Gadobutrol 1.0-molar in Cardiac Magnetic Resonance Imaging (MRI) – Further Enhancing the Capabilities of Contrast-enhanced MRI in Ischaemic and Non-ischaemic Heart Disease?

a report by

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There are many things in life everybody wants more of, and this is particularly true for magnetic resonance imaging (MRI). The major challenge in the daily life of an MRI professional is gaining maximal image signal and contrast in a reasonable amount of time. The application of gadolinium (Gd)-based MR contrast material has offered contrast features in MRI that have been used and appreciated for almost 20 years in both neurological and whole-body MRI. For example, state-of-the-art MRI is not possible in brain tumours, vascular pathologies or focal liver disease without the use of Gd. Cardiac MRI has also benefited enormously from Gd enhancement; indeed, some of the most important and established cardiac MRI applications are based on the use of Gd contrast.1,2 Although there are strong data in support of the superiority of dedicated contrast-enhanced MRI techniques over other modalities in many clinical indications, there is still a need for improvements in image quality and stability, whether in terms of the hardware, software or ‘vettware’ (contrast agents). In terms of cardiac MRI, in general more contrast would be preferable since many cardiac pathologies are difficult to distinguish from normal myocardium. Therefore, the use of higher-concentration Gd compounds could improve the reliability of cardiac MRI. The aim of this article is to summarise recent knowledge about gadobutrol, the only approved 1.0-molar Gd contrast agent, in MR angiography (MRA) and neurological and whole-body MRI, and to provide an outlook on expected future developments in cardiac MRI.

Gadobutrol

Chemistry and Safety Profile

Most MR contrast media are based on Gd as a paramagnetic ion. The Gd3+ ion has strong magnetic properties, which lead primarily to a T1-relaxation shortening of protons and the production of a high signal in T1-weighted MR sequences. However, the free Gd3+ ion has to be bound in chelates to reduce unwanted side effects and create desirable pharmacokinetic properties.3 Many Gd-based contrast agents have been clinically approved and commercially available for more than a decade. Typically, Gd agents are extracellular, non-tissue-specific, non-protein-binding, water-soluble compounds such as gadopentetate dimeglumine (Gd-DTPA), gadoteridol (Gd-HPD30A), gadoterate (Gd-DOTA), gadoversetamide (Gd-DTPA-BMA) and gadodiamide (Gd-DTPA-BMA).4 Gadobenate dimeglumine (Gd-BOPTA) and gadofosveset, on the other hand, interact with serum albumin, resulting in a higher in vivo relaxivity and longer plasma half-lives. All of the above-mentioned compounds are prepared at a concentration of 0.5mol/l. Gadobutrol (Gd-BT-D30A, GadovistTM, Bayer Healthcare, Leverkusen, Germany) is the only approved 1.0-molar solution of Gd; it is approved for cranial and spinal MRI, MRI of the liver and kidneys and contrast-enhanced MRA. Its cyclic ligand forms a macrocyclic, non-ionic Gd chelate that is both thermodynamically and kinetically very stable; the chelate is neutral and highly hydrophilic with low protein-binding and good biological tolerance.5 The relaxivity of gadobutrol is higher than that of other non-protein-binding agents, leading to better image contrast.6 The safety profile of gadobutrol is comparable to that of the approved 0.5-molar Gd formulations. In a phase III multicentre trial, safety evaluations found a good tolerability, with only 4.6% of at least ‘possibly related’ adverse reactions in 435 patients undergoing gadobutrol-enhanced MRA at a mean dose of 0.18±0.05mmol/kg bodyweight.7 No influence on renal function or clinically relevant changes in safety parameters were observed. It was therefore concluded that Gd-1.0-molar-enhanced MRI at clinical doses is safe; other studies have confirmed this.8 As regards the risk of nephrogenic systemic fibrosis (NSF) associated with Gd-based contrast agents, there have been no reports of NSF in association with the sole administration of gadobutrol as of November 2007. In one case of a dialysis patient, the administration of multiple injections of Gd-DOTA and a single injection of gadobutrol led to NSF.

Clinical Features of Gadobutrol 1.0-molar

There are four ways to improve image contrast when using Gd contrast agents, irrespective of the applied MR technique:

- use higher Gd doses, which means injecting larger amounts of the drug;
- administer contrast agents with a higher relaxivity (one of the advantages of protein-binding formulations);
- form a ‘tight’ or ‘narrow’ bolus profile in MRA, which means there is a shorter but higher peak concentration of the agent at the time of sampling the centre of k-space – this can be achieved by applying optimised injection protocols; and
- use a higher-concentration contrast agent formulation, which will lead to image contrast improvement.

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Gadobutrol has promised to combine two of the above-mentioned features: compared with other non-protein-binding compounds it yields a higher relaxivity\(^9\) and, through the doubled concentration, tighter boluses seem possible with the same injection protocol and the same overall Gd dose. So, during ‘first-pass’ applications such as perfusion imaging and contrast-enhanced MRA, the reduction of the injection volume by 50% at comparable dose levels may yield a sharper bolus peak, which would be advantageous.

**The Use of Gadobutrol in Non-cardiac Clinical Applications**

Many studies have tested gadobutrol in MRA (see Figure 1). In a large multicentre trial, gadobutrol-enhanced MRA proved feasible compared with digital subtraction angiography (DSA) of the pelvic and thigh arteries.\(^{10}\) Goyen et al. found a dose-independent beneficial effect of gadobutrol, with contrast improvement in both whole-body and pelvic MRA.\(^{11,12}\) Another study in pelvic arteries confirmed these findings.\(^{13}\) On the other hand, no improvement has been found in pulmonary MRA\(^{14}\) or pulmonary perfusion imaging.\(^{15}\) This may be due to the T2\(^*\) effects of high Gd doses in central vessels or difficulties in bolus timing to hit peak enhancement. In time-resolved MRA, a tighter bolus could help to enhance only one of the vessel territories and avoid overlay (see Figure 1). In terms of liver imaging, higher image contrast was found in hepato-cellular carcinoma, although there was no additional diagnostic yield.\(^{16}\) An animal study confirmed a higher image contrast when using the 1.0-molar formulation compared with the 0.5-molar formulation.\(^{17}\) An early study by Vogl et al. showed both better contrast features and higher diagnostic accuracy in patients with brain metastases when using high-dose gadobutrol compared with standard-dose Gd-DTPA.\(^{18}\) In terms of brain perfusion MRI, dynamic susceptibility imaging is performed. The T1-shortening features of Gd are not useful here, but the T2\(^*\) effects that reduce the signal are used to depict and quantify cerebral perfusion defects in ischaemia or infarction. The relative signal reduction caused by the contrast agent depends on the dose, concentration and relativity of the contrast agent. Therefore, there is a benefit to the use of the 1.0-molar gadobutrol formulation compared with the 0.5-molar formulation in brain perfusion imaging.\(^{19}\) In two studies, Essig et al. confirmed the feasibility of gadobutrol in brain perfusion imaging, as well as its superiority to conventional Gd contrast agents.\(^{20,21}\) Thilmann et al. described the feasibility of gadobutrol also at 3T.\(^{22}\)

**Contrast-enhanced Cardiac Magnetic Resonance Imaging – How to Benefit from Gadobutrol**

MRI was used successfully in cardiac disease even before high-gradient scanners allowed ultra-fast imaging and contrast-enhanced cardiac imaging became possible. However, the major breakthrough of cardiac MRI as a reliable tool in clinical cardiology – indeed, it is the standard of reference in certain indications nowadays – has been based on contrast-enhanced applications. Three clinical applications of contrast-enhanced cardiac MRI have been broadly used. The following paragraphs will describe these three techniques, as well as proven and possible benefits arising from higher-concentration contrast agents such as gadobutrol.

**Myocardial Perfusion Imaging in Coronary Artery Disease**

There is a large amount of interest surrounding the use of non-invasive imaging techniques in the assessment of coronary artery disease (CAD), particularly in the early detection of CAD in its asymptomatic stages. A decrease in myocardial perfusion under stress conditions represents the first effect of occlusive CAD. Therefore, the assessment of myocardial perfusion seems to be the most promising basis for a non-invasive test to detect early CAD. Perfusion MRI – based on ultra-fast, time-resolved T1-weighted data sets acquired during injection of an intravenously administered contrast bolus using the first-pass kinetics of the contrast – has been developed to approach CAD.\(^{23-25}\) The resulting differences in signal intensity of normally perfused myocardium compared with myocardium that is undersupplied by an occluded coronary artery allow myocardial perfusion to be assessed (see Figure 2). The first successful patient study on perfusion MRI was published in 1991;\(^{26}\) several clinical studies have since confirmed its feasibility.\(^{25}\) Perfusion MRI requires the injection of a tight contrast bolus, which is tracked during the first pass across myocardial circulation. The increase of the blood pool and myocardial signal intensities due to the T1-shortening effect of gadolinium depends on the maximum arterial Gd concentration, which is proportional to the flow rate of the intravenous injection and inversely proportional to the cardiac output. The employed contrast doses vary between 0.025 and 0.15mmol/kg of extracellular Gd chelates in different studies,\(^{26}\) but most of the studies used 0.5-molar Gd formulations. Gadobutrol has also been tested for advantages in myocardial perfusion imaging on the basis that the opportunity for tighter boluses using 1.0-molar agents as appreciated in MRA should also hold true for myocardial perfusion imaging. The feasibility of gadobutrol has been proved in clinical studies;\(^{27,28}\) however, in an early study the higher concentration of 1.0-molar gadobutrol did not increase the degree of signal intensity changes nor sharpen the bolus profile at the low application volumes used for myocardial perfusion imaging.\(^{25}\) In this context, in a recent study of 25 CAD patients Fenchel et al. showed the ability of gadobutrol perfusion to detect CAD to be comparable to that of 0.5-molar agents, although “favourable signal properties were exhibited in phantom studies”.\(^{29}\) In summary, early clinical studies suggest that there is no clinical benefit of the higher-concentration Gd compound despite the superior contrast features. Further studies are needed to compare 0.5- and 1.0-molar agents.
Imaging  Magnetic Resonance Imaging

Figure 3: Transmural Scar in Chronic Myocardial Infarction

Patient with known pulmonary sarcoid and clinical suspicion of cardiac involvement. T1-weighted inversion-recovery TurboFLASH images acquired 10 minutes after intravenous administration of 0.2mmol/kg gadobutrol showing very high contrast between late gadolinium enhancement (LGE) areas and normal myocardium. A: 4-chamber view showing transmural LGE (arrow) of the apex and the apical parts of the lateral and septal left ventricular (LV) wall representing transmural scar (American Heart Association [AHA] segments 13, 14 and 17). B: Mid-ventricular short-axis slice of the LV showing wall thinning and transmural LGE (arrows) in the anterior and anterolateral wall (AHA segments 7 and 8).

Figure 4: Myocardial Oedema

T1-weighted inversion-recovery TurboFLASH images acquired 10 minutes after intravenous administration of 0.2mmol/kg gadobutrol showing very high contrast between late gadolinium enhancement (LGE) areas and normal myocardium. Arrows show mid-myocardial areas of subtle and weak late gadolinium enhancement (LGE) in the anteroseptal and inferolateral parts of the basal left ventricle (LV) wall representing transmural scar (American Heart Association [AHA] segments 2 and 3). This led to acute cardiac involvement of the sarcoid being diagnosed. Higher contrast between LGE and normal myocardium would be helpful – a possible benefit of gadobutrol?

Figure 5: Eccentric Hypertrophic Cardiomyopathy

Patient with known pulmonary sarcoid and clinical suspicion of cardiac involvement. T1-weighted inversion-recovery TurboFLASH images acquired 10 minutes after intravenous administration of 0.2mmol/kg gadobutrol showing very high contrast between late gadolinium enhancement (LGE) areas and normal myocardium. A: 3-chamber view with eccentric hypertrophy and subtle, not-well-defined late gadolinium enhancement (LGE) areas (arrows) representing fibrotic tissue in the basal and mid-portions of the anteroseptal wall (American Heart Association [AHA] segments 2 and 3). B: Basal short-axis view with mid-myocardial LGE (arrows) in the hypertrophic area of the anteroseptal wall. In both images, higher contrast between LGE and normal myocardium would be helpful – a possible benefit of gadobutrol?

Myocardial Viability Imaging – Scar Detection in Chronic Myocardial Infarction

Myocardial viability imaging is the most established and robust technique in contrast-enhanced cardiac MRI, and the ‘late gadolinium enhancement’ (LGE) method is at the forefront of MRI in clinical cardiology. LGE refers to delayed-enhancement imaging does not assess myocardial perfusion, but rather is used in the detection of myocardial changes such as scar, oedema, necrosis and fibrosis. The main application of LGE is differentiating functionally abnormal but viable (hibernating) myocardium from irreversibly damaged myocardium (scar) in patients with global or regional myocardial dysfunction. It has been shown that late accumulation of gadolinium in chronic myocardial infarction reflects irreversible damage. Studies in CAD patients have, in this context, proved MRI to be superior to standard methods. In recent years, LGE in chronic infarction has even been proved to be a prognostic factor for major cardiac events and cardiac mortality.

Therefore, LGE imaging has quickly become an established clinical tool and the standard of reference owing to its ease of application, robustness and unique value in differential diagnosis. In 2001, Simonti et al. designed an optimised electrocardiogram (ECG)-triggered, segmented inversion-recovery turbo-gradient echo sequence that has become the standard for this type of investigation. The key improvement over all previously used sequences is the use of an inversion pulse to produce maximum contrast between normal and abnormal myocardium after contrast administration. This sequence has been proved to be very robust and stable, yielding high contrast between LGE areas – representing scar – and normal, viable myocardium (see Figure 3). Some comparison studies published as abstracts or conference proceedings show that gadobutrol offers higher signal-to-noise and contrast-to-noise ratios in LGE of chronic myocardial infarction. However, due to the intrinsic high contrast between enhancing scar and normal myocardium, there may not be a significant benefit of gadobutrol compared with 0.5-molar Gd formulations. Further studies are needed to investigate whether gadobutrol can improve the technique in certain indications.

Late Enhancement in Cardiomyopathy and Inflammation

While LGE is highly sensitive for myocardial infarction, it is not specific for ischaemic damage since Gd generally accumulates in tissue with increased water content. Thus, LGE occurs in myocardial areas of fibrosis, inflammation and oedema of any kind where the extracellular volume is enlarged. The knowledge of different patterns and locations of LGE in specific diseases seems to facilitate the differential diagnosis of non-ischaemic heart disease. Gd-enhanced MRI has been applied in inflammatory diseases of the myocardium. In acute myocarditis and peri-myocarditis, as well as in chronic lymphocytic myocarditis, areas of LGE seem to represent higher activity of the inflammatory process. Friedrich et al. applied Gd to monitor tissue changes in viral myocarditis and found that MRI is able to identify localisation, activity and extent of the inflammation by defining the area of enhancement. LGE was found in the subendocardial, subepicardial or mid-portions of the left ventricular (LV) wall, but none of the subjects in this study showed transmural LGE. Therefore, the localisation of LGE may help to characterise myocarditis. Patients with cardiac sarcoid show patchy, diffuse or sharply demarcated LGE, which is partially transmural and may disappear or diminish after therapy (see Figure 4). Many other myocardial inflammatory or ‘infiltrative’ diseases also present with LGE. Secondary fibrotic tissue replacement as well as primary cardiomyopathy may present with LGE. In hypertrophic cardiomyopathy patients, a typical LGE pattern has been described in animal and human studies as being subepicardial or in the middle of the wall and not sharply delineated (see Figure 5). In contrast, patients with dilative cardiomyopathy often reveal a very sharp delineated band of mid-ventricular LGE, which has very recently been described as pathognomonic for this particular type of disease. Fibro-fatty myocardial replacement of the right ventricular (RV) wall has been reported to present with LGE in amyotrophic RV cardiomyopathy/dysplasia, which may make diagnosis easier in this particular patient cohort.
In general, the typical location and pattern of LGE help to distinguish cardiomyopathy from chronic infarction. Among the various non-ischaemic pathologies, LGE seems to enhance diagnostic capabilities. However, in contrast to acute or chronic infarction, in many cases of inflammation or cardiomyopathy only very weak and indistinguishable LGE may be seen. Often, one wishes to produce higher contrast to reliably distinguish hyperintense areas within the myocardium from artefacts. Although there are currently no available studies comparing gadobutrol with 0.5-molar Gd compounds, the large range of non-ischaemic heart diseases may be a target group for gadobutrol in view of stronger contrast leading to more reliable diagnosis.

Conclusions

Gadobutrol as the only approved 1.0-molar Gd-based MR contrast agent has been widely used in clinical routine. The combination of higher Gd concentration and improved relaxivity makes it a valuable tool when used like any other conventional Gd-based agent in applications—such as brain perfusion imaging and, particularly, MRA—gadobutrol has been proved to be superior to the conventional extracellular 0.5-molar agents. With regard to contrast-enhanced applications in cardiac MRI, only a few studies are available on the possible additional value of gadobutrol. In viability imaging using the LGE technique, gadobutrol seems to offer higher contrast between scar and normal myocardium. However, due to the high intrinsic contrast, there may be no significant benefit in terms of diagnostic quality. While gadobutrol seems feasible and equivalent to other Gd compounds in myocardial perfusion imaging, no clinical benefit has been exhibited so far. The field of LGE in non-ischaemic myocardial disease such as inflammation and cardiomyopathy seems to be the most exciting. Although no studies have been published on this particular topic, it can be suggested that conditions with low intrinsic contrast benefit from both the higher Gd concentration and the relaxivity of gadobutrol compared with other compounds. In myocardial areas of subtle fibrosis or oedema, one has to rely on the highest possible contrast. Therefore, larger studies are needed to prove the theory that gadobutrol offers higher diagnostic accuracy.