How can pharmacokinetic modeling decompose the overall MR signal intensity obtained from Gd-BOPTA into predicted signal intensity in both hepatocytes and extracellular space

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Purpose

We recently showed that transport of Gd-BOPTA, an hepatobiliary contrast agent (CA), can be studied via MR signal intensity (SI) enhancement in isolated perfused rat livers[1] and in hollow fiber bioreactors containing isolated hepatocytes[2]. In this study, control and cirrhotic rat livers were perfused with Gd-DTPA, an extracellular CA, and Gd-BOPTA and the SI was recorded over time. The aim was to develop a pharmacokinetic model to better define the SI obtained by MRI during perfusion of isolated rat livers with Gd-BOPTA.

Materials and Methods

Biliary cirrhosis was induced by a bile duct ligation (BDL) performed 30 and 60 days before the experiments. To evidence the extracellular diffusion space, each liver was first perfused with KHB solution + 0.5 mM Gd-DTPA (37°C, 35 mL/min) during 20 min (extracellular distribution of Gd-DTPA) and KHB solution during 10 min (hepatic elimination of Gd-DTPA). Then, the same livers were perfused with 0.5 mM Gd-BOPTA during 30 min (extracellular distribution and hepatocyte entry of Gd-BOPTA) and KHB solution during 30 min (hepatic elimination of Gd-BOPTA). Four rats in each group were perfused (control, 30-days BDL, and 60-days BDL).
MRI was performed at 1.5 T. Axial image was obtained using a fast-gradient echo T1 weighted MR sequence (FAST) preceded by a 90° saturation pulse with the following parameters: repetition time (6.8 msec); echo time (3 msec); flip angle (90°); matrix 256 x 256; 1 image / 8 sec; FOV 14 cm; slice thickness 0.7 cm. Mean SI was measured in a region of interest (ROI) drawn on the short axis view of the liver excluding all large vessels. For each liver, the SI measured in the ROI was normalized to muscle SI.
Modeling was performed considering compartmental pharmacokinetics as depicted in Fig. 1, where central compartment described the amount of CA in extracellular space $A_1(t)$ and peripheral compartment described the amount in hepatocytes $A_2(t)$. The transfer of CA from central to peripheral compartment was modeled as a Michaelis-Menten kinetics. The following equation was used to model SI in the ROI: $SI(t) = s_0 + g_1 \times A_1(t) + g_2 \times A_2(t)$, where s_0 is baseline signal and g_1 and g_2 proportionality constants. The model was implemented in the NONMEM software (version V, University of California, San Francisco, USA). Primary parameters of the model were rate constants k_{10}, k_{21}, Michaelis-Menten V_m and K_m, and proportionality constants g_1 and g_2. The best model was identified by considering the objective function value, standard errors of parameter estimates and correlations between them. Graphical assessment of goodness of fit was performed through analysis of residuals.

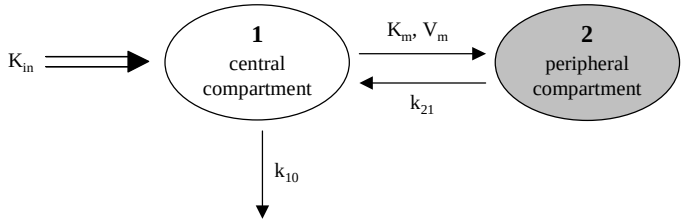

Fig. 1: Model scheme depicting the disposition of Gd-BOPTA and Gd-DTPA in the liver. Entry of CAs into the system was modeled as a zero-order infusion rate K_{in}. First-order rate constant k_{10} reflected elimination from central compartment (extracellular space) and k_{21} exchange from peripheral (hepatocyte pool) to central compartment. The transfer of CA from central to peripheral compartment was modeled as a Michaelis-Menten kinetics with V_m and K_m constants.

Results and discussion

During the perfusion of the extracellular CA Gd-DTPA, the SI increased and rapidly reached a steady-state (Fig. 2). The SI returned to baseline value during the following KHB perfusion. The increase in SI was much higher during the perfusion of Gd-BOPTA that enters into hepatocytes. During the following KHB perfusion the SI slowly decreased.
Modeling of data from Gd-DTPA and Gd-BOPTA was performed simultaneously, considering that they belonged to the same individual. Thus, Gd-DTPA depicted the extracellular space, providing robustness to the model. The model developed described very well the experimental data. While the predicted steady-state SIs of Gd-DTPA and Gd-BOPTA in the central compartment did not differ according to the BDL duration, the predicted steady-state SIs in the peripheral compartment significantly decreased (Kruskal-Wallis test: $P < 0.05$). Thus, cirrhosis did not change the extracellular distribution of Gd-BOPTA, but the entrance into the hepatocytes was impaired.

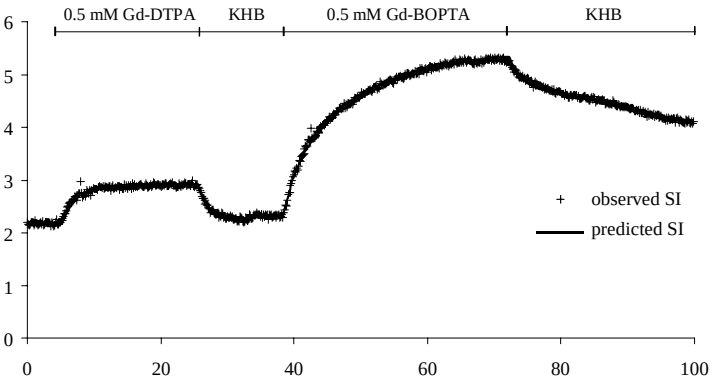

Fig. 2: Representative observed SI - time curve of Gd-BOPTA and Gd-DTPA (0.5 mM) perfused in a 30-days BDL rat. The overall predicted curve resulting from the pharmacokinetic analysis with a compartmental model completely fitted the observed SI-time curve.

Conclusion

Modeling Gd-BOPTA kinetics obtained from dynamic MRI in isolated perfused rat livers allowed distinction of the SI coming from the diffusion in the extracellular space and from specific uptake by hepatocytes. SI in hepatocytes significantly decreased in injured hepatocytes compared to healthy hepatocytes.

References

1. Pastor CM et al. Radiology 2003, 229, 119-125
2. Planchamp C et al. Biotechnol Bioeng 2003, In Press