Gadovist in Multiple Sclerosis

a report by
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Multiple sclerosis (MS) is an autoimmune inflammatory disease of the nervous system due to a still unknown antigen.[1] While the diagnosis of MS relies primarily on a combination of typical clinical symptoms and paraclinical findings (cerebrospinal fluid [CSF] findings from lumbar puncture), neuroimaging plays an important role in its management.[2] While plaques can sometimes be seen on computed tomography (CT), nowadays CT plays no role whatsoever except as a rule-out method in patients with acute symptoms in whom haemorrhage or stroke must be diagnosed/excluded; instead, imaging today relies entirely on magnetic resonance imaging (MRI).

As diagnosis using imaging relies on counting the number of demyelinating lesions in the white matter, the presence of enhancing lesions will increase the diagnostic yield of the method. As a result, contrast-enhanced imaging is mandatory in the assessment of patients with known or suspected MS.[3–6]

> Gadovist has been found to have a higher relaxivity than other macrocycle contrast media, which leads to the highest available T1-shortening per volume and should also allow increased contrast at the same concentration.

Neuroimaging plays an important role not only in the diagnosis but also in the management of these diseases: indeed, imaging and contrast enhancement can demonstrate disease activity and thus be used not just to monitor the natural history of the disease, but also to look at the impact of treatment.

Imaging Approach

Multiplanar fluid-attenuated inversion recovery (FLAIR) and T2 sequences (usually axial T2 and FLAIR and sagittal FLAIR) together with axial pre-contrast T1 and post-contrast T1 in all three planes constitutes the traditional approach to the patient with MS. It must be stressed that imaging of the orbits (with coronal T2 and axial and coronal fat-saturated T1-weighted post-contrast images) can often be performed in addition to imaging the whole spinal cord. Additionally, techniques such as diffusion tensor imaging, diffusion-weighted imaging, spectroscopy and magnetisation transfer have been used with success in this disease.

In addition to clinical and laboratory criteria, classifications such as those proposed by MacDonald or Barkhof are usually used in order to make the diagnosis of MS more precise. These classifications include a count of the number of lesions visible on T2-weighted images in the white matter, as well as of lesions that enhance.

Rationale for Gadovist

One-molar Contrast Material

Gadovist (gadobutrol) is a one-molar gadolinium chelate that has found wide acceptance in applications in the central nervous system (CNS). It has been used for applications in the brain relating to imaging of primary brain tumours and metastases, as well as for optimising brain perfusion in stroke.[7–11] Besides its uniquely high concentration, Gadovist has been found to have a higher relaxivity than other macrocycle contrast media (see *Figure 1*), which leads to the highest available T1-shortening per volume and should also allow increased contrast at the same concentration.[12]

Delayed Magnetic Resonance Images

Due to its higher T1-shortening and relaxivity, which seem to increase with time, there is an apparent advantage to the use of Gadovist together with late images: indeed, the conspicuousness of lesions increases with time after injection with Gadovist. This has been nicely demonstrated in the paper by Uysal et al.,[13] who found that the use of 1.0mol/l gadolinium chelate enabled them to detect an increased number of enhancing lesions and patients with active disease. They also found that a delay of five minutes after the injection of the gadolinium chelate might be sufficient to detect active lesions in patients with MS. We have also found that performing late imaging with Gadovist with sequential images being performed up to 12 minutes after administration enhances the capacitiy of Gadovist to detect MS lesions (see *Figures 2* and *3*).

Gadovist was the first commercially available MR contrast agent at a concentration of 1.0mol/l. This means that it is available at a higher

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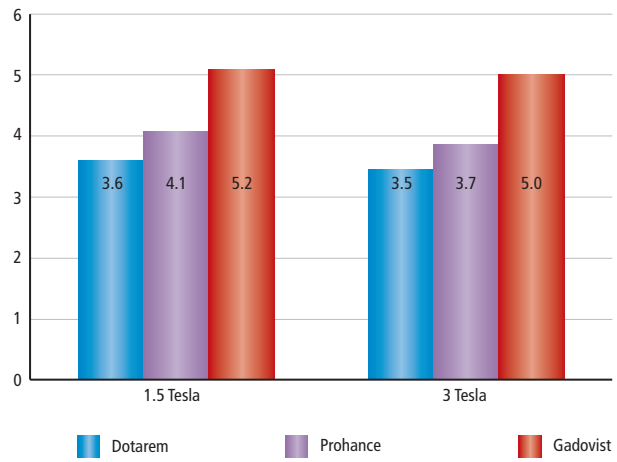
Figure 1: Relaxivity* – Macrocyclic Magnetic Resonance Contrast Media



** Relaxivity r1 of macrocyclic contrast media in plasma at 37°C (values: l/mmol/s). The high efficacy of Gadovist can to a large extent be explained by its higher relaxivity compared with other macrocyclic contrast media.*

concentration at the same dose: this can allow a double dose at the same injected volume, or allow the volume to be reduced by half while retaining the same effect as another (half-molar) compound.

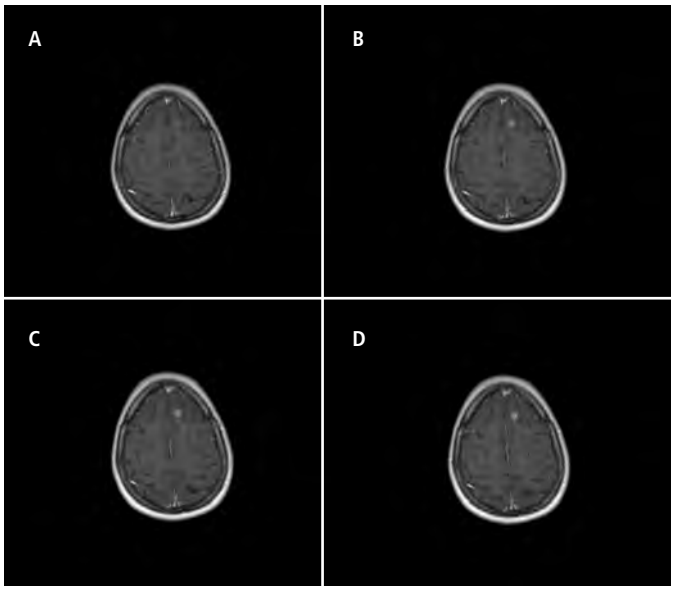
Safety Concerns and Nephrogenic Systemic Fibrosis

Recently, an association has been found between the administration of gadolinium compounds and the occurrence of nephrogenic systemic fibrosis (NSF).[14] Gadovist, which is a macrocyclic compound, seems more stable and much less susceptible to causing such complications. However, NSF does tend to occur in a more elderly population with co-morbidities that are often not present in the younger MS population. Indeed, NSF is mostly associated with cases of renal failure and patients who have received multiple doses of linear Gd-chelates. However, caution still needs to be exercised, and renal function should be tested.

Conclusion

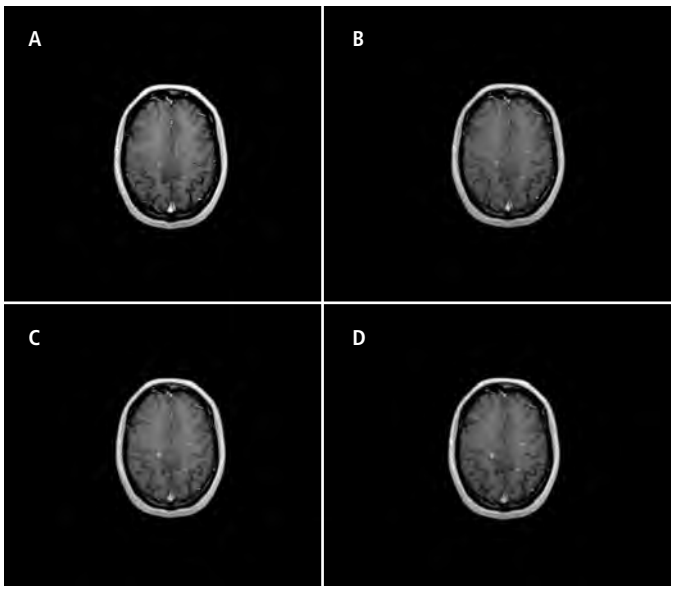
Gadovist is a safe gadolinium chelate compound that has been used successfully for neuroimaging with MRI of the nervous system for many years. Its advantages are a higher concentration and a higher relaxivity. This allows higher contrast at the same dosage, or lower injected volumes with maintained or even improved contrast effect. Due to the fact that it is a more stable compound that can be used at half volume, it should also be a safer molecule, which is important in the context of growing concern regarding NSF. ■

Figure 2: A 19-year-old Patient after Administration of Gadovist



Images of a 19-year-old patient at A. three, B. six, C. nine and D. 12 minutes after administration of Gadovist. There is a persistent increase in enhancement over time.

Figure 3: A 35-year-old Patient after Administration of Gadovist



Images of a 35-year-old patient at A. three, B. six, C. nine and D. 12 minutes after administration of Gadovist. There is a persistent increase in enhancement over time.

1. Ge Y, Multiple sclerosis: the role of MR imaging, *AJNR Am J Neuroradiol*, 2006;27:1165–76.
2. Simon JH, Li D, Traboulsee A, et al., Standardized MR imaging protocol for multiple sclerosis: Consortium of MS Centers consensus guidelines, *AJNR Am J Neuroradiol*, 2006;27(2): 455–61.
3. Polman CH, Reingold SC, Edan G, et al., Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria", *Ann Neurol*, 2005;58(6):840–46.
4. McDonald WI, Compston A, Edan G, et al., Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis, *Ann Neurol*, 2001;50(1):121–7.
5. Barkhof F, Filippi M, Miller DH, et al., Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis, *Brain*, 1997;120(Pt 11):2059–69.
6. Barkhof F, Rocca M, Francis G, et al.; Early Treatment of Multiple Sclerosis Study Group, Validation of diagnostic magnetic resonance imaging criteria for multiple sclerosis and response to interferon beta1a, *Ann Neurol*, 2003;53(6):718–24.
7. Lemke AJ, Sander B, Balzer T, et al., Safety and use of gadobutrol in patients with brain tumors (phase III trial), *ROFO*, 1997;167(6):591–8.
8. Essig M, Lodemann KP, Le-Huu M, et al., Intraindividual comparison of gadobenate dimeglumine and gadobutrol for cerebral magnetic resonance perfusion imaging at 1.5 T, *Invest Radiol*, 2006;41(3):256–63.
9. Tombach B, Benner T, Reimer P, et al., Do highly concentrated gadolinium chelates improve MR brain perfusion imaging? Intraindividually controlled randomized crossover concentration comparison study of 0.5 versus 1.0 mol/L gadobutrol, *Radiology*, 2003;226(3):880–88.
10. Benner T, Reimer P, Erb G, et al., Cerebral MR perfusion imaging: first clinical application of a 1 M gadolinium chelate (Gadovist 1.0) in a double-blinded randomized dose-finding study, *J Magn Reson Imaging*, 2000;12(3):371–80.
11. Vogl TJ, Friebe CE, Balzer T, et al., Diagnosis of cerebral metastasis with standard dose gadobutrol vs. a high dose protocol. Intraindividual evaluation of a phase II high dose study, *Radiologe*, 1995;35(8):508–16.
12. Rohrer M, Bauer H, Mintorovitch J, et al., Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths, *Invest Radiol*, 2005;40:715–24.
13. Uysal E, Erturk SM, Yildirim H, et al., Sensitivity of immediate and delayed gadolinium-enhanced MRI after injection of 0.5 M and 1.0 M gadolinium chelates for detecting multiple sclerosis lesions, *AJR Am J Roentgenol*, 2007;188(3):697–702.
14. Bongartz G, Imaging in the time of NFD/NSF: do we have to change our routines concerning renal insufficiency?, *MAGMA*, 2007;20(2):57–62.

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* Based on Rohrer M, et al, Comparison of magnetic properties of MRI contrast media solutions at different magnetic field strengths. Invest Radiol 2005; 40: 715-724
** M. Forsting, Neuroradiology (2006) 48 (Suppl. 2): 87

Gadovist® 1.0 mmol/mL solution for injection. Composition: 1 mL solution for injection contains 604.72 mg gadobutrol (equiv. 1.0 mmol) as active ingredient. **Excipients:** calcobutrol sodium, tromethamol, hydrochloric acid, water for injections. **Indications:** contrast enhancement in cranial and spinal magnetic resonance imaging (MRI). • Contrast enhanced MRI of liver or kidneys in patients with high suspicion or evidence of having focal lesions to classify these lesions as benign or malignant • Contrast enhancement in Magnetic Resonance Angiography (CE-MRA). **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Special warnings and precautions for use:** Gadovist® 1.0 should not be used in patients with uncorrected hypokalemia. In patients with severe cardiovascular disease Gadovist® 1.0 should only be administered after careful risk benefit assessment because only limited data are available so far. Gadovist® 1.0 should be used with special care in patients with known congenital long QT syndrome or a family history of congenital long QT syndrome; with known previous arrhythmias after taking medicinal products that prolong cardiac repolarisation; who are currently taking a medicinal product that is known to prolong cardiac repolarisation e.g. a Class III antiarrhythmic (e.g. amiodarone, sotalol). The possibility that Gadovist® 1.0 may cause torsade de pointes arrhythmias in an individual patient cannot be excluded (see section 5.3 Preclinical safety data). Since contrast medium elimination is delayed in patients with severely impaired renal function, the benefits must be weighed very carefully against the risks in such cases. In particularly severe cases, it is advisable to remove Gadovist® 1.0 from the body by extracorporeal haemodialysis: For removal of the agent from the body, at least 3 dialysis sessions within 5 days of the injection should be performed. No impairment of renal functions has been observed during clinical trials performed on a limited number of patients. Data are too limited to exclude the possibility of renal toxicity or aggravation of renal impairment. There have been reports of nephrogenic systemic fibrosis (NSF) associated with use of some gadolinium-containing contrast agents in patients with severe renal impairment (GFR < 30 ml/min/1.73m^2). As there is a possibility that NSF may occur with Gadovist® 1.0, it should only be used in these patients after careful consideration. Haemodialysis shortly after Gadovist® 1.0 administration in patients currently receiving haemodialysis may be useful at removing Gadovist® 1.0 from the body, but its potential to prevent NSF is unknown and should not be used as a preventative measure in other patient groups. Hypersensitivity reactions, as have been reported for other contrast media containing gadolinium, have also been observed after administration of Gadovist® 1.0. In patients with an allergic disposition the decision to use Gadovist® 1.0 must be made after particularly careful evaluation of the risk-benefit ratio. In rare cases delayed anaphylactoid reactions (after hours to days) have been observed. Like with other gadolinium containing contrast agents special precaution is necessary in patients with a low threshold for seizures. Gadovist® 1.0 is not recommended for use in population below age 18 due to a lack of data on safety and efficacy. **Undesirable effects:** Following adverse reactions have been observed in clinical trials. Uncommon (≥ 1/1,000 to < 1/100): Headache, Dizziness, Paresthesia, Dysgeusia, Nausea, Vasodilatation, Injection site pain, Injection site reaction. Rare (≥ 1/10,000 to < 1/1,000): Parosmia, Dyspnoea, Vomiting, Urticaria, Rash, Hypotension, Anaphylactoid reaction. Following additional adverse reactions have been reported from postmarketing spontaneous reporting: Rare (≥ 1/10,000 to < 1/1,000): Cardiac arrest, Tachycardia, Loss of consciousness, Convulsion, Conjunctivitis, Eyelid oedema, Respiratory arrest, Bronchospasm, Cyanosis, Oropharyngeal swelling, Cough, Sneezing, Face edema, Hyperhidrosis, Pruritus, Erythema, Circulatory collapse, Flushing, Feeling hot, Malaise, Anaphylactoid shock. Additional safety information: Short-lasting mild to moderate feelings of coldness, warmth or pain at the injection site have been uncommonly observed in association with the venous puncture or contrast medium injection. On paravascular injection Gadovist® 1.0 may cause tissue pain lasting up to several minutes. Hypersensitivity reactions (e.g. urticaria, rash, vasodilatation) have been uncommonly reported and were mostly of mild to moderate intensity. In rare cases anaphylactoid reactions ranging to shock may occur. Delayed anaphylactoid reactions (after hours to days) have been observed rarely. Patients with an allergic disposition suffer more frequently than others from hypersensitivity reactions. **Date of revision of text:** May 2007 **Please note!** For current prescribing information refer to the package insert and/or contact your local Bayer Schering Pharma organisation.
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