Intrathecal Gadolinium-Enhanced MR-Cisternography:

Depiction of the Subarachnoidal Space and Evaluation of Gadobenat-Dimeglumin-(Gd-BOPTA, "Multihance®") Toxicity in an Animal Model and a Clinical Case[1]

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RATIONALE AND OBJECTIVES

As other gadolinium-based contrast medias (CM) intravenously administered, gadobenate dimeglumine has proved to be well tolerated and safe (1). The application of gadolinium within the subarachnoidal space has been tested in several studies with promising results (2,3). This technique has not entered routine clinical use.

Because of its particular molecular structure, Gd-BOPTA showes T1 relaxivity values almost twice those seen with conventional CM due to its weak interactions with macromolecules (4). This characteristic leads to improved results in diagnostics and a lower required concentration. Encouraged by these results, Gd-BOPTA was used for this study to determine the best concentration of gadobenate dimeglumine in the cerebrospinal fluid and to evaluate the diagnostic value of MR-Myelography with intrathecal gadobenate dimeglumine. Additionally, the presence of toxic side effects to the CNS were investigated.

Due to certain clinical circumstances, one patient received gadobenate dimeglumine by lumbar puncture to evaluate a spinal cyst.

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MATERIALS AND METHODS

The optimum concentration of Gd-BOPTA for MR-Myelography was specified by diluting Gd-BOPTA in artificial cerebro-spinal fluid (aCSF) to 0.05 - 20 μmol/ml. The samples were scanned using an extremity coil in a 1.5 T MRI ('Vision', Siemens, Erlangen, Germany) with sequences shown in Table 1. 19 new-zealand-white rabbits with an average weight of 3.6 kg were included in the study.

Under general anesthesia, acess to the subarachnoidal space was established by cisternal puncture. After removing 0.1 to 0.5 ml cerebro spinal fluid (CSF) either a dose of 0.1 ml (50 μmol) (n = 3) or 0.16 ml (80 μmol) (n = 3) Gd-BOPTA was administered into the subarachnoidal space. The gabobenate was taken from fresh commercial bottles with the concentration of 0.5mol/l (MultiHance, Bracco SpA, Milano, Italy). As controls either 0.17 ml (n = 3) or 0.35 ml (n = 3) of 20%-mannitol was administered into the subarachnoidal space. The cisternal puncture in these animals was performed using a 21-gauge needle (n = 12). To examine the dynamic dispersion of the CM, a 22-gauge plastic cannula was placed into the cisterna magna and 0.4 ml (3 μmol of gadobenate dimeglumine, 7.5 μmol/ml) were applied (n = 3). During slow injection with approximately 0.05 ml/sec the spreading of the CM was visualized with fast T1-weighted sequences. A stenosis of the cervical subarachnoidal space was established in two rabbits by placing a long thick cannula into the dura dorsal to the spinal cord. In two animals an artificial CSF-leakage was induced by using a

16-gauge needle. These two groupes were also examined with 3 μmol gadobenate.

All rabbits were observed for behavioural changes and neurological alterations until sacrificied 3, 7, or 28 days after treatment. The CSF was analysed for leukocytes and protein levels. Paraffin slices of the cerebrum, the brainstem and the spinal cord were stained with hematoxylin-eosin.

Clinical application of Multihance in one patient because of an allergy to iodinated contrast media: The patient was treated according to good clinical practise and informed consent was obtained. Special regard was given to the lack of approval for intrathecal application. To evaluate a spinal cyst in a 58 year old female patient 1ml CM was intrathecally installed by lumbar puncture. Imaging was performed by MRI in supine and by MRI and CT in prone position. 3 hours after CM injection a second MRI examination was performed. Sagittal T1 and T2 as well as axial and coronary T1-series and a MPR-3D were conducted at each session.

RESULTS

Best contrast of Gd-BOPTA in T1-weighted images was achieved at a concentration of 1 μmol gadobenate dimeglumine per ml aCSF. At higher concentrations an extinction of T1- (>20 μmol/ml) and a reversal of the T2-signal (>5 μmol/ml) were noticed (Fig 1). Concerning tolerance and safety gadobenate dimeglumine at a dosage of 50 or 80 μmol caused no behavioural changes or neurological deficites in rabbits.

The histological examination of the cerebrum, the brainstem and the spinal cord did not show any apparent signs of toxicity.

In nine cases an assessment of CSF-parameters was not possible due to contamination or lack of sufficent CSF. Animals treated with 3 μmol gadobenate showed no significant increase of leukocytes or protein levels. In contrast at a dosage of 50 and 80 μmol gadobenate in two of six cases a rise in protein levels and leukocytes within the CSF after 3 days was noted. In the first case the initial examination showed 2 cells and 193 mg/l protein and in the final control after application of 50 μmol Gd-BOPTA 11 cells and 592 mg/l protein were found. In the second case using 80 μmol an increase from 2 cells and 203 mg/l protein to 97 leukocytes and 931 mg/l protein was detected. In the other four cases contamination of CSF impeded its evaluation.

MR Sequences

Type	TR	TE	Acq.-Time
Turbo-Flash	11.0	4.2	3 sec
T1	400	14	1 min 10 sec
T2	3500	120	2 min 9 sec
Flair	800	110	2.0 min
Hemo	608	15	1 min 52 sec
MPRage	9.7	4	5 min 58 sec
Ciss 3D	12.25	5.9	5 min 21 sec

No diffusion of the gadobenate dimeglumine into the brain parenchyma or spinal cord was detected in delayed studies up to 12 hours. Figure 2 shows a sequence of several images during slow injection of CM and its spreading within the subarachnoid space. T1-weighted images with CM in the subarachnoid space allowed a precise delineation between the CNS and the subarachnoid space.

Animal experiments were conducted in accordance with the guidelines set by the National Institutes of Health and the policies set by the University Animal Research Committee of the University of Freiburg, Germany.

The Gd-BOPTA in the subarachnoidal space of the 58 year old lady showed a sedimentation of the CM in MR imaging as well as in CT imaging immediately after injection. The sedimentation as independant of the examining position appearing in supine and prone position (Fig 3a). Two hours later a complete loss of T2-signal and homogeneous high signal of CSF in T1-weighted images was observed (Fig 3b). In contrast the sacral Tarlov cyst continued to demonstrate sedimentation effects on T1-weighted images. During the following days no focal neurological deficit developed.

CONCLUSION

In contrast to conventional x-ray contrast agents, strong enhancement is not depending on high concentrations of CM. To achieve optimal enhancement of CSF only low concentrations of about 1μmol/ml of Gd-BOPTA are necessary. Even though these volumes of gadobenate dimeglumine in the CSF are quite low, tolerance to the CNS is of major interest. In addition to its good general tolerance and safety, various studies about Gd-BOPTA suggest a good neurotolerability as well. Neither intravenous administered Gd-BOPTA in animals with disrupted blood-brain barriers nor directly injected Gd-

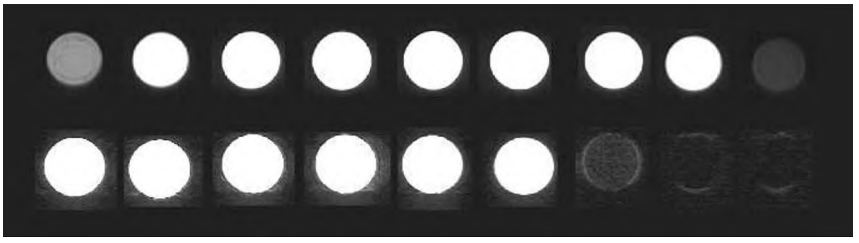


Figure 1. Gd-BOPTA diluted in aCSF in a concentration from 0.05 to 20.0 μmol/ml.

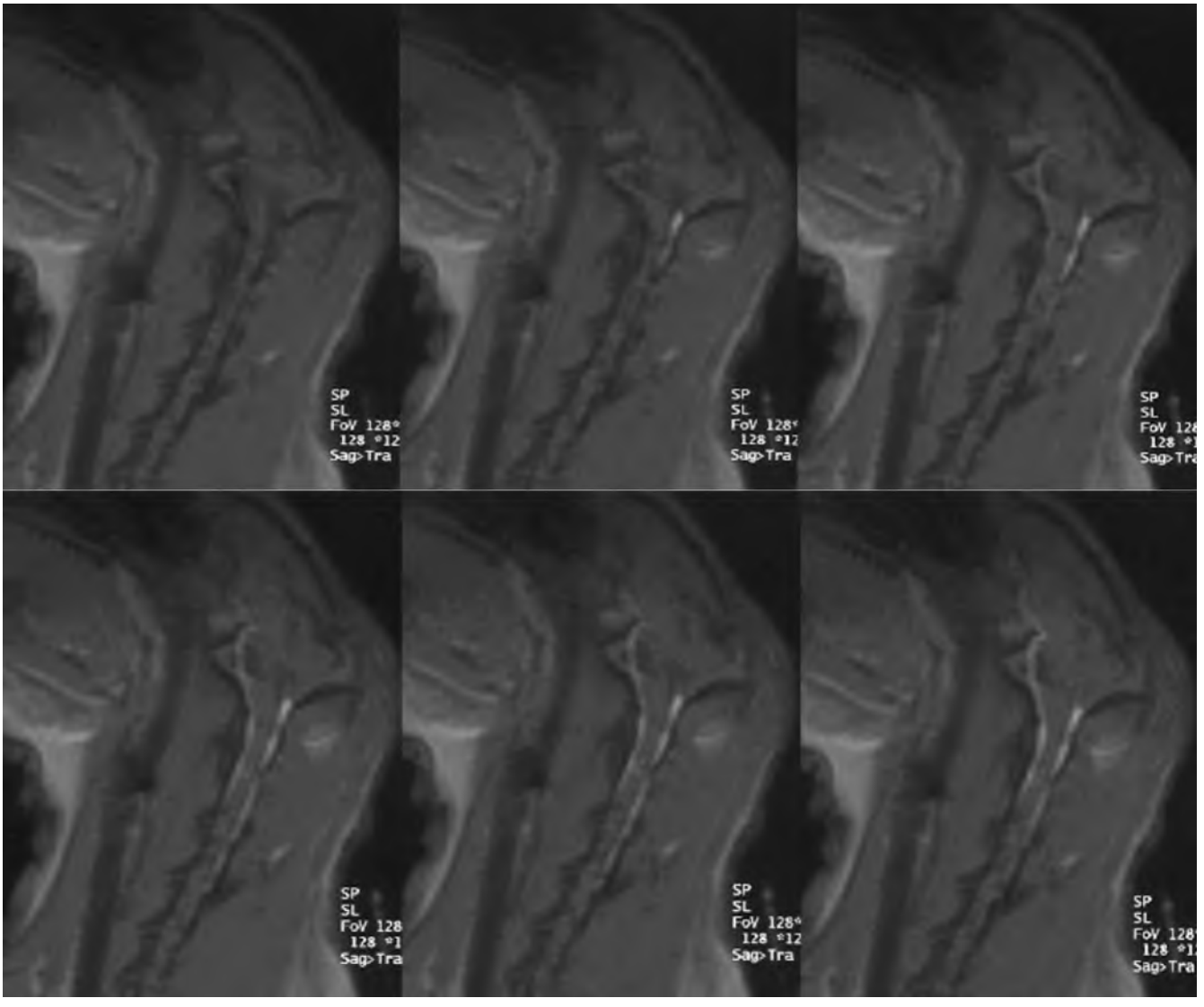
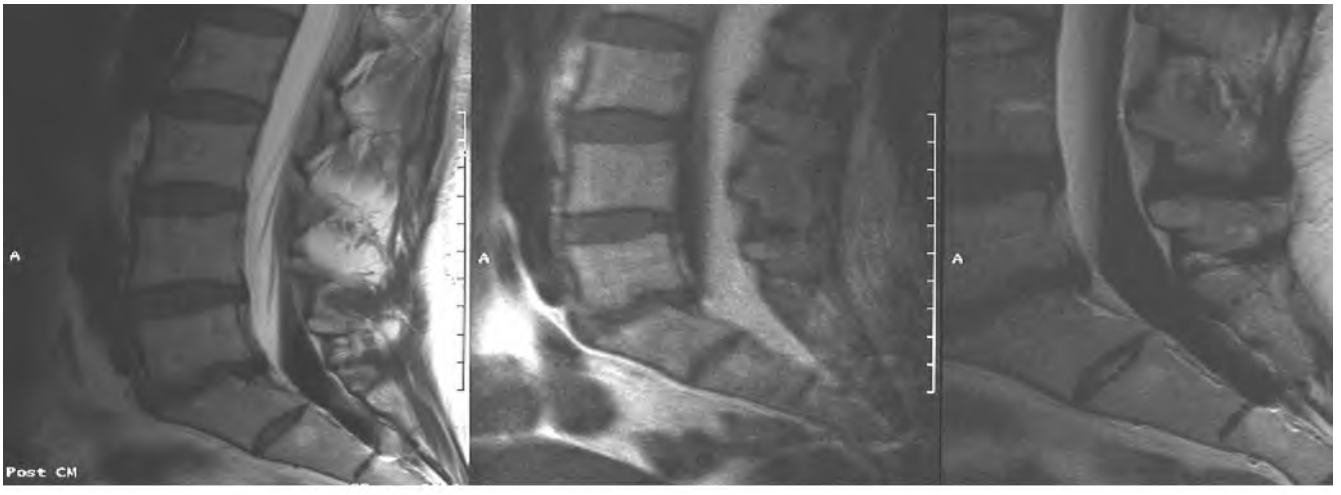
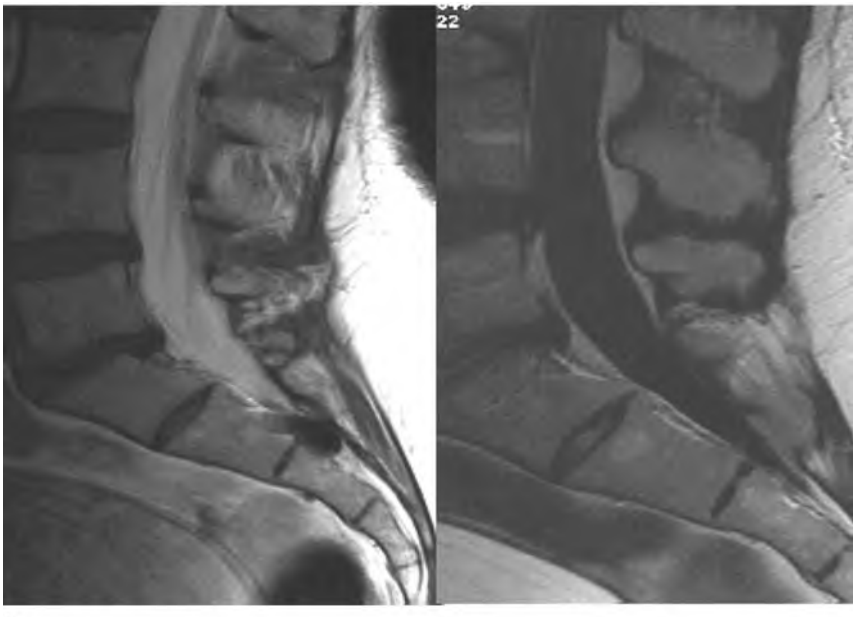


Figure 2. Spreading of the CM during slow injection (0.05 ml/sec). (sagittal T1-weighted images of the brain and cervical spine, slice-thickness 6 mm, TR 11.0, TE 4.2/1, aquisitions 2, time of aquisition 3.23 sec).



a.

Figure 3a. After intrathecal Gd-BOPTA application: The sedimentation as independant of the examining position appearing in supine and prone position in CT-, early T1- and T2-weighted imaging. **Figure 3b.** Two hours later homogeneous high signal of CSF in T1-weighted images and a complete loss of T2-signal was observed.



b.

BOPTA into the brain caused any significant changes of metabolites (5,6) or significant alterations in EEG (7) or behaviour. Whereas, in one study intrathecal administered Gd-BOPTA in rats caused a slight disturbance on motor coordination (8). The ED50 of 0.018 mmol/kg matches about the 80 μmol Gd-BOPTA used in this study. This animals showed no neurological changes and there were no apparent pathological changes found in histological examination, although protein levels and cells were increased in two cases.

In other studies Gd-DTPA administered venticularly caused cellular lesions (9) and a progressive diffusion of Gd-DTPA (about 25 μmol/ml CSF) into brain parenchyma was seen (2,10). Although it is known that the small water-soluable molecules can pass freely from CSF into neural tissue, this trait could not be verified using Gd-BOPTA. Thus no penetration of Gd-BOPTA into the parenchymal tissue of the CNS even several houres after inital CM-injection can be detected. This observation was made in the animal model and in the human patient.

In contrast to the samples administered to the animals resulting in a precise and uniformly enhanced CSF, the CM injected to the lumbar subarachnoidal space of the human patient led to a sedimentation of the CM. The higher concentrations in this zone resulted in an inverse hypointensity of the CSF in T1, whereas the rest of the

CSF showed good enhancement. These inverse effects were observed using high concentrations of gadobenate dimeglumine in the in vitro experiments compared to the concentration in the patient of about 3.0 μmol/ml CSF. This is three times the dosage found to be the optimum in this study. Repositioning of the patient from supine to prone mixed the two compartments insufficently. Three hours later, the patient was asked to turn, the Gd-BOPTA was spread equally and the entire subarachnoidal space was enhanced.

In our opinion three points have to be considered to avoid the effect of sedimentation: Firstly using lower concentrations (0,3 ml = 1 μmol/ml CSF), secondly movement of the patient after application and thirdly mixing the CM with some volume CSF of the patient.

MR-myelography with gadobenate dimeglumin seems to be a safe and feasible technique for the diagnostics of the subarachnoidal space. The intrinsic characteristics of gadobenate dimeglumine enable the use of low concentrations, whereas higher doses lead to unrequested effects.

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