Hepatic kinetics of MRI contrast agents in the isolated perfused rat liver

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Introduction

In the intact organ, voxel resolution is not high enough to differentiate between extracellular and intracellular MRI signal intensities (SI). Because hepatic kinetics of contrast agents can be assessed by perfusing contrast agents in isolated livers, we compared, in the same experiment, the kinetics of Gd-DTPA, a contrast agent which diffuses exclusively in the extracellular space to Gd-BOPTA, a contrast agent which enters into hepatocytes and is eliminated in the bile.

Methods

Isolated perfused rat livers:

Livers were perfused in the MRI room with a Krebs-Henseleit bicarbonate (KHB) solution bubbled with 95% O₂ and 5% CO₂ in a non-recirculating system. The flow rate was constant in each experiment: 35 ml/min. Normal livers were perfused with KHB + 0.5 mM Gd-DTPA and KHB + 0.5 mM Gd-BOPTA (n = 3). Additional livers were perfused with KHB + 0.5 mM Gd-BOPTA + 0.5 mM Bromosulfophthalein (BSP) which competes with the contrast agent for hepatic uptake (n = 2). Finally, to decrease biliary excretion of Gd-BOPTA, 2 livers had a bile duct ligation (BDL) and were perfused with KHB + 0.5 mM Gd-BOPTA.

MRI

A fast-gradient echo sequence (RF-FAST) preceded by a 90° saturation pulse was used with the following parameters: TR/TE/FA 6.8/3/90°, matrix 256 x 256, 1 image / 8 sec, FOV 15 cm, slice thickness 0.7 cm.

Data analysis

The liver SI was normalized by a factor measured during the Gd-DTPA perfusion in steady state. A one compartment monoexponential model was used to fit the SI curves of Gd-DTPA and Gd-BOPTA according to the following equations:

SIwashin = a0 . (1- exp(- a1 . time))
SIwashout = a0 . exp(- a1. time)

According to this model, a0 is related to the distribution volume and a1 is related to the kinetics of the contrast media. An ANOVA analysis was used to compare a0 and a1 in the groups perfused with the extracellular and the intracellular contrast agents, in normal and BDL livers.

Results and Discussion

7 min after the start of Gd-DTPA perfusion a steady-state SI was observed, while SI continued to increase over 30 min during Gd-BOPTA perfusion (Figure 1). a0 and a1 were statistically different during Gd-DTPA and Gd-BOPTA perfusions (p < 0.002) (Figure 2). The Gd-BOPTA a1 was significantly different in the washin and washout periods (p = 0.009) but the Gd-DTPA a1 was similar in the two periods (p = 0.87). The BSP perfusion completely suppressed the increased a1 response observed with Gd-BOPTA alone (p = 0.02). BDL did not modify the parameters obtained during BOPTA perfusion in normal livers (p = 0.86).

Because a steady-state condition was observed 7 min after the start of Gd-DTPA perfusion, we conclude that any changes observed during Gd-BOPTA perfusion after that delay is related to processes occurring in hepatocytes or bile ducts. SI enhancement in hepatic tissue during Gd-BOPTA perfusion might be explained by an increased volume of distribution of the contrast agent, an increased T1 relaxivity following modifications of intrahepatic microviscosity, and by high hepatic Gd-BOPTA concentrations (biliary excretion is lower than hepatic uptake).

Conclusion

The hepatic kinetics of SI following the perfusion of MRI contrast agents can be easily assessed in the isolated perfused rat liver. This model differentiates extracellular and intracellular MRI SI. Moreover, inhibition of Gd-BOPTA uptake by hepatocytes is clearly evidenced. In contrast, bile duct ligation has no effect on the hepatic kinetics of BOPTA.

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