Kinetic Analysis of Gd-EOB Uptake by Hepatocytes with Gd-EOB-enhanced Dynamic MR imaging

H. Onishi[1], T. Kim[1], M. Hori[1], T. Murakami[2], T. Tsuboyama[1], M. Tatsumi[1], A. Nakamoto[1], Y. Nakaya[1], K. Tomoda[1], and H. Nakamura[1]

[1]Department of Radiology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan, [2]Department of Radiology, Kinki University School of Medicine, Osakasayama, Osaka, Japan

Purpose

Gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB) is a liver-specific MR imaging contrast agent that is considered to be taken up from the blood circulation by the hepatocytes via the membrane protein such as organic anion transporting polypeptide (OATP) (1). The purpose of the present study was to analyze the kinetics in the uptake of Gd-EOB by the hepatocytes by using a Michaelis-Menten model.

Materials and Methods

The hepatic uptake of bilirubin is mediated by human OATP2 and the kinetics displays a Michaelis-Menten behavior (2). Therefore, the uptake rate of Gd-EOB to the hepatocytes was assumed to be based on a Michaelis-Menten equation and to depend on the concentration of the enzyme (i.e. OATP) and the substance (i.e. Gd-EOB). The chemical reaction formula and reaction rate equation was demonstrated as follows:

$$\mathbf{OATP + EOB_{EC} \leftrightarrow OATP{\cdot}EOB \rightarrow OATP + EOB_{IC}}$$

OATP:	Organic anion transporting polypeptide	EOB_{EC}:	Extracellular Gd-EOB
OATP·EOB:	Complex of OATP and Gd-EOB	EOB_{IC}:	Intracellular Gd-EOB

$$v = \frac{V_{max} \cdot [EOB_{EC}]}{[EOB_{EC}] + K_m} \quad \text{(Michaelis-Menten equation)}$$

v:	Initial uptake rate of Gd-EOB	V_{max}:	Maximum uptake rate of Gd-EOB
K_m:	Michaelis constant	$[EOB_{EC}]$:	Exracellular concentration of Gd-EOB

In five patients with normal liver function, the uptake rate (v) and extracellular concentration of Gd-EOB ($[EOB_{EC}]$) was approximately estimated from the data of Gd-EOB-enhanced dynamic MR imaging of the liver. To evaluate whether the relationship between the uptake rate and the Gd-EOB concentration obey Michaelis-Menten kinetics, an Eadie-Hofstee Plot was analyzed. A Hanes-Woolf Plot was also generated to obtain an apparent Michaelis constant.

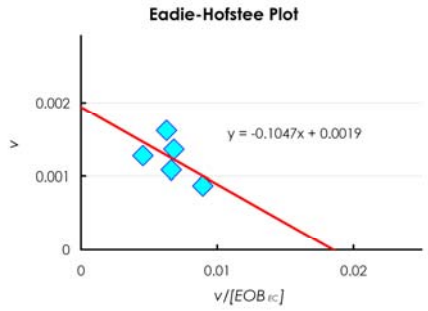

Fig 1. Eadie-Hofstee Plot

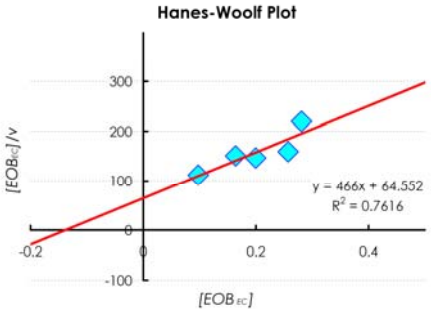

Fig 2. Hanes-Woolf Plot

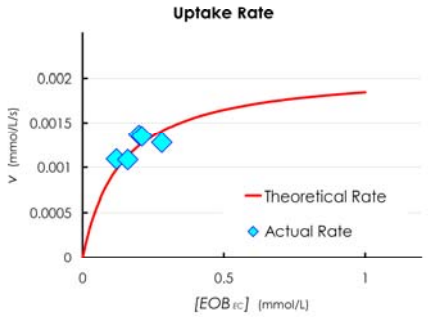

Fig 3. Hepatic uptake rate and Gd-EOB concentration

Results

In the Eadie-Hofstee Plot (Fig 1), (v / $[EOB_{EC}]$) and (v) had a negative relationship (rs = - 0.5). The apparent Michaelis constant (K_m) was estimated to be 0.1 mmol/L from the Hanes-Woolf Plot (Fig 2). Figure 3 shows theoretical uptake rate related to the concentration of Gd-EOB based on the Michaelis-Menten kinetics.

Discussion

In the present study, we investigated the approach to the quantitative evaluation for the hepatic uptake of Gd-EOB in the Gd-EOB-enhanced dynamic MR imaging. By means of the Michaelis-Menten equation, the maximum uptake rate (V_{max}) of Gd-EOB in each patient can be obtained, which does not depend on the concentration of Gd-EOB. In addition, the effect on maximum uptake rate caused by competitive inhibition of serum bilirubin can be corrected. Maximum uptake rate may be considered to reflect the expression of OATP on the hepatocytes membrane. Further investigations are needed to verify the relationship between the expression level of the OATP on the hepatocytes and the maximum uptake rate obtained from the kinetic analysis of the dynamic Gd-EOB-enhanced MR imaging data.

In conclusion, our results suggested that the kinetics in the hepatic uptake of Gd-EOB displayed the Michaelis-Menten behavior and conduced to the apparent Michaelis constant for Gd-EOB in vivo.

References

1. van Montfoort JE, et al. Hepatic Uptake of the Magnetic Resonance Imaging Contrast Agent Gadoxetate by the Organic Anion Transporting Polypeptide Oatp1. JPET 1999; 290:153–157.
2. Britz O, et al. Role of anion-transporting polypeptides, OATP-A, OATP-C and OATP-8, in the human placenta-maternal liver tandem excretory pathway for foetal bilirubin. Biochem J. 2003; 371:897-905.