Gadoxetate-enhanced MRI in rats with liver cirrhosis: comparison between functional liver parameters obtained with deconvolution analysis and compartmental models as markers of hepatocyte transporter expression

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TARGET AUDIENCE: Researchers and clinicians with interest in liver function and DHCE-MRI

PURPOSE: In liver cirrhosis, drug transport through the hepatocytes decreases because of decreased expression of membrane transporters, mainly of the oatp/mrp family. We have previously shown that the hepatic functional parameters (hepatic extraction fraction (HEF) and mean residence time (MRT)) obtained with deconvolution analysis at gadoxetate-enhanced MRI correlate with the expression of the oatp/mrp transporters in liver cirrhosis[1]. Another way to assess transporter activity could be to use a pharmacokinetic model yielding intercompartmental rates, as previously done in nuclear medicine[2]. The aim of this study was therefore to assess if a multicompartmental model of hepatocytic transport gives further insight into the expression of the oatp/mrp transporters in liver cirrhosis.

SUBJECTS AND METHODS: Dynamic hepatospecific contrast-enhanced MRI (DHCE-MRI) was performed on a 7T small animal system in normal (n = 9) and cirrhotic (n = 17) rats injected with gadoxetate (Eovist™, 0.025mmol/kg)[1]. Concentration versus time curves were calculated in the liver and portal vein from FLASH images (temporal resolution 0.94 s, 55-minutes total acquisition time). Deconvolution analysis was performed to obtain the HEF and MRT[3]. Additionally, the deconvoluted curve was fitted with a three-compartmental model (Fig.1) to get the uptake rate (k_{21}), the backflux rate (k_{12}) and the hepatobiliary efflux rate (k_3) according to the pharmacokinetic model[2]:

$$h(t)=x_2(t)+x_3(t)=k_{21}\left(1-\frac{k_3}{k_{12}}\right)e^{-(k_{12}+k_3)t}+\frac{k_{21}k_3}{k_{12}}e^{-k_3 t}$$

Goodness of fits was assessed by calculation of Akaike Information Criteria (AIC) for both methods. The distributions of the functional parameters between normal and cirrhotic rats were compared with a Wilcoxon rank test. Multiple regression analysis was performed to assess the correlations between the functional parameters and the expression of the membrane transporters (oatp1b2, mrp2 and mrp4) determined by reverse transcription polymerase chain reaction.

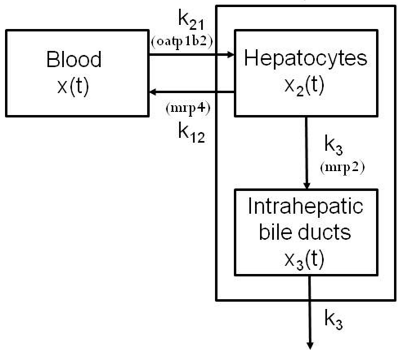

Fig1. Three-compartment model representing gadoxetate exchanges between sinusoidal blood, hepatocytes and bile ducts, and associated transporters

RESULTS: In cirrhotic rats, HEF and MRT decreased significantly, as did k_{21} and k_3, whereas k_{12} increased significantly (Table1, Fig.2). At multiple regression analysis, the multicompartmental parameter k_{21} and HEF correlated significantly with the uptake transporter oatp1b2 expression ($p<0.001$, $r=0.77$ for both), whereas the simple deconvolution parameters HEF and MRT correlated significantly with the efflux mrp2 and backflux mrp4 transporters expression ($p<0.001$, $r=0.70$ and $p=0.026$, $r=0.44$, respectively). AICs of both methods did not differ significantly ($p=0.36$).

	Deconvolutional analysis		Compartmental analysis		
	HEF (%)	MRT (s)	k_{21} (min^{-1})	k_{12} (min^{-1})	k_3 (min^{-1})
Normal rats	35.3 ± 3.4	421 ± 119	1.920 ± 0.190	0.310 ± 0.044	0.074 ± 0.043
Cirrhotic rats	21.4 ± 7.9	311 ± 188	1.430 ± 0.580	0.380 ± 0.086	0.039 ± 0.035
p-value	0.001	0.034	0.037	0.016	0.034
AIC	-11010 ± 610		-11209 ± 801		

Table 1. Estimated parameters measured with deconvolution and compartmental approaches (mean ± standard deviation).

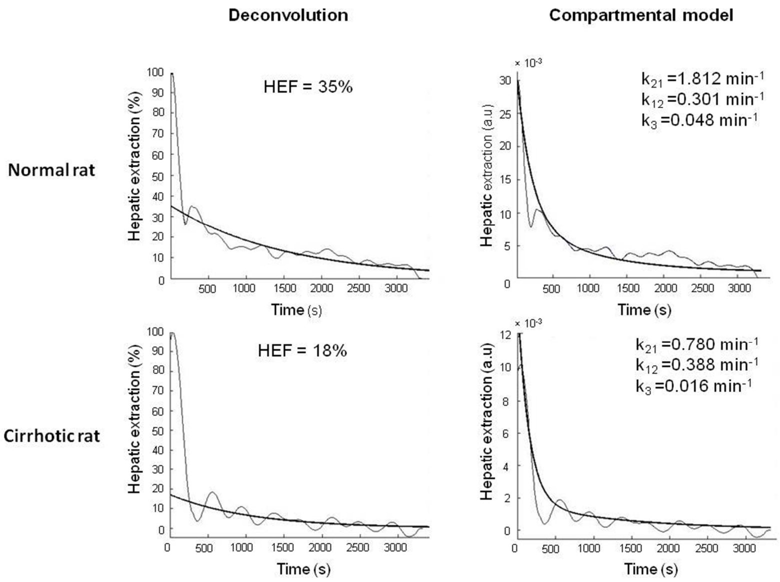

Fig2. Fitted deconvoluted curves of a normal and a cirrhotic rat (*light gray*: deconvoluted curve, *bold*: fitted curve).

DISCUSSION AND CONCLUSION: As shown by AICs, both models are of equivalent quality to derive quantitative parameters from DHCE-MRI acquisitions. The expression of the uptake transporter oatp1b2 is identically correlated with the parameters k_{21} and HEF. However, better correlations are obtained between deconvolution parameters and expression of efflux and backflux transporters. This probably comes from the fact that the hepatocyte outflow of gadoxetate is influenced not only by the local expression of its outflow transporters, but also by the expression of the uptake and concurrent outflow transporters. Consequently, constant rates are closely related to each other and a multicompartmental approach does not provide more information than a single deconvolution approach about the changes of hepatocyte membrane transporter expression in cirrhosis. The superiority of a multicompartmental relative to a deconvolution model remains thus to be proven in this case.

REFERENCES

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