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Defining contrast: latest data on the safety of gadobutrol-enhanced MRI and efficacy in CNS applications



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Gadolinium-based contrast agents for magnetic resonance imaging have broadly similar tolerability profiles, but can vary in their efficacy for image enhancement. In this article, the latest efficacy and safety data for 1.0 molar gadobutrol are reviewed and compared against 0.5 molar agents.

Contrast-enhanced magnetic resonance imaging as a valuable diagnostic tool

Since its emergence in the 1980s, magnetic resonance imaging (MRI) has now become a routine imaging tool with many clinical applications. The use of gadolinium (Gd)-based contrast agents (GBCAs) with MRI improves the visualisation of pathologies in the central nervous system (CNS), liver, kidney, heart, and whole-body imaging, as well as in angiographic, perfusion, and other functional MRI applications [1].

Newer developments in MRI techniques, many in conjunction with contrast agents, are increasing the applications of MRI further. These developments include the emergence of higher field strength magnets, providing better image clarity; faster, more dynamic imaging protocols, which have expanded the utility of MRI; and modern post-processing software, which allows the radiologist to obtain more information from the data acquired.

A number of GBCAs are available for use in contrast-enhanced MRI. Increasing evidence is characterising differences in the efficacy and safety of these agents that are relevant for clinical practice.

Gadolinium-based contrast agents: how are they different?

Before discussing differences between GBCAs, we must first appreciate the principles of contrast-enhanced MRI. MRI signals are generated from the relaxation of particles within the body tissues after they are ‘excited’ by magnetic pulses. Gadolinium is a paramagnetic element which shortens the relaxation times of hydrogen protons (so-called ‘T1 shortening’). GBCAs reduce relaxation times to differing extents, as a function both of their relaxivity—which is a measure of an agent’s ability to reduce the relaxation time—and of their local tissue Gd concentration [2–4]. The more efficient a GBCA is in shortening the tissue T1, the higher is the signal that can be detected.

Contrast agents can also differ in their safety profile, especially with regard to their chelate stability.

been associated with the rare syndrome of nephrogenic systemic fibrosis (NSF) in patients with severe renal impairment [5]. All GBCAs consist of a central Gd³⁺ ion surrounded by a chelating ligand, but the chelate complexes of GBCAs differ in their electrical charge and structure, which impacts on their stability [6, 7].

There are two main categories of chelate structure: linear chelates, in which the ligand wraps around the Gd³⁺, but does not enclose it, and macrocyclic chelates, which consist of a rigid cage-like ligand around the Gd³⁺. Macrocyclic chelates have a reduced propensity for dechelation.

Gadobutrol—the unique gadolinium-based contrast agent

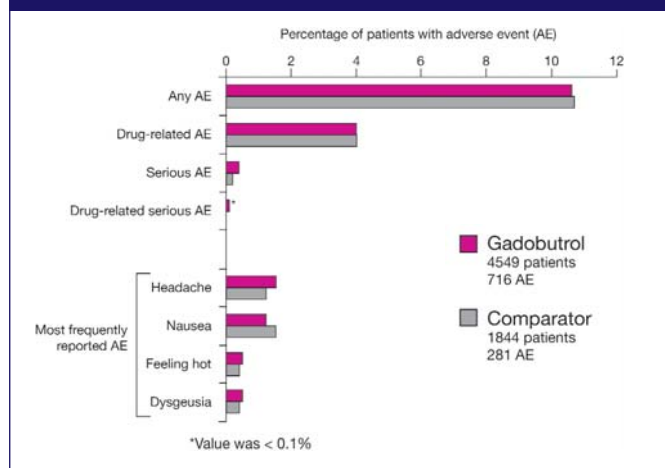
Gadobutrol (Gadovist/Gadavist, Bayer HealthCare) is formulated at a gadolinium concentration of 1.0 mol/L, which is twice the concentration of other available GBCAs. As noted above, a higher local gadolinium concentration is associated with improved imaging performance, and it additionally allows a smaller injection volume to be used, providing a more compact bolus geometry that is favourable in dynamic studies, e.g. angiography and perfusion techniques [8]. Gadobutrol possesses high relaxivity and has the highest available T1 shortening per unit volume among available GBCAs, see Table 1. Gadobutrol is also a macrocyclic agent, the class with the highest complex stability, and as a result, gadobutrol has been placed in the lowest risk category for NSF [5]. This unique combination of properties contributes to the favourable efficacy and safety profile of gadobutrol.

Unchelated Gd is potentially toxic, and the release of Gd³⁺ ions into the body has

Table 1: Comparison of T1 shortening of 1.0 molar gadobutrol and the 0.5 molar GBCAs—calculated from r¹ relaxivity data at 37°C taken from Rohrer et al. [4]

Gadolinium-based contrast agents (GBCAs)	T1 shortening per unit volume (second)
Gadobutrol (Gadovist/Gadavist)	1.034
Gadobenate dimeglumine (MultiHance)	0.949
Gadoteridol (ProHance)	0.886
Gadodiamide (Omniscan)	0.865
Gadopentetate dimeglumine (Magnevist)	0.853
Gadoversetamide (Optimark)	0.853

Figure 1: Adverse events for gadobutrol and comparator agents in clinical trials [16]



Gadobutrol is approved for a broad range of indications at a recommended dose of 0.1 mmol/kg body weight (bw) for both adult and paediatric use—although adult dosages up to 0.3 mmol/kg bw are approved in several regions. Gadobutrol is administered intravenously as a bolus injection.

Efficacy studies have investigated the advantages of gadobutrol compared with other GBCAs in numerous applications [9-15]. In addition, the safety profile of gadobutrol has been characterised in both clinical trials and routine clinical use. Some of the latest published studies on gadobutrol are summarised below.

The safety of gadobutrol—experience from clinical trials and everyday clinical use

Voth et al. recently reviewed the safety and tolerability data for gadobutrol, based on experience in 34 clinical trials and on surveillance studies now estimated to include more than 6.1 million administrations [16].

Clinical trial data

Clinical trials investigating gadobutrol and comparator GBCAs have included 5,545 patients in total, including patient subgroups with coexisting medical disorders (renal or hepatic impairment, cardiovascular disorders) and paediatric patients aged 2–18 years.

Adverse events (AEs) associated with gadobutrol were reported in 182/4,549 (4.0%) patients overall. This incidence was similar to that of comparator GBCAs, where drug-related AEs were reported in 74/1,844 patients (4.0%), see Figure 1. The frequency of AEs associated with gadobutrol was similarly low in patients with severe/moderate renal im-

pairment (9/366, 2.5%), severe/moderate hepatic impairment (9/214, 4.2%), and cardiovascular disorders (42/1,506, 2.8%), as well as in paediatric patients (8/138, 5.8%).

The most common AEs associated with gadobutrol include headache (1.5%), nausea (1.2%), injection-site reaction (0.6%), dysgeusia (0.5%), and feeling hot (0.5%). Comparator GBCAs showed a similar AE profile, see Figure 1.

Clinical use data

From the first approval of gadobutrol in 1998 up to September 2010, worldwide surveillance has identified 1,175 suspected adverse drug reactions. Of these reports, 317 were classified as serious events, including cardiac arrest, respiratory arrest, anaphylactoid shock, and NSF-like symptoms.

NSF-like symptoms have been recorded in 10 cases after the reported administration of gadobutrol. For seven cases, insufficient information was available for further assessment, while in three cases an association of NSF with administration of gadobutrol could not be excluded. In no case was a definite causal role for gadobutrol determined.

The safety profile of gadobutrol in worldwide clinical use is therefore broadly consistent with the profile reported in clinical trials. The tolerability of gadobutrol is confirmed in patient subgroups with coexisting disorders and is equivalent to other GBCAs.

The efficacy of gadobutrol for detecting and characterising brain lesions

Imaging of brain lesions is the most extensively investigated application of contrast-enhanced MRI. The efficacy of a GBCA to aid in localising and characterising brain lesions influences the accuracy of diagnosis and decisions for treatment planning. Treatment algorithms for choosing between whole-brain irradiation, surgical resection, or stereotactic surgery incorporate the number and size of brain lesions derived from imaging studies.

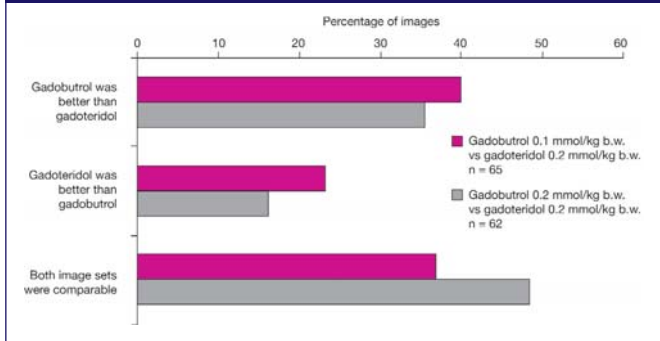
Two recent trials have investigated the characteristics of gadobutrol compared with other macrocyclic GBCAs for imaging brain lesions [17, 18]. Both trials used an intraindividual trial design, by which two (or more) GBCAs are administered using the same protocol to the same patients, separated by an appropriate interval; intraindividual trials are widely used for comparing the efficacy of GBCAs.

Gadobutrol versus gadoteridol for imaging brain metastases

Katakami et al. compared the efficacy of a single or a double dose of 1.0 molar gadobutrol (0.1 and 0.2 mmol/kg bw) against a double dose of 0.5 molar gadoteridol (0.2 mmol/kg bw, ProHance, Bracco Diagnostics) in 151 patients with known or suspected brain metastases [17]. For safety reasons, a standard 0.1 mmol/kg bw gadolinium dose is widely employed at centres for initial investigation, with use of increased doses in cases of diagnostic doubt, although some centres employ the 0.2 mmol/kg bw dose initially because of its improved imaging performance. In this study, contrast-enhanced images were evaluated in blinded readings by three independent, experienced radiologists.

A single dose of gadobutrol (0.1 mmol/kg bw) was non-inferior in identifying a similar number of lesions compared with gadoteridol (0.2 mmol/kg bw). The degree of contrast enhancement and the delineation of lesion borders were rated 'good' or 'excellent' for the majority of lesions using both agents. In terms of

Figure 2: Radiologists' confidence in contrast agent for radiosurgery planning [17]



confidence for planning of stereotactic radiosurgery, however, raters assessed gadobutrol to be superior to gadoteridol in twice as many cases as they rated gadoteridol superior to gadobutrol, see Figure 2; the two gadobutrol doses were rated equivalent.

The authors concluded that single-dose gadobutrol (0.1 mmol/kg) is as effective as double-dose gadoteridol (0.2 mmol/kg) for the detection of brain metastases, and that this gadobutrol dose can be used successfully for treatment planning.

Gadobutrol versus gadoterate meglumine for imaging cerebral lesions

Anzalone et al. compared 1.0 molar gadobutrol and 0.5 molar gadoterate meglumine (Dotarem, Guerbet), both at 0.1 mmol/kg bw, for imaging neoplastic cerebral lesions [18]. This multicentre study included 136 patients with CNS pathologies including meningiomas, glial tumours, metastases, and pituitary adenomas. Three blinded radiologists rated images for overall preference of GBCA and for specific features including intensity of lesion enhancement, lesion delineation, and information on the internal lesion structure.

In the overall reader assessment, gadobutrol was preferred in 32% of procedures and gadoterate meglumine was preferred in 12% of procedures—representing a statistically significant difference in favour of gadobutrol ($p = 0.0004$), see Figure 3. In addition, gadobutrol was rated significantly superior to gadoterate meglumine for lesion enhancement and for information on internal lesion structure ($p < 0.0001$ and $p = 0.004$, respectively), while the GBCAs

were equivalent for lesion delineation, see Figure 3.

The authors concluded that gadobutrol provides superior imaging performance to gadoterate meglumine at the same dose for the characterisation of CNS lesions.

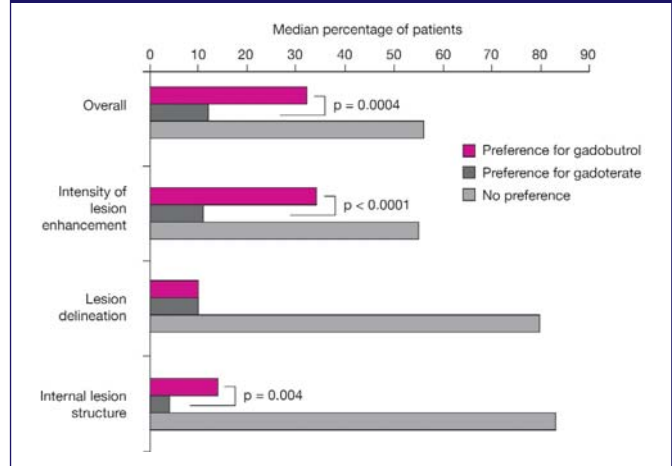
Conclusion

The use of GBCAs improves the imaging performance of MRI in many indications, leading to increased confidence in diagnosis and treatment planning. The GBCAs available differ in their physical characteristics including their ability to shorten tissue relaxation times, which impacts their efficacy for imaging. Their chelate structures also differ, with relevance for their propensity to release Gd^{3+} ions.

Gadobutrol is a 1.0 molar agent with a stable chelate structure and the highest T1 shortening among currently available agents. The tolerability profile of gadobutrol is comparable to that of other available GBCAs, and is consistent over 10 years of experience in clinical trials and routine clinical use.

Recent studies have reported that gadobutrol demonstrates enhanced imaging performance in CNS imaging compared with other macrocyclic GBCAs with similar chelate stability. Gadobutrol was preferred to gadoteridol by radiologists for imaging of brain metastases relevant to treatment planning, and was favoured over gadoterate meglumine for characterisation of a range of brain lesions.

Figure 3: Radiologists' preference of contrast agent for imaging brain lesions [18]



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