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REVIEW ARTICLE

Use of gadoxetate disodium for functional MRI based on its unique molecular mechanism

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ABSTRACT

Gadolinium ethoxybenzyl dimeglumine (gadoxetate) is a recently developed hepatocyte-specific MRI contrast medium. Gadoxetate demonstrates unique pharmacokinetic and pharmacodynamic properties, because its uptake in hepatocytes occurs *via* the organic anion transporting polypeptide (OATP) transporter expressed at the sinusoidal membrane, and its biliary excretion *via* the multidrug resistance-associated proteins (MRPs) at the canalicular membrane. Based on these characteristics, gadoxetate-enhanced MRI can provide functional information on hepatobiliary diseases, including liver function estimation, biliary drainage evaluation and characterization of hepatocarcinogenesis. In addition, understanding its mode of action can provide an opportunity to use gadoxetate for cellular and molecular imaging. Radiologists and imaging scientists should be familiar with the basic mechanism of gadoxetate and OATP/MRP transporters.

INTRODUCTION

Gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid (hereafter referred to as gadoxetate) is a novel dual-function contrast agent for MRI. It acts as an extracellular contrast agent to evaluate haemodynamic change and at later times enhances hepatocytes.^{1,2} This dual function of gadoxetate provides valuable information on differential diagnosis and thus the use of gadoxetate has been rapidly increasing in clinical practice.

Since gadoxetate is designed to function in both dynamic phase (*i.e.* arterial phase, portal venous phase and 3-min delayed phase) and hepatobiliary phase (*i.e.* 20-min delayed phase), it has different pharmacokinetic and pharmacodynamic properties unlike most other extracellular gadolinium contrast agents.^{3,4} Although its distribution and kinetics in the dynamic phase is similar to other gadolinium contrast agents, gadoxetate behaves differently in the hepatobiliary phase because the excretion of this agent is mediated by membrane transport proteins such as organic anion transporting polypeptides (OATPs) and multidrug resistance proteins (MRPs).^{1,2} These receptor-based influx and efflux mechanisms make gadoxetate the most successful hepatocyte-specific MRI contrast agent. The benefits of gadoxetate in the detection and characterization of liver

tumours have been proven in many clinical investigations. Based on these unique molecular mechanisms, it seems that gadoxetate can be further utilized in functional MRI studies. Potential applications of gadoxetate for functional MRI are currently being actively investigated and some noteworthy reports have been recently published.

In this article, we introduce the pharmacological properties and beneficial aspects of gadoxetate in clinical practice. In addition, we review the molecular mechanisms underlying the membrane transport system in hepatocytes and discuss the potential applications of gadoxetate as a functional MRI agent.

PHARMACOLOGICAL PROPERTIES OF GADOXETATE

The characteristics of gadoxetate are summarized in Table 1. Gadoxetate is an amphipathic derivative of gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA), which is a prototype of gadolinium MRI contrast agent. It can be categorized as an ionic linear-structure contrast agent with a lipophilic ethoxybenzyl (EOB) moiety covalently bound to Gd-DTPA.¹ This ethoxybenzyl moiety enables hepatocytes to take up the gadoxetate into their cytosol and to excrete it into the bile duct. Moreover, as it is

Table 1. Characteristics of gadoxetate disodium in comparison with gadopentetate dimeglumine

Characteristics	Gadoxetate disodium	Gadopentetate dimeglumine
Drug name	Primovist® (outside USA) Eovist® (USA)	Magnevist®
Abbreviation	Gd-EOB-DTPA	Gd-DTPA
Classification	Dual function agent	Extracellular agent
	Extracellular agent	
	Hepatobiliary agent	
Pharmacokinetics: distribution	Distributes into the vascular and extravascular spaces, and progressively into the hepatocytes and bile ducts	Distributes into the vascular and extravascular spaces
Pharmacokinetics: excretion	Renal (50%), hepatobiliary (50%)	Renal (100%)
Pharmacodynamics	Hepatocyte uptake <i>via</i> OATP receptor	No specific interaction with receptor
T_1 relaxivity at 1.5 T	6.9 (1 mmol ⁻¹ s)	4.1 (1 mmol ⁻¹ s)
Clinical application	Tumour detection Tumour characterization Liver function evaluation Biliary function evaluation	Tumour detection Tumour characterization

OATP, organic anion transporting polypeptides.

Eovist, Bayer Healthcare Pharmaceuticals, Wayne, NJ; Magnevist, Bayer Schering Pharma AG, Berlin Germany; Primovist, Bayer Schering Pharma AG.

an ionic linear-structure contrast agent, its stability is higher than that of non-ionic linear contrast agents.³

Pharmacokinetics of gadoxetate

With regard to the pharmacokinetic properties of gadoxetate, approximately 50% of the administered dose is excreted through the hepatobiliary system and the other 50% is excreted through the kidney in patients with normal liver and kidney function.^{3,4} Serial dynamic MRI can demonstrate the hepatobiliary excretion and renal excretion (Figure 1). However, for those patients who have either abnormal kidney function or impaired hepatobiliary excretion, gadoxetate can still be eliminated by either the kidney or the hepatobiliary pathway unless the function of both organs are severely compromised. These compensation mechanisms were characterized in pre-clinical research in rats.⁵ These pharmacokinetic properties can enable the evaluation of liver function and the biliary excretion system.

Pharmacodynamics of gadoxetate

As gadoxetate is handled by the hepatocyte transport system, its pharmacodynamic properties are distinctive. The pharmacodynamic effects of MRI contrast agents also depend on their paramagnetic properties, protein-binding capacity and distribution in the intracellular or extracellular compartments. The most important feature is that gadoxetate is transported into the intracellular space of hepatocytes, which results in intense contrast enhancement of the normal liver parenchyma. By contrast, liver tumours, which deplete OATPs (*i.e.* influx system) and overexpress MRPs (*i.e.* efflux system), show a lack of contrast enhancement.⁶ Hence, the lesion-to-liver contrast between liver parenchyma and liver tumours is much higher in gadoxetate-enhanced MRI than in MRI with other extracellular gadolinium contrast agent, which is very helpful in the detection

of liver tumours.⁷ Because the marked hepatic uptake of gadoxetate is usually reached around 20 min after contrast injection, a 20-min delayed scan is most helpful to study liver function and is known as a “hepatobiliary phase” or “hepatocyte-specific phase”.^{3,4}

In addition, gadoxetate has a higher protein-binding capacity than Gd-DTPA does (10% *vs* 1.5%). This property also increases the T_1 relaxivity of gadoxetate, which implies that it can provide more intense contrast enhancement than other contrast agents.⁸ Owing to its high relaxivity, the clinical recommended dose of gadoxetate is much lower than that of other contrast agents (*e.g.* 0.025 mmol kg⁻¹ for gadoxetate *vs* 0.1 mmol kg⁻¹ for Gd-DTPA).⁴ In addition, a low dose of gadoxetate may lower the incidence and severity of adverse events compared with other gadolinium contrast agents.^{9,10}

Membrane transport proteins for gadoxetate

In hepatocytes, there are several kinds of transporters to control the influx and efflux of endogenous or exogenous molecules (Figure 2).¹¹ Of these, the OATP and MRP families play important roles in the influx and efflux of hepatocyte-specific MRI contrast agents, respectively. OATPs are mainly expressed in the sinusoidal (*i.e.* basolateral) side of hepatocytes, and MRPs are mainly expressed in the canalicular side. Of several OATP transporters, OATP1B1 and OATP1B3 are thought to be responsible for the influx of gadoxetate into hepatocytes.^{12,13} Among various MRPs, MRP2 is located in the canalicular side of hepatocytes and is responsible for excretion of gadoxetate into the bile duct.

Historically, the nomenclature system for OATPs has changed. Currently, the naming and the classification of OATPs are based on their amino acid sequence similarities.¹⁴ Based on phylogenetic

Figure 1. Excretion routes of gadoxetate. (a) In subjects with normal liver and kidney functions, 50% of administered gadoxetate is excreted through the hepatobiliary system and the other 50% is excreted through the kidney. (b, c) Serial MR images can visualize the biliary excretion and renal excretion of gadoxetate. On serial coronal MR images of a normal rat, the bile duct (black arrows) is visualized from 3 min after gadoxetate administration and excreted into the bowel (curved arrow) (b). Regarding the renal excretion, the kidney cortex is first visualized (white arrows), the kidney medulla is then enhanced and finally the renal pelvis and ureter is enhanced after 3 min after gadoxetate administration (asterisks) (c).

relationships and chronology of identification, OATPs are divided into families designated by an Arabic numeral (e.g. OATP1). At this level, many OATP1 proteins share >40% of amino acid sequence identity. Subfamilies are designated by a capital letter (e.g. OATP1B), in which individual proteins share >60% amino acid sequence identity. Finally, the individual gene products and genes are designated by an Arabic numeral (e.g. OATP1B1).¹⁴

At the mRNA level, OATP1B1 is expressed mainly in the liver and also in other tissues.^{15–17} At the protein level, OATP1B1 is only found in the liver, especially at the basolateral membrane of hepatocytes.¹⁸ Another protein in the OATP1B subfamily, OATP1B3, is also highly expressed in the human liver.^{19,20} Both are thought to be the main transporters of gadoxetate. However, OATP1B1 is expressed uniformly throughout the whole liver, whereas OATP1B3 is more restricted around perivenous regions.²¹

The exclusive expression of OATP1B1 and OATP1B3 in hepatocytes may suggest that they play essential roles in the hepatic metabolism of endogenous/exogenous materials. Primary and secondary bile acids as well as bilirubins are substrates of OATP1B1, indicating the role of this transporter in bile excretion.²⁰ Substrates of the OATP1B subfamily are often anionic amphipathic molecules with a relatively high molecular weight and often have high protein-binding capacities.¹⁴ Gadoxetate fits all these conditions, as it is an amphipathic derivative of Gd-DTPA and also shows relatively high protein binding (10%). However, large numbers of drugs are also substrates of OATP1B1 (Figure 3).

The fact that gadoxetate and many other drugs share OATP1B1 and OATP1B3 as transporters suggests that there might be many drug–drug interactions. Kato et al investigated the effect of 11 drugs on the hepatic enhancement of gadoxetate. Among these agents (prednisolone, rifampicin, doxorubicin hydrochloride, cisplatin, propranolol hydrochloride, scopolamine butylbromide, theophylline, ampicillin, cefotaxime sodium, verapamil hydrochloride and diazepam), only rifampicin exerted a significant decrease in the hepatic enhancement, suggesting it has a competitive inhibitory effect.²² In terms of endogenous substrates, the fact that primary and secondary bile acids competitively inhibit the influx of gadoxetate *via* OATP1B1/B3 can explain why the contrast enhancement of liver parenchyma on gadoxetate-enhanced MRI is low in patients with jaundice. These interactions should be further investigated in the future.

CLINICAL APPLICATIONS OF GADOXETATE-ENHANCED MRI

Evaluation of liver function

Assessment of liver function is important in predicting the prognosis of patients with liver cirrhosis. It is also important to decide the proper time for liver transplantation and to choose the appropriate candidates for hepatic partial resection.^{1,23} Estimating the functional reserve of the remnant liver in patients with liver cirrhosis or severe steatosis is especially important to minimize the risk of post-operative liver failure. Traditionally, indocyanin green (ICG) clearance test and scintigraphy with technetium-99m (^{99m}Tc) mebrofenin have been used for evaluating liver function.¹⁹ Interestingly, ICG is a substrate for OATP1B3 and mebrofenin is

Figure 2. Cellular transporters in the hepatocytes. Cellular transporters that control influx and efflux of the endogenous/exogenous compounds. Organic anion transporting polypeptides (OATPs) are mainly expressed in the sinusoidal (*i.e.* basolateral) membrane of hepatocytes, and multidrug resistance-associated proteins (MRPs) are mainly expressed on the canalicular side. Through the transporters expressed in the sinusoidal side of the hepatocytes, the compounds are transported between the blood and hepatocytes. Through the transporters expressed in the canalicular side of the hepatocytes, the compounds are excreted into the bile duct.

a substrate of both OATP1B1 and OATP1B3. Moreover, both are excreted in the bile through MRP2.²⁴ Recently, there have been several reports that proposed to use gadoxetate-enhanced MRI for the evaluation of liver function, as gadoxetate is also a substrate of OATP1B1 and OATP1B3. Indeed, in patients with impaired liver function such as liver cirrhosis, the hepatobiliary phase images of gadoxetate-enhanced MRI show the markedly decreased enhancement of liver parenchyma compared with patients with normal liver function (Figure 4).

The methods for hepatic function assessment with gadoxetate-enhanced MRI can be categorized into three main approaches: direct measurement of liver parenchymal signal intensity (SI), MRI relaxometry (*i.e.* measurement of T_1 or T_2^* relaxation time) and dynamic contrast-enhanced MRI (DCE-MRI).^{25–28} These methods are based on the fact that hepatic dysfunction causes a reduction of liver parenchymal enhancement in gadoxetate-enhanced liver MRI. The differential degree of liver parenchymal enhancement on gadoxetate-enhanced MRI can be used to assess hepatic function quantitatively.²⁹ Similarly, a recent pre-clinical study using a cirrhotic rat model also showed reduced liver parenchymal enhancement, attributed to slower hepatocyte uptake and rapid elimination due to decreased OATP1 activity and increased MRP2 activity.³⁰

With regard to the methods for direct measurement of liver parenchyma, the absolute value of the MRI SI differs significantly across patients and MRI machines, and corrected measurement

methods using internal tissue standards such as the spleen or muscles thus seem necessary.^{25,26,31} Motosugi et al³¹ introduced the method that calculates the liver–spleen contrast ratio in gadoxetate-enhanced MRI, which has been shown to correlate with ICG clearance and the Child-Pugh score. Yamada et al²⁶ proposed hepatocellular uptake index (HUI) which is computed using the volume and SI of the liver and spleen measured on gadoxetate-enhanced MRI. The HUI showed strong correlation with ICG clearance rate ($r = 0.87$).

Regarding the MR relaxometry, hepatic function is estimated by measuring T_1 or T_2^* relaxation time. MR relaxometry can overcome the shortcomings of direct measurement of the SI on T_1 weighted image. Using absolute values of T_1 or T_2^* relaxation times might be more reliable and less subjective than direct SI measurement for liver function estimation. Indeed, the T_1 or T_2^* relaxation times correlate well with gadoxetate concentration, and T_1 values were significantly longer in patients with liver cirrhosis than in normal subject on the gadoxetate-enhanced MRI.^{27,32}

The DCE-MRI techniques enable us to use sophisticated pharmacokinetic modelling based on a time–intensity curve of hepatic parenchyma and vessels. As techniques for DCE-MRI have seen great advances, DCE-MRI methods have been increasingly adopted for liver function assessment. Among various DCE-MRI parameters, hepatic extraction fraction has been widely used and the correlation between ICG clearance and Child-Pugh score has been demonstrated in both pre-clinical and clinical studies.^{28,33}

Assessment of liver function with gadoxetate-enhanced MRI has several advantages over traditional ICG clearance and hepatic scintigraphy with ^{99m}Tc -mebrofenin.²⁹ First, gadoxetate-enhanced MRI can provide information on hepatic function in localized hepatic abnormalities, which is more clinically relevant than a global assessment.³⁴ ICG clearance is a method for global assessment of liver function. Although the scintigraphic method is used for the evaluation of regional hepatic function, it is limited by poor spatial resolution. Second, gadoxetate-enhanced MRI is non-invasive, whilst the ICG clearance method requires repeated blood sampling and the scintigraphic method causes radiation exposure. Thirdly, MRI can provide superb anatomic detail of the underlying abnormalities.

To incorporate gadoxetate-enhanced MRI in the clinical practice for liver function estimation, several shortcomings should be solved. Currently, various MRI techniques have been used using different parameters across institutions, which may hamper reproducibility of MRI to estimate liver function.²⁹ Therefore, standardization of the MRI technique is an essential pre-requisite to use gadoxetate-enhanced MRI routinely for liver function estimation. Second, gadoxetate is excreted through the hepatobiliary system as well as the kidney, whereas the other compounds being used for liver function estimation such as ICG or ^{99m}Tc -mebrofenin are excreted predominantly through the hepatobiliary system. The dual excretion routes of gadoxetate may increase complexity in liver function estimation based on gadoxetate-enhanced MRI, T_1 relaxometry or DCE-MRI, requiring further investigation and validation.³⁵

Figure 3. Competition between endogenous/exogenous compounds and gadoxetate for the organic anion transporting polypeptide (OATP) transporters. There are many substrates of OATP receptors which compete with gadoxetate for being transported into the hepatocytes. MRP, multidrug resistance-associated protein.

Bile duct evaluation

Gadoxetate-enhanced MRI can provide functional information on bile excretion, because approximately 50% of the injected gadoxetate dose is excreted *via* the bile duct. Thanks to this property, gadoxetate-enhanced MRI can provide T_1 weighted MR cholangiography images (Figure 5a).³⁶ Recently, Ringe et al³⁷ evaluated the hepatobiliary transit time of gadoxetate, revealing that this contrast agent could be detected in the intrahepatic bile ducts and the common bile duct in all patients (100%), and in the gallbladder in 86.9% of patients on 20-min hepatobiliary phase images. The mean transit times for contrast appearance in that study were 12 min 13 s for intrahepatic bile ducts, 12 min 27 s for the common bile duct and 13 min 32 s for the gallbladder in normal patients. By contrast, the biliary excretion of gadoxetate was found to be significantly reduced

and delayed in patients with liver dysfunction such as chronic hepatitis or liver cirrhosis.³⁸ In the hepatic segment where the bile duct obstruction occurs owing to stone or tumour, the biliary excretion of gadoxetate is reduced or absent regionally (Figure 5b).³⁶ In addition, gadoxetate can be used as a biliary contrast agent to detect bile leakage with high sensitivity (Figure 5c).³⁹

Although unenhanced T_1 weighted cholangiography is a standard MRI technique to evaluate bile duct diseases, it provides anatomic rather than functional information. Instead, gadoxetate-enhanced T_1 weighted cholangiography could be helpful in the evaluation of hepatic function, bile duct obstruction, biliary-enteric anastomoses, diagnosis of cholecystitis and in the detection of bile duct injury, including leakage and stricture.^{36,39} However, in gadoxetate-enhanced

Figure 4. Change of gadoxetate-enhanced MRI findings according to liver function. (a) In a patient with normal liver function, the hepatobiliary phase images of gadoxetate-enhanced MRI show homogeneous enhancement of liver parenchyma. The bile ducts (arrows) are well-visualized owing to biliary excretion of gadoxetate. (b) In a patient with liver cirrhosis and moderately impaired liver function (Child B classification), the liver parenchymal enhancement is relatively low. The bile ducts are still depicted (arrowhead). (c) In a patient with severely impaired liver function (Child C classification), the degree of liver parenchymal enhancement is markedly decreased and heterogeneous. The bile ducts are not visualized.

cholangiography, the visualization of the bile ducts may be poor or even absent in cases with severe liver dysfunction or bile duct obstruction, which is a limitation of gadoxetate-enhanced cholangiography. Thus, both T_2 weighted and gadoxetate-enhanced MR cholangiography should be used concurrently for a thorough evaluation of bile duct diseases.

Characterization of hepatocarcinoma nodules

In patients with chronic hepatitis, a stepwise development of cancer from regenerative nodules to advanced hepatocellular carcinomas (HCCs), referred to as “multistep hepatocarcinogenesis”, is a widely accepted model. In general, normal hepatocytes express abundant OATP transporters, whereas HCCs lack OATP proteins. This phenomenon is helpful in the detection of HCC because of the improved lesion-to-liver contrast in the normal liver parenchyma showing high SI and hepatocyte-depleted liver tumours showing dark SI on the hepatobiliary phase of gadoxetate-enhanced MRI.⁴⁰ Emerging evidence suggests that the expression of OATP receptors decreases during hepatocarcinogenesis. In the stage of regenerative nodules and dysplastic nodules, the expression level of the OATP receptor is high. By contrast, in HCCs, either in early or advanced stages, the expression level of OATP transporter is low or absent (Figure 6). In addition,

the degree of OATP expression correlates inversely with the histopathological grade of HCC, which is helpful to differentiate early HCC from more aggressive HCC.^{13,41}

POTENTIAL CELLULAR APPLICATIONS OF GADOXETATE FOR FUNCTIONAL MRI

The recent advancements in imaging techniques have led investigators to use MRI for molecular imaging research. Since MRI can provide tomographic imaging of internal organs at high anatomical resolutions, imaging methods to track the cells of interests have been examined. Especially, the needs to track the cells by live imaging have been greatly increased nowadays owing to dramatic advances in cell therapy that inject stem cells or immune cells to treat osteoarthritis, stroke or cancer. In general, visualization of biodistribution of the injected cells is commonly required in development process of cell therapy.⁴² Moreover, as MRI reporter genes can be expressed in the progeny of proliferating cells, they can be used to track cells of interest over a long period of time. Therefore, many investigators have expected MRI reporter gene techniques to be useful in biomedical research.

Although several reports have shown the possibility of many MRI reporter genes as cell-trafficking tools, their low sensitivity,

Figure 5. Evaluation of biliary excretion with gadoxetate-enhanced MRI. (a) T_1 weighted MR cholangiography. In a liver donor, the hepatobiliary phase images can provide accurate anatomy information of the bile duct (left). Maximum-intensity projection images (middle) can provide three-dimensional T_1 weighted MR cholangiography images, which are similar to conventional T_2 weighted MR cholangiography (right). (b) Functional evaluation of biliary excretion. In a patient with cholangiocarcinoma which obstructs the proximal left intrahepatic bile ducts (IHDs), the distal left IHDs are dilated (arrows). The hepatobiliary phase image (left) demonstrate absence of biliary excretion, however, the T_2 weighted image (right) cannot provide such functional biliary excretion information. (c) Evaluation for bile leakage. In a patient who underwent cholecystectomy, hepatobiliary phase image clearly demonstrates the bile leakage (arrows) from the cystic duct stump into the perihepatic space.

Figure 6. Characterization of hepatocellular nodules. In a pre-operative MRI for liver transplantation including arterial phase (a), hepatobiliary phase (b) and T_2 weighted image (c), three nodules in the cirrhotic liver are found. The nodule in the segment II of the liver (arrows) shows arterial enhancement, low-intensity on hepatobiliary phase and T_2 hyperintensity, indicative of typical hypervascular hepatocellular carcinoma (HCC). The nodule in segment VII of the liver (arrowheads) shows no arterial enhancement, low-intensity on hepatobiliary phase and subtle T_2 hyperintensity, suggestive of early HCC. The nodule in segment VIII of the liver shows no arterial enhancement, subtle low-intensity on hepatobiliary phase and T_2 hypointensity, suggestive of dysplastic nodule. These MRI diagnoses are confirmed on surgical specimen.

which is the main disadvantage of MRI reporter genes, has hindered their widespread use for molecular imaging. Known MRI reporter genes such as the chemical exchange saturation transfer reporter, transferrin receptor and ferritin have shown reproducibility from many research groups, but none have been able to overcome the sensitivity issues.⁴³

Recently, Patrick et al⁴⁴ investigated the feasibility of the OATP1A1 MRI reporter gene as a MRI reporter candidate. The authors transfected an OATP1A1-expressing vector into several cell lines including human embryonic kidney cells (HEK 293T), breast adenocarcinoma cells (MCF-7) and human colon adenocarcinoma cells (HCT 116), and confirmed the feasibility of OATP1A1 as an MRI reporter gene. They observed signal enhancement in T_1 weighted images of HCT 116 xenograft mice after administration of gadoxetate and found that the OATP-expressing cells showed a 4- to 6.8-fold increase in signal enhancement compared with the control tumours. These results indicated that OATP is more effective than previous MRI reporters.⁴³

However, to utilize an OATP-based MRI reporter in translational research, some issues have to be considered. First, as hepatocytes abundantly express the OATP1B1 and OATP1B3 genes, that encode the main transporters for gadoxetate, overexpression of either gene by plasmid transfection into hepatocytes cannot yield a signal enhancement. Although other members of the OATP superfamily can be utilized as alternative reporter genes, additional proof of signal enhancement experiments should be performed. Second, considering that overexpression of OATPs may affect the physiology and function of transfected cells, this must also be assessed. In particular, as the OATP genes play important roles in transporting many drugs, changes in cell behaviours associated with such agents should be evaluated. The OATP gene-based MRI reporter is in its initial stage of development, and

reports on this model are currently sparse. However, it seems that it might become a useful tool for providing information on cells or organs during the longitudinal monitoring time.

There are other potential cellular applications of gadoxetate other than that as MRI reporter. Although extensive investigations have been performed to evaluate the function of OATPs such as transporting drugs and natural substrates, there has been no tool to visualize or quantify the function of OATPs in living cells.²⁰ Currently, immunohistochemistry, western blots and polymerase chain reaction are widely used to evaluate presence of OATP proteins or expression of OATP genes; however, these methods are basically *in vitro* assays and cannot evaluate the OATP function. Owing to recent advances in cellular MRI technique to image the cells *in vivo*,⁴⁵ gadoxetate can be used to evaluate the OATP function *in vivo* using MRI. These are very good future research topics in the cellular MRI field.

CONCLUSION

A new hepatocyte-specific MRI contrast agent, gadoxetate disodium, demonstrates unique pharmacokinetic and pharmacodynamic properties, which enable combined morphologic and functional information to be obtained. The evaluation of hepatobiliary pathology beyond morphology gives rise to the possibility of using gadoxetic acid-enhanced MRI as a functional imaging tool for hepatobiliary diseases. In addition, an understanding of the mode of action could provide an opportunity to apply gadoxetate to cellular or molecular imaging.

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