New possibilities to study biliary tree and gallbladder: functional magnetic resonance cholangiography contrast-enhanced with mangafodipir trisodium (Mn-DPDP)

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The bile ducts have been classically studied with fast spin-echo T2-weighted sequences with acquisitions in half-Fourier pulse sequences. Stagnant fluids appear in hyperintensity. These hydro-MRI sequences make it possible to visualize the anatomy of the bile ducts in excellent conditions, but they do not allow analysis of bile secretion and excretion.

Mangafodipir-trisodium (Teslascan*) is a hepatobiliary contrast agent that provides noninvasive opacification of the bile ducts. Using this contrast medium combined with a T1-weighted gradient echo enhanced sequence provides functional imaging of the bile ducts.

Second-intention MRI was obtained after the usual morphological study of the bile ducts using heavily T2-weighted sequences (SS-FSE Te eff long and SS FSE Te eff short). This method can detect many biliary duct anomalies: biliary leakage in the postoperative context, mapping of bile ducts and the gallbladder in the search for anatomical variants, analysis of biliodigestive or bilioiliary anastomoses, or a dynamic study of bile secretion and excretion. Opacification of the bile ducts has only been possible until now with invasive tests aggravated by a certain co-morbidity rate and their functional study using biliary scintigraphy limited by mediocre spatial resolution. This new possibility provides access not only to morphological imaging, but also to functional imaging with excellent spatial resolution.

Résumé
Les nouvelles possibilités d’exploration des voies biliaires en IRM : de l’imagerie morphologique à l’imagerie fonctionnelle avec perfusion de Mangafodipir Trisodium (Mn DPDP)

Le Mangafodipir Trisodium (Teslascan*) est un agent de contraste hépatobiliaire permettant une opacification non invasive des voies biliaires. L’utilisation de ce produit de contraste couplée à la réalisation de séquence volumique en écho de gradient pondéré T1 permet d’accéder à une imagerie fonctionnelle des voies biliaires. Il s’agit d’une IRM de deuxième intention obtenue après une étude morphologique habituelle des voies biliaires à l’aide des séquences fortement pondérées T2 (SS-FSE Té eff long et SS FSE Té eff court). De nombreuses anomalies des voies biliaires peuvent ainsi être détectées : fuite biliaire dans les contextes post opératoires, cartographie des voies biliaires et de la vésicule avec recherche des variantes anatomiques, analyse des anastomoses bilio-digestives ou bilio-biliaires ou encore étude dynamique de la sécrétion et de l’excrétion biliaire. L’opacification des voies biliaires n’était possible jusqu’alors qu’avec des examens invasifs grevés d’un certain taux de morbidité et leur étude fonctionnelle par la scintigraphie bilaire limitée par une résolution spatiale médiocre.

Cette nouvelle possibilité permet d’accéder non seulement à une imagerie morphologique et également fonctionnelle avec excellente résolution spatiale.

Mots-clés : IRM. Voies Biliaires.

Abstract
Mangafodipir trisodium (Teslascan) is a hepatobiliary contrast agent that provides noninvasive opacification of the bile ducts. Using this contrast medium combined with a T1-weighted gradient echo enhanced sequence provides functional imaging of the bile ducts.

Second-intention MRI was obtained after the usual morphological study of the bile ducts using heavily T2-weighted sequences (SS-FSE Te eff long and SS FSE Te eff short). This method can detect many biliary duct anomalies: biliary leakage in the postoperative context, mapping of bile ducts and the gallbladder in the search for anatomical variants, analysis of biliodigestive or bilioiliary anastomoses, or a dynamic study of bile secretion and excretion. Opacification of the bile ducts has only been possible until now with invasive tests aggravated by a certain co-morbidity rate and their functional study using biliary scintigraphy limited by mediocre spatial resolution. This new possibility provides access not only to morphological imaging, but also to functional imaging with excellent spatial resolution.

Key words: MRI. Bile ducts.
Review of the physical and chemical properties of mangafodipir-trisodium

Mangafodipir-trisodium (Mn-DPDP) is a contrast agent that contains manganese (Mn 2+), a metal with paramagnetic properties. It shortens T1 proton relaxation time, resulting in a positive contrast in T2-weighted sequences (2). After IV injection, the manganese is captured by healthy hepatocytes and the parenchyma shows up in hyperintensity on T1-weighted sequences. It was initially proposed to improve detection of focal liver lesions that appeared as hypointense. Teslascan* excretion is 59% biliary and is therefore also responsible for an increase in the bile signal in T1-weighted images, which in turn shows as hyperintensity. In T2-weighted sequences, like all paramagnetic agents, it erases the biliary signal. Manganese also accumulates in the pancreas, the renal cortex, and the central nervous system (caudate nucleus, in particular the striatum). The neurotoxicity of manganese is well known in occupational medicine because the intoxication indicators for manganese are close to those of Parkinson disease. Studies conducted on rats (3, 4) showed that the accumulation of manganese following Mn-DPDP perfusion reaches its maximal concentration 1 day after the injection, persists at its maximum rate for 1 month and declines to one-third the maximal concentration after 3 months. When biliary elimination is blocked, the manganese concentration found in the brain is doubled. In cases of severe jaundice, the use of Mn-DPDP is contraindicated. The other contraindications are pregnancy, breastfeeding, known hypersensitivity to one of the components, and kidney failure.

There are other agents, amphipathic derivatives of gadolinium DTPA, that contribute to biliary evaluation, but they can be associated with dynamic vascular and parenchymatous study. Given the specific characteristics of the contrast medium on the bile ducts, functional imaging of bile excretion and secretion is becoming accessible. The images classically obtained in spontaneous contrast with fast spin-echo, heavily T2-weighted sequences for analysis of the signs of morphological anomalies can be completed by functional imaging in certain clinical indications.

Technique

The standard recommended dose is 0.1 ml/kg. It is administered intravenously over 15-20 min. The time window available for exploration is 40-120 min after the injection. The acquisition protocol initially includes, before injection of Mn-DPDP, a cholangio-MR associating rapid heavily T2-weighted sequences: 20-mm-single shot fast spin-echo (SS-FSE) long TE eff radial slices and short SS-FSE TE eff sequences in the axial and frontal planes in 7-mm slices. After Mn-DPDP enhancement, the bile ducts are explored with 3D, gradient echo T1-weighted sequences on two orthogonal planes: axial and frontal. We specify the following parameters: TR 4.5/TE: 2.2/157/40 partitions/slice thickness interpolated to 1.2 mm/ZIP 2/Matrix 48×256/ZIP 512/Field of view 460/Phase FOV 0.9/BW: 83 kHz. Parallel SENSE imaging was used with a factor 2.

When there is no bile duct dilatation, a first acquisition is obtained 30 min after the end of the injection. In indications of biliary duct leakage with voluminous bila- loma, one acquisition at 1 h or even 2 h is obtained. In this clinical situation, delayed views are very important to obtain because they can confirm potential leakage. This requires having a sufficient quantity of contrast medium in the collection to objectify it. The native 3D images are visualized and transferred to a post-treatment workstation for multiplanar reconstruction and specific post-treatments such as MIP (maximal intensity projection), MPR (multiplanar reconstructions), and MPVR (multiplanar volume rendering). The acquisition in the two orthogonal planes is preferable: since the voxels are not isotropic, the reconstructions show better quality in the acquisition plane. T2-weighted acquisitions can also be obtained after Mn-DPDP perfusion. They are useful to show whether possible cystic lesions communicate since manganese erases the signal on T2-weighted sequences.

The examinations presented in this report were done on a 1.5-T MRI using a 12-element phased array coil.

Comparison with other techniques

Bile duct exploration techniques include noninvasive methods in spontaneous contrast: transparietal sonography, CT, and MRI cholangiography, noninvasive methods with bile duct opacification (hepatobiliary scintigraphy and CT cholangiography), and finally invasive methods (endoscopic retrograde cholangiography and transparietal cholangiography). Ultrasound is the first-intention examination done to evaluate the common bile duct and the intrahepatic bile ductules, but, as on CT, only the morphological defects are visualized. Similarly, MRI cholangiography in spontaneous contrast obtained with highly T2-weighted sequences provides a morphological study of excellent quality but sometimes remains insufficient for a functional study. CT cholangiography (5, 6) provides a complete study in a single examination of one part of the vascular axes and then bile duct anatomy after injection of a specific contrast medium. CT cholangiography is done after injection of iodipamide meglumine 52% (Chlorografin, Bracco, Princeton, NJ), which opacifies the bile ducts (20 ml in 80 ml of saline solution). The perfusion lasts 30 min. The main indications are for demonstrating anatomic variants of the biliary tree for live donors before cholecystectomy using coelioscopy, and demonstrating biliary calculi or biliary leakage. Hepatobiliary scintigraphy (7, 8) provides a functional study of biliary excretion and secretion (marker, 99 mTc-mebrofenin). It is highly sensitive in detecting biliary leakage: 87%-100%. This technique has low spatial resolution, which impedes visualization of the cause of obstruction because the extrabiliary structures cannot be analyzed. Filling defects and certain stenoses are not objectified and when these stenoses are partial, the diagnosis is made in only 50% of cases. Moreover, scintigraphy can also generate false-positive results, notably for patients who do not have an empty stomach or who have severe hepatic insufficiency or hyperbilirubinemia. Invasive examinations such as endoscopic cholangiography (9) or transparietal cholangiography have a high diagnostic sensitivity, but their complication rate is not insignificant (11%-20%).
Clinical applications of functional MRI cholangiography

Biliary leakage (fig. 1 and 2)

Although a rare complication, biliary leakage results most often from surgery (10). Leaks can occur during any surgical intervention on the biliary tree: liver transplantation, liver resections, or cholecystectomy with coelioscopy. This last technique increases the risk of injury during the common bile duct procedure, and even more so when the local conditions are difficult, notably when there is pronounced inflammation. Ultrasound or CT demonstration of a postoperative supramesocolic intraperitoneal collection or effusion cannot define the type of injury. Until now, invasive tests (rarely CT cholangiography) confirmed this diagnosis: retrograde or transparietal cholangiography. With biliary leakage, the diagnostic difficulties are bile duct dilatation upstream from the injury and demonstration of the exact site of leakage. In cases of complete ligation of a bile duct, the diagnostic problem is indeed much simpler since dilatation of the bile ducts upstream from the section can be seen and in this context morphological imaging suffices.

The value of Mn-DPDP enhancement in this indication was described by Vitellas et al. in 2001 (11). The case involved a bile duct leak secondary to injury to the bile duct that occurred in a context of cholecystectomy using coelioscopy performed in difficult conditions. Since then, several studies (12, 13) have demonstrated excellent diagnostic performance when using Mn-DPDP. In a study including 11 patients with suspicion of bile duct leakage, Vittelas et al. found an 86% sensitivity and an 83% specificity (14).

The acquisition technique should be adapted, with 3D sequences that can visualize the bile ducts, the leakage site, and the multiplanar reconstructions indispensible to the diagnosis. Results with volume acquisition are better (15) than 2D acquisitions.

Similarly, a 30- to 40-min delay should be respected before taking sequences, particularly if there is a voluminous collection (16), because false-negative results are related to an excessively short delay between Mn-DPDP perfusion and acquisition. If no leakage is demonstrated on a first acquisition done 40 min after perfusion, an acquisition should be done 1 h or even 2 h later.

One of the limitations of using Mn-DPDP in this indication is the differential diagnosis between complete or partial stenosis of a bile duct. MRI tends to overestimate stenosis, which could be erroneously considered totally obstructive when obstruction is actually only partial. Indeed, the absence of pressurized injection makes analysis of poorly opacified biliary ducts very delicate.

Fig. 1: A 42-year-old female patient. Three days after cholecystectomy using coelioscopy. Collections in the hilum and area of the cholecystectomy seen on ultrasound. Suspicion of biliary leakage.

a Frontal slice (20 mm) long SS-FSE TE eff. Moderate dilatation of the intrahepatic bile ducts. Centimeter-size collection at convergence (white arrowhead).

b Three-dimensional sequence enhanced with Mn-DPDP. Frontal MIP (maximal intensity projection), 10 mm thick. Opacification of the small hilar collection (black arrowhead) 1 h after injection.

c Three-dimensional sequence enhanced with Mn-DPDP. Frontal oblique view. Contrast medium located outside bile ducts and leakage toward the gallbladder bed (black arrowhead).

d Three-dimensional sequence after Mn-DPDP injection. Axial MIP (7 mm). Contrast-medium leakage outside bile ducts in the gallbladder bed (black arrowhead).
Study of bile duct complications after liver transplantation (fig. 3a-b)

After liver transplantation, many complications can occur, either vascular or extra-vascular (17). Vascular complications can cause biliary duct complications such as necrosis of the bile ducts (ischemic cholangitis). Mechanical bile duct complications can be of two types: anastomotic stenosis or leakage, and they require rapid diagnosis for optimal management. They are susceptible to generating substantial morbidity and can be responsible for graft loss. The frequency of complications is 11%-30%, depending on the center. Bile duct complications have no specific diagnostic test even though the biological workup is very sensitive to this situation. In this particular context, MRI with Mn-DPDP enhancement can be valuable (18, 19). Analysis of the anastomosis is excellent, as is analysis of the extrahepatic bile duct and the intrahepatic ductules. This imaging modality is superior to heavily T2-weighted sequences. In a series including 25 patients, all the anastomoses, whether bilio-biliary or bilio-enteric, were always demonstrated, whereas analysis was not as good with classical MRI cholangiography sequences, with statistically significant ($p<0.001$) differences (17).

Study of bilioenteric anastomoses (fig. 4-6)

Patients with a biliodigestive anastomosis present a high risk of developing complications: bile duct obstruction, cholangitis, stenoses of the intrahepatic ductules, and calculi. Biliodigestive anastomoses are very difficult to analyze because of the aerobilia by reflux hindering analysis of the anastomosis and the underlying bile ducts. MRI cholangiography in thick slices is delicate to interpret because of the superimpositions of digestive tract segments that are very close to the biliary anastomosis. As for the morphological study, it is also particularly difficult because of the orientation and small size of the anastomoses. With Mn-DPDP injection, the anastomosis can be opacified and analysis of 3D thin slices can overcome these limitations. The anastomosis can be studied in the different planes with variable thickness MPR. In the study by Hottat et al., the anastomosis is individualized in 85% of...
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cases with highly T2-weighted MRI cholangiography sequences, whereas this is always the case with Mn-DPDP perfusion (20). MRI cholangiography’s false-negative results are secondary to the presence of intraparietal fluid, which may superimpose on the zone of interest. The Mn-DPDP excretion delay is variable depending on the patient: a 1-h delay for 11 patients, 2.5 h for one patient, and 3 h for one patient. In these last two situations, the anastomosis was considered to be obstructed. Compared to the transhepatic cholangiographic results, MRI with Mn-DPDP enhancement presented a sensitivity of 100% and a specificity of 100%, whereas the classical heavily T2-weighted sequences had a 50% sensitivity and a 57% specificity (13).

Mapping the intrahepatic bile ductules of living donors

One of the challenges in selecting living donors is being able to map the bile ducts so as to demonstrate any anatomical variants. Bile duct anatomy is variable and up to 45% of the population have variants (only 62.5% of donors have a conventional bile duct anatomy). However, detecting and describing intrahepatic bile duct (IHBD) anomalies, particularly when they are not dilated, is difficult. The invasive techniques, burdened with a certain morbidity rate, are not proposed for healthy donors. With classical MRI cholangiography sequences, visualization of certain defects on T2-weighted images is very difficult because of the superimposition of different structures, and the spatial resolution of these images is not good enough in this context. These anatomical variations are not visualized because of the small caliber of the nondilated IHBDs and accessory ducts. For example, differentiating an authentic trifurcation from normal bile duct anatomy depends on the position of the right hepatic duct, which can measure on the order of 1 mm (21).

In this context, as early as 2000, Lee et al. proposed mapping the IHBDs with Mn-DPDP-enhanced MRI (22). High-quality reconstructions using optimized acquisition parameters (parallel imaging, thin native slices, zero filling interpolation methods) can allow one to obtain particularly valuable and indispensable post-treatments. With this technique, the nondilated IHBDs are visible for all potential candidates, which means more often detecting the anatomical variants than with classical highly T2-weighted sequences (23, 24).

In 2004, a second study by the same author (25) on 108 potential donor candidates confirmed, in this field of application, that this technique was better than classical MRI cholangiography sequences. In 99% of cases, the bile ducts were demonstrated with this technique, whereas this was not done in 82% of cases with classical heavily T2-weighted sequences. When these two techniques are compared to the cholangiographic data per operator, the results obtained are better with Mn-DPDP enhancement (92%) than with classic heavily T2-weighted sequences (84%).

Other potential applications

Cystic lesion communicating or not communicating with the bile ducts

Assessing a cystic lesion communication with the intra- or extrahepatic biliary ducts with certainty can be difficult. In this situation, one must not forget to take heavily weighted sequences before and after Mn-DPDP perfusion because erasing the bile signal on heavily T2-weighted acquisitions can confirm cyst communication (fig. 7-9).
Fig. 6: **Male, 57 years old. History of cephalic duodenopancreatectomy with double biliodigestive anastomosis.**

a  Frontal view, SS FSE long TE eff: right anastomosis clearly visible, anomalies of the left anastomosis caliber. Raised ansa (white asterisk).

b  Enhancement with Mn-DPDP. No stenosis on the right branch, with view of left anastomosis stenosis and moderate dilatation of upstream intrahepatic bile ducts. Fast filling of raised ansa (black asterisk).

Fig. 7: **Male, 62 years old. Known polycystic kidney and liver disease. History of cephalic duodenopancreatectomy for ampulloma with biliodigestive anastomosis.** Recently hospitalized for pain, fever, and jaundice.

a  Axial view, SS-FSE short TE eff (7 mm). Association of peribiliary cysts (white circle), biliary cysts (white arrow), and intrahepatic bile duct dilatation (thin white arrow).

b  Axial view, SS-FSE long TE eff (20 mm). Confirmation of material within bile ducts above anastomosis (white arrow).

c  Axial view (MPR, 4 mm) enhanced with Mn-DPDP. Opacification of right bile ducts (curved arrow). Hyposignal showing lacunae of right intrahepatic bile ducts corresponding to calculi (thin black arrow). No opacification of peribiliary cysts, confirming lack of communication (normal view).

d  Frontal view (MPR, 5 mm) enhanced with Mn-DPDP. Analysis of biliodigestive anastomosis (thin white arrow). Note that this anastomosis could not be analyzed on SS-FSE long TE eff sequences.
**Fig. 8:** Female, 39 years old. Workup for cystic lesion of the liver hilum. Frontal view enhanced with Mn-DPDP. Complete opacification of the hilum cyst, showing communication with common bile duct: bile duct cyst (white arrowhead). Normal common bile duct (curved arrow) and gallbladder (black circle).

**Fig. 9:** A 47-year-old female. Pancreatic cyst workup. 

- **a** Frontal view, SS-FSE long TE eff. Large fluid lesion of the lower bile duct (white arrowhead).
- **b** Frontal view (MPR, 6 mm) enhanced with Mn-DPDP. Complete opacification of fluid lesion: choledochocele (white arrowhead).

**Fig. 10:** Female, 54 years old. MRI cholangiography for suspected common bile duct stone.

- **a** Frontal view, SS-FSE long TE eff (20 mm). Common bile duct and IHBDs normal. Cystic duct and gallbladder not visible.
- **b** Axial view, SS-FSE TE eff court (7 mm). No gallbladder.
- **c** Frontal MIP enhanced with Mn-DPDP. Absence of gallbladder confirmed. Gallbladder agenesis. Common bile duct and IHBDs normal.
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For intrahepatic cysts, apart from the classical biliary cyst, diagnosing Caroli disease, a congenital anomaly with communicating cysts, must be made. The injection of Mn-DPDP provides a totally noninvasive manner to detect with certainty whether there is communication. Likewise, peribiliary cysts can be confused with intrahepatic bile duct dilatation. Even if their topography is pathognomonic of this diagnosis, i.e., situated on both sides of the portal branches, Mn-DPDP injection can confirm that there is no communication between these minuscule cysts and the IHBDs (26).

The problem of a cystic lesion lying near the bile duct communicating with the common bile duct can arise. Choledochus cysts are grouped according to the Todani classification (27): type 1 and 2 cysts correspond to cystic dilatations of the extrahepatic bile duct, type 3 to choledochocele, type 4 to intra- and extrahepatic bile duct dilatations, and type 5 to intrahepatic bile duct dilatation (Caroli disease).

Type 1 and 2 cysts require surgical resection to prevent cholangiocarcinoma. Opacification of this type of lesion confirms the diagnosis of the cyst. Type 3 cysts can be confused with a cystic lesion of the pancreas (false cyst) or a groove (in groove pancreatitis). Opacification of this cystic dilatation after Teslascan® confirms that it communicates with the common bile duct and can confirm the diagnosis of type 2 cyst.

Anatomical variants of the gallbladder (28-30)
Certain morphological variants of the gallbladder are sometimes difficult to diagnose.

Some anomalies are exceptional: double gallbladder or agenesis (fig. 10). Opacification with Mn-DPDP can confirm these conditions.

Gallbladder drainage anomalies
IHBD filling is rapid if there is no biliary obstruction (approximately 10 min). Some authors have proposed Mn-DPDP MRI to analyze gallbladder filling for differential diagnosis of acute or chronic cholecystitis. The gallbladder does not fill in cases of acute cholecystitis (fig. 11), whereas delayed filling is observed in cases of chronic cholecystitis. Kim et al. (31) reported their experience in 12 patients by comparing the Mn-DPDP MRI results with biliary scintigraphy results. They concluded that this test is highly valuable, with better performance on scintigraphy for diagnosing obstructive acute cholecystitis, with the diagnostic criteria being visualization of the common bile duct, the cystic duct, and opacification of the duodenum when the gallbladder was not opacified. These authors considered that this technique could be useful in the differential diagnosis of cholecystitis secondary to the presence of a calculus embedded in the cystic duct vs nonlithiasic cholecystitis.

Furthermore, Mn-DPSP biliary opacification has the potential of allowing precise exploration of gallbladder evacuation

Fig. 11: Female, 52 years old. Search for common bile duct calculus after stone migration.

a Frontal view, SS-FSE long TE eff (20 mm). Common bile duct moderately dilated with no calculus. Principal pancreatic duct normal. Gallbladder not visible because of multiple calculi.
b Frontal view, SS-FSE short TE eff (7 mm). Gallbladder nearly empty, seat of large stone (white arrowhead).
c Frontal view enhanced with Mn-DPDP (MPR, 7 mm). Opacification of common bile duct (white arrowhead), IHBDs, and cystic duct (white curved arrow). No gallbladder opacification. Cholecystitis with obstacle.
dynamics after injection of cholecystokininetics. It can therefore be substituted for biliary scintigraphy in this indication since the patient is subjected to no radiation, while providing much more precise images of the common bile duct and the sphincter of the lower bile duct (32).

In the same type of indication, Mn-DPDP injection was proposed for early diagnosis of bile duct atresia (31). Twenty-three children in whom bile duct atresia was suspected had MRI with Mn-DPDP with T1-weighted gradient echo sequences obtained 1 h, 2 h, and 3 h after injection. The diagnosis of bile duct atresia was rejected if there was opacification of the duodenal context. This technique was compared to biliary scintigraphy. No false-positive results were found with this technique, whereas the other methods showed false-positive results in 42% for classical MRI cholangiography, 35% for scintigraphy, and 11% for the triangular cord sign with sonography.

In adults, studying biliary drainage can have many advantages in clinical practice. The first is being able to assess the permeability of prostheses/stents. Indeed, if quickly enhanced with Mn-DPDP, opacification of the duodenal area is observed and its permeability can be confirmed (27) (fig. 12).

**Conclusion**

Use of Mn-DPDP provides access to functional imaging of biliary excretion and secretion and offers many new clinical applications. This technique makes it possible to go beyond morphological anomalies to noninvasively explore and opacify the bile ducts, even if they are thin or distal. In addition, recent technological progress in MRI-phased array coil, powerful gradient, parallel imaging for high spatial resolution volume sequences, and the possibility of excellent multiplanar reconstructions for analyzing these small structures.

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