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

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INTRODUCTION

- Kinetics of an injected contrast agent are studied in dynamic contrast enhanced (DCE-) MRI for the monitoring of antiangiogenic therapy in oncology.
- Established pharmacokinetic (PK) analysis methods using 1- or 2- compartment models [1,2] do not sufficiently reflect the complex anatomical and physiological constituents of the analyzed tissue.
- These models rely on the knowledge of the contrast agent's concentration dynamics in the local, tissue specific blood supply, i.e. the arterial input function (AIF).

AIM

The aim of this study was to develop and evaluate a multi-compartment population pharmacokinetic model for gadopentetate dimeglumine (Gd-DTPA) without the need for an AIF.

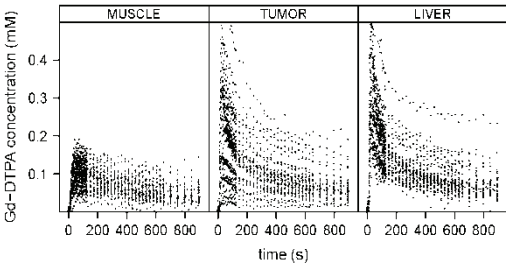


Figure 1. DCE-MRI data for model building / selection consisting of simultaneously, densely sampled Gd-DTPA concentration time curves from muscle, liver and tumor of hepatocellular carcinoma rats.

METHODS

Structural model selection and evaluation

- Full Markov-Chain Monte-Carlo (MCMC) Bayesian estimation (NONMEM 7.1).
- No priors for the model estimates (*THETA*s) and uninformative inverse Wishart distribution as prior for covariance matrix (*OMEGA*s).
- Full covariance matrix with initial values of 0.1 for the diagonal and 0.01 for the off-diagonal coefficients.
- Stochastic approximation expectation maximization (*SAEM*) for initial parameter estimates from 120 iterations.
- 3000 samples for burn-in and estimation phase in the Bayesian analysis.
- Random lag term (variations in injection time point) as a nuisance parameter uncorrelated to PK model parameters.
- A mixed proportional and additive error model.
- Model building and selection based on histological (tumor necrosis) and anatomical considerations (tumor in liver tissue).
- Numerical criteria: stability of resulting Bayesian chain plots (*CPS*), conditional weighted residuals (*CWRES*), objective function value (*OFV*), standard error (*SE*) and 95% confidence interval (*95%-CI*) of parameters in that order as listed.
- Deviance information criterion (*DIC*) for Bayesian model comparison.

Covariate model building

- Anesthesia and percentage of residual vital tissue in tumor included as binary (*anest*) and ordered categorical with 4 levels (*vti*) covariables.
- Covariate model building based on physiological observations and histological considerations supported by the generalized additive model (GAM) procedure.
- Covariable *anest* applied to spinal muscle or liver transfer constants and *vti* applied to the tumor transfer constants, i.e. k_{T2T3} or k_{T3T2}.
- The MTL3 model nested within all covariate models.

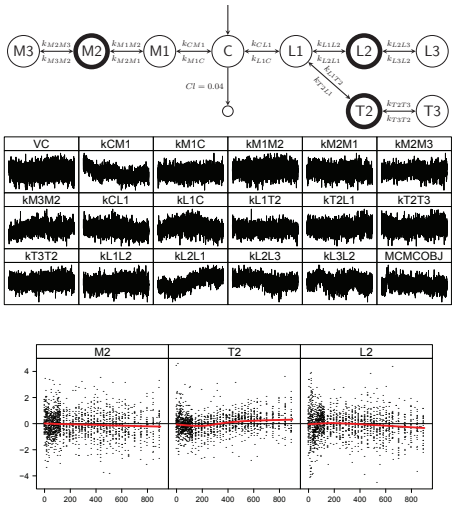
Model diagnostics and statistics

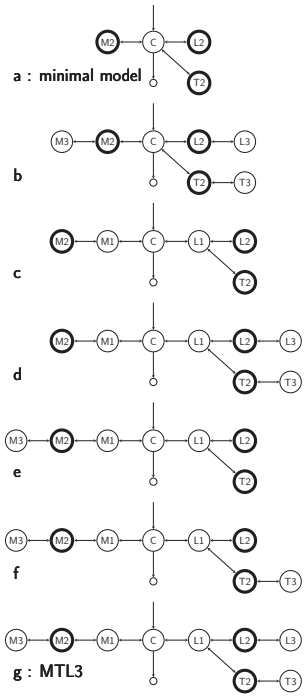
- Diagnostic plots for model building and evaluation created using the R software package and the xpose4 library.
- The *THETA*s, *ETA*s and the respective standard errors *SE*s [%] computed by NONMEM® 7.1. The *95%-CI* was computed by the R package coda.

RESULTS

- Final structural model (MTL3 model) displayed in **Figure 2** (**left**) consisting of the 3 measured compartments (M2, T2, L2; thick border) and 6 computed compartments (C, M1,M3, T3, L1, L3).
- *CPS* and *CWRES* of tested reduced models showed unsteady behavior and systematic deviations.
- Higher *DIC* values of > 81 and >1130 for the second (model f) and third (model d) best model, respectively.

Figure 2. (**Left**) The schematic, CPS and CWRES of the MTL3 model. (**Right**) The tested reduced models.





- Including the covariables improved fit quality of the MTL3 model without changing *SE* or *95%-CI* and numerical stability.
- Maximum drop ΔOFV = -85 achieved by applying both covariables *vti* and *anest* to the tumor transfer constant k_{T3T2} and spinal muscle transfer constant k_{M1C}.
- Models *with SE*s <= 50% for the included covariates considered as valid.

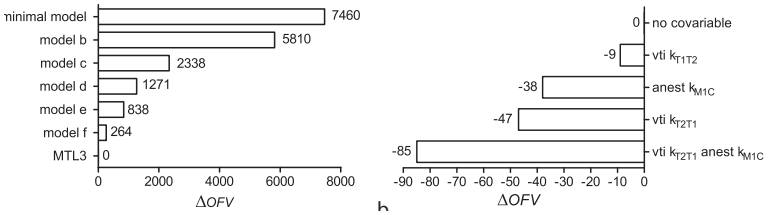


Figure 3. Bar graphs showing deltas in the *OFV* relative to the MTL3 model (*OFV* = 0). **(Left)** ΔOFVs for the competing reduced models. *DIC* confirmed best fit quality for the MTL3 model. **(Right)** ΔOFVs for the valid covariate models. *DIC* indicated improved fit quality for covariate models.

DISCUSSION and CONCLUSION

- A multi-compartment PK model was developed allowing the more detailed description of Gd-DTPA kinetics in a rat HCC tumor model.
- This was achieved by population PK modeling of DCE-MRI data from multiple tissues, i.e. spinal muscle, tumor and liver.
- The proposed MTL3 model demonstrated that tumor compartment covariates can be used as predictors of tumor tissue physiology and that no knowledge of the arterial input function or tissue specific characteristics is required.
- The presented approach has the potential for enhanced identification and specification of effectors of vascular and tissue physiology and thus may be of interest in the evaluation of antiangiogenic therapy response in oncology.

REFERENCES: [1] Brix G. et al. Eur J Nucl Med Mol Imaging 2010; 37 Suppl 1: S30-51. [2] Tofts P.S. et al. J Magn Reson Imaging 1999; 10: 223-32.