

Are All Gadolinium-based Contrast Agents Similar? The Importance of High Stability, High Relaxivity and High Concentration

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Abstract

Gadolinium-based contrast agents (GBCAs) are commonly used to enhance image acquisition via magnetic resonance imaging, but they differ in their physicochemical characteristics and therefore their function. The stability, concentration and relaxivity of a GBCA can have a major impact on clinical efficacy. Stability is related to safety. GBCAs can be categorised into three stability classes: non-ionic linear agents, ionic linear agents and macrocyclic agents, in order of increasing stability. Relaxivity and concentration are contributing factors to the level of enhancement that can be achieved with any given GBCA. Gadobutrol, gadobenate and gadoxetic acid have relatively high relaxivities. Among these compounds, only gadobutrol is commercially available at a higher concentration of 1.0M, whereas the others are used at a standard concentration of 0.5M. With high stability, relaxivity and concentration, gadobutrol has been shown in a number of clinical studies to be safe while improving image enhancement with increased conspicuity and sensitivity over other commonly used GBCAs.

Keywords

Gadolinium-based contrast agent (GBCA), contrast-enhanced magnetic resonance imaging, stability, relaxivity, concentration

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Since the original conception and introduction of magnetic resonance imaging (MRI) gadolinium-based contrast agents (GBCAs) in the 1980s, many such contrast agents have been approved for use in contrast-enhanced MRI. These contrast agents have been used extensively in a large range of indications, particularly central nervous system examinations, as well as neurodegenerative diseases and tumoural disease processes, among others.

Contrast enhancement has enabled improved tissue contrast and lesion characterisation and more sensitive detection of even very small lesions. The differences between the molecular structures of the gadolinium chelates affect their physicochemical characteristics. Greater importance has recently been placed on GBCAs and chelate stability, particularly with the possible association between the development of nephrogenic systemic fibrosis (NSF) in patients with kidney failure.¹⁻³

In response to the growing interest in this topic, this article will address the differences between gadolinium-based MRI contrast agents with regard to their molecular structure and physicochemical properties, providing evidence of the advantages of some compounds in terms of stability, relaxivity and concentration.

Molecular Structure and Physicochemical Characteristics

GBCAs consist of the active substance gadolinium and a chelating agent. They can be categorised by their chemical structures into linear and macrocyclic agents and further subdivided by their charge (ionic or non-ionic). While differences do exist among the

gadolinium compounds in terms of various physicochemical characteristics, stability, concentration and relaxivity appear to have a major clinical impact.

Stability

The chelation of gadolinium to organic ligands promotes bio-distribution within the extracellular interstitial space while enhancing renal filtration.² After intravenous administration, GBCAs distribute into accessible extracellular spaces, with a distribution half-life of approximately 10 minutes.⁴ GBCAs are typically excreted by the kidneys, with an elimination half-life of approximately 90 minutes in patients with normal renal function. Over 90% of the injected dose is eliminated renally within the first 24 hours.^{2,5} By comparison, patients with reduced kidney function encounter a prolonged elimination half-life of several hours, depending on the degree of renal impairment, with >80% of the administered dose excreted over the subsequent week.⁶ Notably, renal impairment does not affect the extracellular distribution half-life.⁷

The greatest concern regarding the stability of gadolinium chelates relates to the risk of transmetallation, where gadolinium has the potential to be exchanged between ligands or even be released as a free Gd³⁺ ion and retained within the body. Great emphasis has been placed on gadolinium chelate stability *in vivo* and patient safety in recent years, particularly given the possible association with the occurrence of NSF.¹⁻³

With the gadolinium ion tightly caged within the ligand cavity by virtue of a rigid and pre-organised ring (see *Figure 1*), the macrocyclic

gadolinium chelates are generally more stable than their linear counterparts.^{8,9} In a recent investigation into the stability of GBCAs, the rates of dissociation of Gd^{3+} ions were determined by incubating the gadolinium compounds in human serum over 15 days at 1mmol/l under physiological conditions (pH 7.4, 37°C).⁹ The non-ionic linear gadolinium chelates were found to be the least stable, with the greatest propensity to release Gd^{3+} ions into native human serum. Non-ionic chelates were followed by ionic linear compounds and finally macrocyclic compounds (see *Figure 2A* and *Table 1*). Notably, the release of Gd^{3+} ions by the macrocyclic compounds gadoterate (Dotarem), gadoteridol (ProHance) and gadobutrol (Gadovist) was below the detectable limit of quantification throughout the 15-day incubation period.

The addition of 10mmol/l of inorganic phosphate to human serum mimics one of the many conditions of acute renal insufficiency, although the phosphate levels are approximately triple those of typical clinical conditions of patients on dialysis. Under these conditions, the initial rates of Gd^{3+} release from formulated versions of gadodiamide (Omniscan) and gadoversetamide (OptiMARK) increased by approximately 100-fold. These two contrast agents are similar in that both are linear, non-ionic agents and have the lowest thermodynamic stability constant among the GBCAs. After 15 days, gadodiamide and gadoversetamide had released about 37% of the total amount of Gd^{3+} , which is roughly 1.8-fold compared with native serum (see *Figure 2B*). While the ionic linear compounds also exhibited a 12–30-fold accelerated rate of Gd^{3+} release in the presence of elevated phosphate levels, the total amount of Gd^{3+} released after 15 days was comparable to that of native serum. Notably, the elevated phosphate levels had no discernable effect on the release of Gd^{3+} ions from the macrocyclic contrast agents. The GBCAs can therefore be divided into three distinct stability classes: non-ionic linear agents, ionic linear agents and macrocyclic agents.

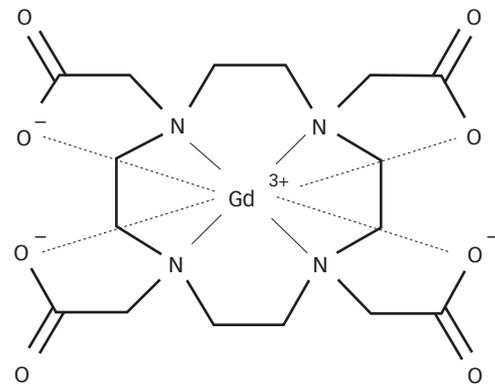
Relaxivity and Concentration

The relaxivity and concentration of any given contrast medium are properties that contribute to an agent's efficacy via the shortening of relaxation times and the resulting enhancement. By definition, relaxivity values are concentration-normalised data. Being independent of gadolinium concentration, the effects of local concentrations of contrast are not accounted for. The relaxivity of different gadolinium chelates had previously been shown to decrease at increasing magnetic field strengths (see *Figure 3*).¹⁰ Significantly different dependencies of relaxivities on field strength exist between GBCAs. Gadobutrol (Gadovist), gadobenate dimeglumine (MultiHance) and the liver-specific gadoxetic acid (Primovist) consistently exhibited higher relaxivity relative to the other compounds across the different magnetic fields that are commonly used in clinical practice.

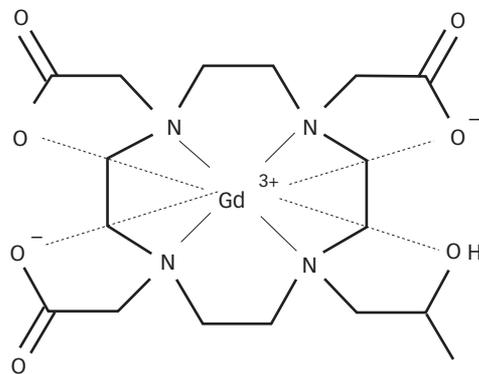
T1 shortening – the parameter that directly influences the available signal intensity in T1-weighted, contrast-enhanced MRI – is also affected by the concentration of the contrast medium. The local contrast medium concentration in turn depends on a number of intrinsic, physical and technical factors, including:

- the cardiovascular physiology of a particular individual;
- the region of interest;
- the injection rate (ml/s);
- the injected dose (mmol); and
- the concentration of the injected contrast agent.

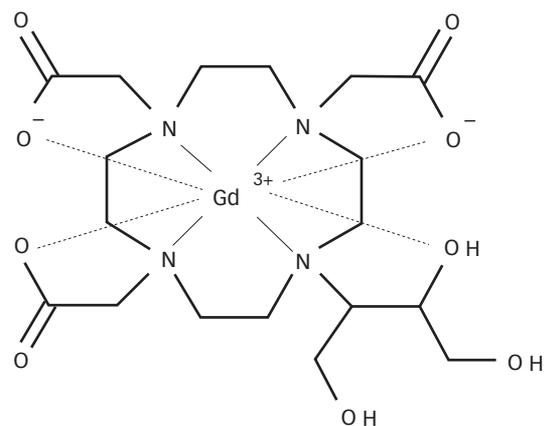
Figure 1: Molecular Structures of the Macrocyclic Chelates



Gadoterate meglumine



Gadoteridol



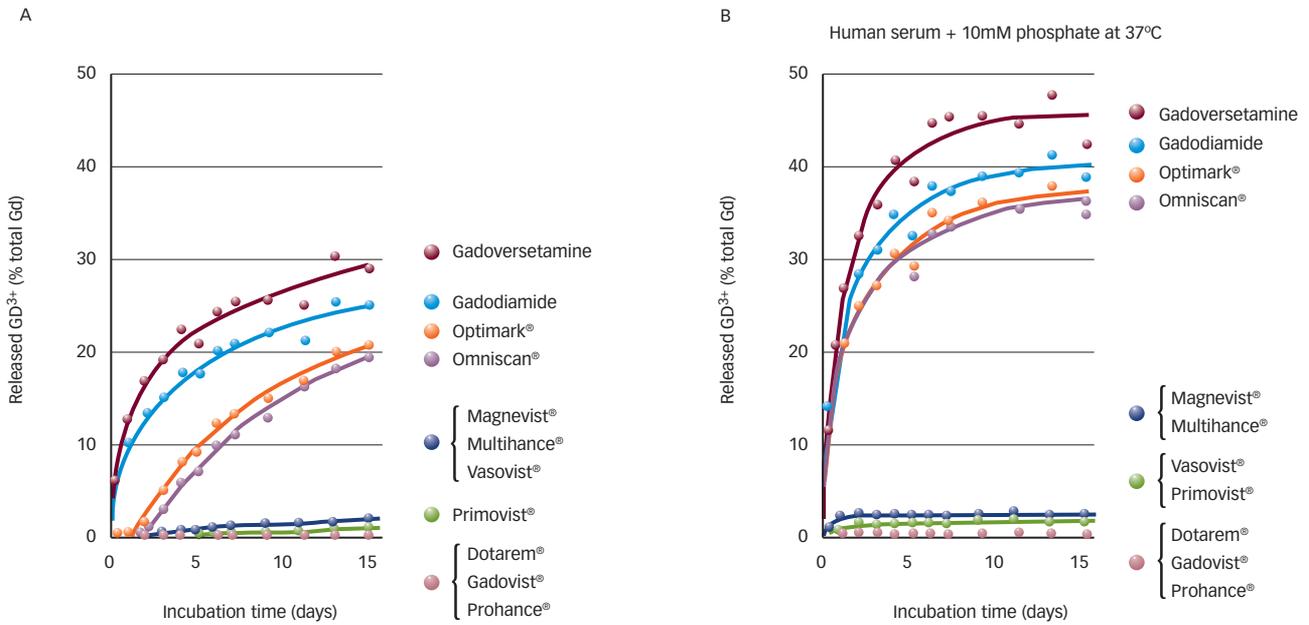
Gadobutrol

In one study using an animal model, identical bolus injections of gadobutrol at two different concentrations resulted in a higher concentration in the common carotid artery by approximately 30% with the 1.0M solution compared with the 0.5M solution.¹¹ Many other studies have since demonstrated a concentration-dependent effect on T1 shortening and imaging enhancement.^{12–16}

Greater Enhancement and Improved Detection

Stability, concentration and relaxivity each have an obvious impact on the clinical performance of a gadolinium chelate. While stability can be linked to safety, relaxivity and concentration can directly

Figure 2: Release of Gd³⁺ into Native Human Serum at 37°C



The release of Gd³⁺ ions from gadolinium-based contrast agents (GBCAs) over 15 days at 1mM at 37°C in native human serum from healthy volunteers (A) and with the addition of 10mmol/l phosphate (B). Source: Frenzel, 2008.⁹

Table 1: Gadolinium-based Contrast Agents by Stability

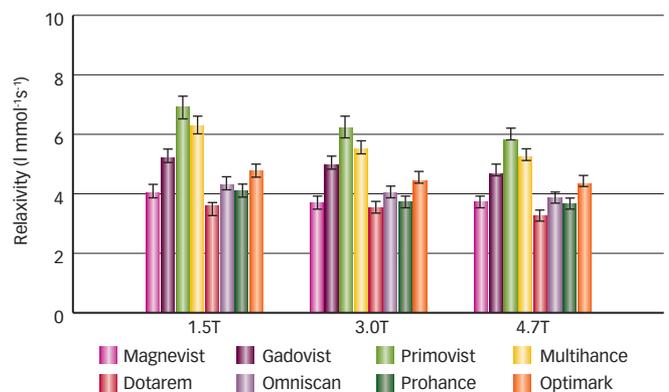
Contrast Agent	Trade Name	Initial Rate of Gd ³⁺ Release (%/day)	Gd ³⁺ Release after After 15 Days (% of total Gd ³⁺)
Gadodiamide	(active agent)	24	25
Gadoversertamide	(active agent)	17	29
Gadodiamide	Omniscan	0.16	20
Gadoversertamide	OptiMARK	0.44	21
Gadopentetate	Magnevist	0.16	1.9
Gadobenate	MultiHance	0.18	1.9
Gadofosveset	Vasovist	0.12	1.8
Gadoxetic acid	Primovist	0.07	1.1
Gadobutrol	Gadovist	<0.007	<0.1
Gadoteridol	ProHance	<0.007	<0.1
Gadoterate	Dotarem	<0.007	<0.1

Source: Frenzel, 2008.⁹

affect the quality of the obtained image via the mode of action and shortening of relaxation times. Advantages in terms of concentration have previously been proposed; for example, the relatively high gadolinium concentration of gadobutrol at 1.0M potentially allows for a 50% reduction in injection volume compared with equimolar dosages of the standard gadolinium chelates at 0.5M. A smaller and more highly concentrated bolus volume may allow for increased intravascular concentration. This is on top of advantages in perfusion-weighted imaging and multiphasic ultra-fast imaging techniques, including magnetic resonance angiography (MRA) and time-resolved MRA.¹⁷ It is also possible that a better-defined bolus stemming from this improved bolus effect may also enhance the contrast-to-noise ratio (CNR) and therefore the imaging characteristics of first-pass MRI techniques.¹⁸

Tombach et al. had previously compared gadobutrol at concentrations of 0.5 and 1.0M in an intra-individually controlled study with magnetic

Figure 3: Relaxivity of Gadolinium Chelates Under Increasing Magnetic Fields



Relaxivities of gadolinium chelates measured in bovine plasma at 37°C at field strengths of 1.5, 3 and 4.7T. Source: Rohrer et al., 2005.¹⁰

resonance brain perfusion imaging.¹⁹ With the higher-concentration formulation of 1.0M, a significantly smaller bolus width was achieved at the half maximum signal intensity decrease. Moreover, the smaller mean peak time observed, higher contrast and higher signal-to-noise ratio (SNR) ultimately led to better brain perfusion images than those obtained with the 0.5M formulation.

In another study where 0.5M gadopentetate (Magnevist), 0.5 M gadobenate and 1.0M gadobutrol were compared in a pelvic 3D MRA setting, the quality of images obtained with either gadobutrol or gadobenate were similar in their superiority over those obtained by gadopentetate when administered at an equal dose and injection rate.²⁰ Undiluted gadobutrol performed better than its diluted counterpart against gadobenate, although statistically significant results were not reached. The results still suggest that a

highly concentrated and compact bolus of gadobutrol can confer substantial improvements in image quality, quantifiable through significantly higher SNRs and CNRs.

Several studies have evaluated the effects of gadolinium chelates on the shortening of relaxation times and contrast enhancement, knowing that there is an influence on these outcomes by both relaxivity and concentration. Data originating from a rat brain tumour model show that the application of gadobutrol at the same gadolinium dose per weight results in markedly higher SNR and CNR values than gadopentetate and gadoterate at three Tesla (3T).²¹ Superior enhancement was observed with the double-concentrated gadobutrol at each post-contrast time-point assessed.

More recent studies have compared the use of 0.5 and 1.0M contrast agents in the imaging of brain tumours. One study used exogenous contrast-based, T₂*-weighted, gradient-recalled echo-planar imaging to determine intracranial perfusion characteristics in 11 patients (six with intra-axial and five with extra-axial tumours). Patients received either 5ml of 1.0M gadobutrol or 10ml of 0.5M gadopentetate.²² The investigators assessed the maximal signal change in the region of interest as the primary outcome measure for perfusion-weighted imaging. They found that at 3T, the higher concentration of 1.0M gadobutrol provided significantly better delineation between grey and white matter. It also better defined the presence of highly vascularised brain tumour tissue than the standard 0.5M strength gadopentetate.

Visualisation of brain metastases has also been reported to be significantly improved with gadobutrol over gadopentetate and the detected lesions were more conspicuous.¹⁶ In this study, equal gadolinium dosages of each contrast agent were injected in a fully randomised sequence into 27 patients with at least one cerebral metastasis, with 18 hours between examinations with contrast-enhanced MRI. A total of 67 metastatic lesions were detected using gadobutrol enhancement compared with 65 lesions detected with gadopentetate; in two cases lesions were observed only with gadobutrol (see Figure 4). A comparison of images on a qualitative level by two fully blinded and experienced neuroradiologists revealed improved lesion conspicuity with gadobutrol in 10/27 of cases (p=0.002; see Figure 5). The comparison also revealed equivalent conspicuity in 17/27 cases, with no reported improvements in conspicuity for gadopentetate over gadobutrol.

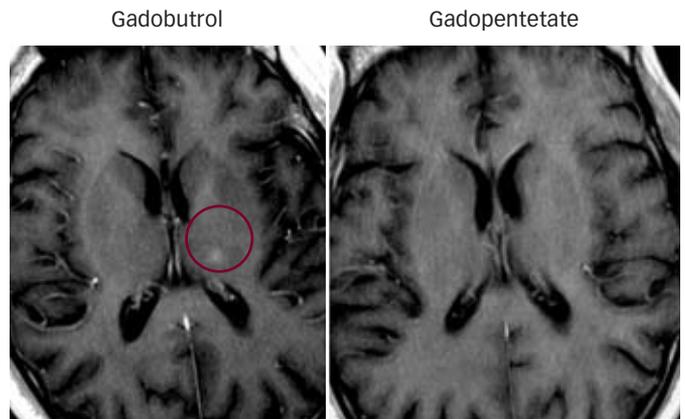
The results from these small studies suggest that highly concentrated GBCAs confer significant advantages in imaging enhancement.

Summary and Conclusions

The differences between the physicochemical properties of GBCAs have an impact on the stability of the chelate. *In vitro* experiments have shown that the macrocyclic compounds (gadoterate, gadoteridol and gadobutrol) are the most stable, with an undetectable release of Gd³⁺ ions under physiological conditions.

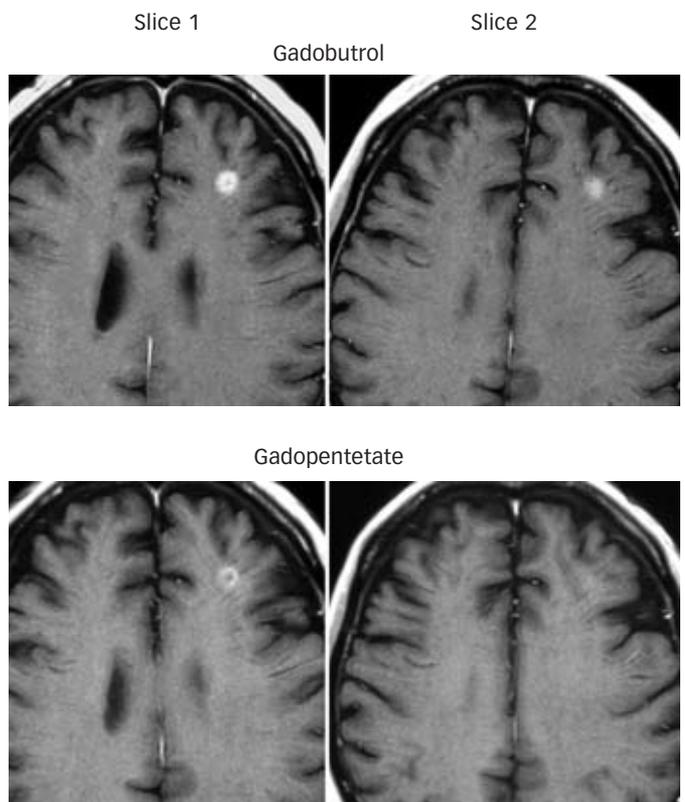
High relaxivity, correlating to improved enhancement, has also been associated with certain gadolinium chelates over others. Studies suggest that highly concentrated formulations may be advantageous, with reduced injection volumes and potentially beneficial bolus effects with a smaller bolus volume and increased intravascular concentration for dynamic examinations. Indeed, emerging data from

Figure 4: Detection of Lesions with Gadobutrol, Undetectable by Gadopentetate, at Equal Gadolinium Doses



Identical slices acquired from a 64-year-old male patient with lung cancer. An additional lesion (circled) was detected in the left thalamus with gadobutrol (left) compared with gadopentetate (right).
Source: Anzalone et al., 2009.¹⁶ Reprinted with permission.

Figure 5: Improved Conspicuity with Gadobutrol and Gadopentetate at Equal Gadolinium Doses



Identical slices acquired from a 70-year-old female patient with breast cancer. The left frontal F2 subcortical lesion is better defined, more conspicuous and more easily assessable with gadobutrol (top) than with gadopentetate (bottom).
Source: Anzalone et al., 2009.¹⁶ Reprinted with permission.

several studies now show that the higher-molar formulation of gadobutrol appears to confer significant advantages in imaging with respect to conspicuity in lesion visualisation and sensitivity in lesion detection compared with other commonly used gadolinium chelates at the standard 0.5M. ■

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