^{l2lt1}=Q_{LTL12}/V_{L2}$	0.01
$K^{l2l3}=Q_{L23}/V_{L2}$	0.05	$K^{l3l2}=Q_{L23}/V_{L3}$	0.00

Results: The stepwise evaluation procedure highlighted the need for the three muscle compartments. Any model having fewer than three serial muscle compartments exhibited systematic deviations in the cwres and cps and had increased OFV and mcn values. Closest to the final model was the model version omitting the additional liver post compartment. However, here a strong vti dependence of muscle tissue in the post-hoc analysis was seen and the model was discarded. The post-hoc analysis showed the expected significant effect of *vti* on tumor intercompartmental distribution (Q_{T23}) and distribution volume (V_{T3}), see figure 2. The SEs of fitted population parameters and respective inter-individual differences are shown in the table (left). The resulting transfer constants are given as well (right).

Discussion: A multi-compartment model for Gd-DTPA is presented. Based on standard numerical model building and selection criteria the presented model is not over-determined. The tumor tissue related model parameters Q_{Tpost} and V_{Tpost} showed a significant linear dependence on *vti*, demonstrating the ability to detect treatment effect (necrosis). Resulting liver model parameters present the liver as a flow-through compartment with minor or no effect on Gd-DTPA uptake and washout (K^{lt1l2},$K^{l2lt1} \approx 0$). However, awaiting further experimental validation, we can only speculate with regard to the physical equivalents and interpretation of the proposed compartments (e.g. vascular, interstitial, intracellular space) (5).

References: 1. Tofts P. et al JMRI (1999) 10:223-232; 2. Brix G. et al Biomed Tech (2006) 51:325–330; 3. Yankeelov TE. et al, MRI (2005) 23:519-29; 4. Steingoetter A. et al (2010) Sep 24. [Epub ahead of print]; 5. Li X. et al MRM (2005) 54(6):1351–1359.