



Image augmentation in MRI – critical factors in selecting optimal contrast agents

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Contrast-enhanced magnetic resonance imaging has become a standard technique for diagnosis and disease management across a wide range of conditions. Choosing between the numerous gadolinium-based contrast agents now available requires an understanding of their different properties and how these relate to safety and efficacy.

The past 20 years has seen a huge expansion in the use of contrast agents in magnetic resonance imaging (MRI). The resulting improvement in diagnostic accuracy and sensitivity has made contrast-enhanced MRI a standard procedure in the management of an increasing number of diseases. Most of the MRI contrast agents approved for human use contain gadolinium (Gd), a paramagnetic element of the lanthanide series. Gd-based contrast agents (GBCAs) are positive contrast agents that result in increased signal intensity on T1-weighted images. The first of these, gadopentetate dimeglumine (Magnevist) was approved for clinical use in whole-body MRI in 1988 and a further eight GBCAs have since become available (see Table 1). In order to

optimise the workflow in a radiology department, it is desirable that most patients can be diagnosed with one preferred contrast agent. Weighing up the options requires a good understanding of the properties of the different compounds and what these mean for the safety of the patient and the quality of the image.

the Gd ion is chelated into either a linear or a macrocyclic structure (see Table 1). The linear agents are commonly further categorised, based on the net charge of the complex, into non-ionic and ionic agents. These three categories of GBCA differ in terms of their stability, i.e. their propensity to release the Gd from the chelate. *In vitro* studies have shown that the macrocyclic chelates (gadobutrol (Gadovist), gadoterate meglumine (Dotarem) and gadoteridol (ProHance)) are the most stable, whereas non-ionic linear chelates (gadoversetamide (OptiMARK) and gadodiamide (Omniscan)) are the least stable [1].

GBCAs can also be divided into protein-binding and non-protein-binding categories. The majority of the extracellular

GBCAs show negligible protein binding, meaning that they have a low tendency to modulate enzyme activities and, thus, have a good tolerability profile. One exception is gadobenate dimeglumine (MultiHance), which exhibits weak, reversible binding to serum albumin. This weak protein-binding plays a role in increasing the T1 relaxivity of this agent but is also implicated in reduced tolerability, giving a higher frequency of nausea/vomiting compared with the non-protein-binding agents [2, 3].

Safety considerations

With more than 200 million doses of GBCAs administered worldwide to date, there is an extensive base of experience in terms of safety and tolerability. In general, GBCAs are well tolerated, with adverse reactions being mostly mild to moderate and transient in nature. The most frequent side effects observed are nausea, vomiting, urticaria and headache. Post-marketing assessments suggest a low frequency of adverse drug reactions with most GBCAs (<1%) [2–6]. Although a direct comparison cannot be drawn between these post-marketing studies, some clear differences between the agents can be observed. For example, nausea/vomiting and headache seem to occur less frequently with gado-

Table 1: Gadolinium-based contrast agents

Organ specific/ blood pool	Extracellular			
	Linear ionic	Linear non-ionic	Macrocyclic	
	0.25 M	0.5 M	1.0 M	
	Gadoxetic acid (Primovist®)	Gadopentetate dimeglumine (Magnevist®)	Gadoversetamide (OptiMARK®)	Gadoteridol (ProHance®)
	Gadofosveset	Gadobenate dimeglumine (MultiHance®)	Gadodiamide (Omniscan®)	Gadoterate meglumine (Dotarem®)
Example of a linear molecule (gadopentetate dimeglumine)				Example of a macrocyclic molecule (gadobutrol)

Characteristics of the available Gd-based contrast agents

GBCAs are low-molecular-weight complexes in which

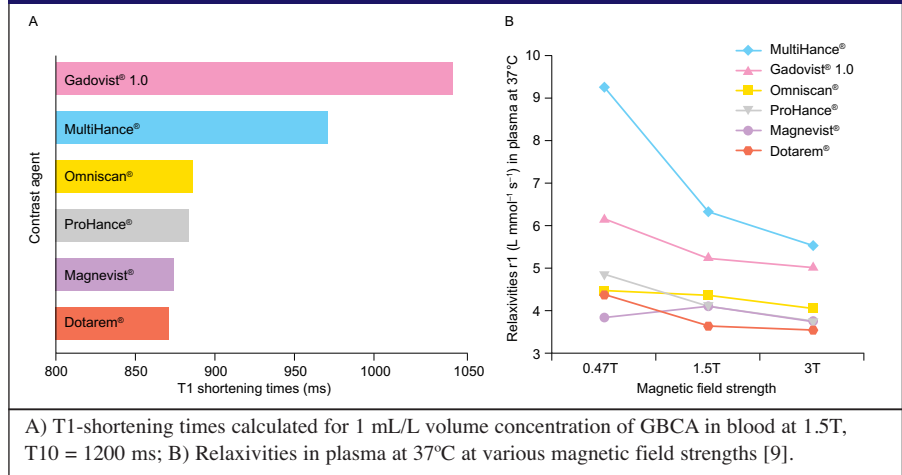
butrol (0.31%) than with gadobenate dimeglumine (0.56%) [2, 3].

With the increasing use of contrast-enhanced MRI, nephrogenic systemic fibrosis (NSF) has emerged as a rare but debilitating potential side effect of GBCAs in patients with severe renal insufficiency. This condition is thought to be due to accumulation of free Gd ions in skin and other tissues. Studies in rats have shown that non-ionic linear agents result in high Gd concentrations in the skin and are more likely to be associated with NSF-like skin lesions [7, 8]. These results are consistent with clinical observations; following a thorough evaluation of all available data on NSF and GBCAs, the EMEA Committee for Medicinal Products for Human Use has classified gadoversetamide, gadodiamide and gadopentetate dimeglumine into a single high-risk group [9], although for gadoversetamide and gadodiamide the risk appears higher compared to gadopentetate dimeglumine based on physicochemical properties and animal studies. These agents should not be used in patients at risk of NSF (patients with severe renal dysfunction, in liver transplant patients and newborn babies) [9]. Agents in the intermediate-risk group include gadofosveset, gadoxetic acid and gadobenate dimeglumine, whereas the low-risk group comprises gadobutrol, gadoteridol and gadoterate meglumine. Agents in these two groups should be used at the minimum recommended dose in patients at risk of NSF [9].

Efficacy considerations

The ability of a contrast agent to increase the intensity of the MRI signal in T1 sequences is determined by how efficiently it is able to shorten T1 relaxation time. This in turn depends on the relaxivity of the agent and its concentration at the region of interest. In a study comparing the relaxivities of all commercially available GBCAs in plasma, the highest relaxivity at all field strengths was produced by gadobenate dimeglumine, followed by gadobutrol (see Figure 1B) [10].

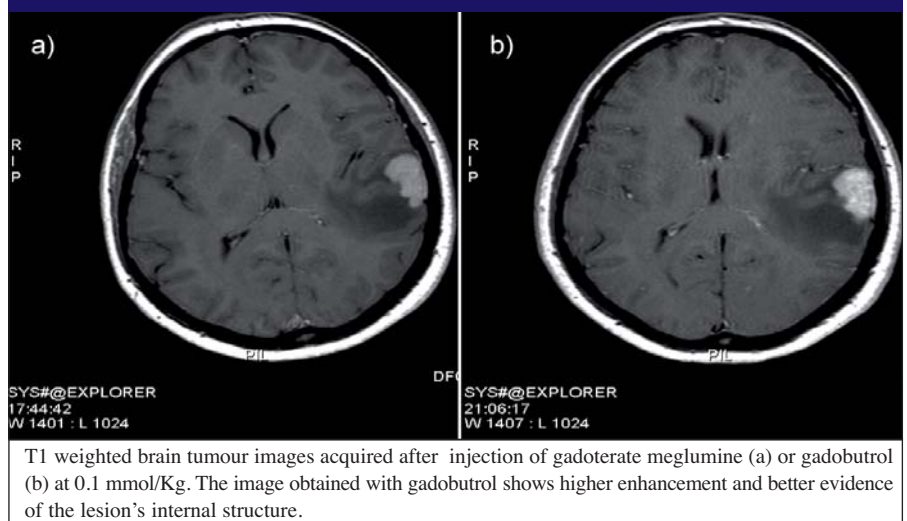
Figure 1: Relaxivity and T1-shortening of gadolinium-based contrast agents



Concentration at the region of interest is affected by many factors, including the location of the region, the injection rate, the total injected dose and the concentration of the Gd solution. With the exception of gadobutrol, all the extracellular agents are formulated at a concentration of 0.5 M. Because of its low osmolarity and low viscosity, gadobutrol can be formulated at 1.0 M, double the standard concentration. This high concentration allows for injection of a smaller volume of agent, providing the highest T1 relaxivity per volume, and therefore the greatest increase in T1-shortening per volume, of any contrast agent (see Figure 1A). It also produces a more

defined bolus that may be less likely to diffuse before arriving at the target area, thus retaining a high local concentration resulting in improved image contrast (see Figure 2). The advantage of the higher concentration of Gd in gadobutrol for brain tumour imaging had been demonstrated in a study in a rat model comparing gadobutrol at 0.1 mmol/kg of body weight with equivalent doses of gadoterate meglumine or gadopentetate dimeglumine. Gadobutrol resulted in superior contrast enhancement at 3T, providing a higher signal-to-noise ratio and significantly improving the contrast-to-noise ratio ($p < 0.0001$) [11].

Figure 2: Gadobutrol is good for brain imaging



Clinical impact

The impact of the different properties discussed above can be illustrated by reference to studies evaluating the diagnostic utility of different GBCAs in a clinical setting. For example, a recent study assessed the effectiveness of 1.0 M gadobutrol compared with 0.5 M gadopentetate dimeglumine, each dosed at 0.1 mmol/kg bodyweight, for the detection of brain metastases in 27 candidates for gamma knife radiosurgery [12]. In 12 patients, the diagnostic performance of MRI was better with gadobutrol than with gadopentetate dimeglumine; with improved lesion conspicuity in 10 patients and detection of additional lesions in two. In the remaining patients, the agents demonstrated equivalent effectiveness. Thus, a major benefit resulting from the high concentration and high relaxivity of gadobutrol may be an improvement in the visualisation of small metastatic brain lesions, which frequently go undetected. Improved imaging of brain lesions with gadobutrol was also demonstrated in a study using perfusion-weighted imaging at 3T, to detect intracranial space-occupying lesions in 11 patients [13]. Compared with gadopentetate dimeglumine, gadobutrol resulted in significantly greater delineation between grey and white matter and significantly better demarcation of highly vascularised tumour tissue. Cranial gadolinium-enhanced MRI is also important in the diagnosis and monitoring of multiple sclerosis (MS). In a study in 30 patients with MS, significantly more brain lesions were detected using 0.1 mL/kg (0.2 mmol/kg) of gadobutrol compared with 0.1 mL/kg (0.1 mmol/kg) of gadopentetate dimeglumine [14]. Importantly, the detection of lesions only visible with gadobutrol resulted in a change in clinical management in six of the 30 patients in this study.

Conclusion

In conclusion, currently available extracellular GBCAs can be divided into three groups based on physicochemical

properties: non-ionic linear agents (gadodiamide and gadoversetamide), ionic linear agents (gadopentetate dimeglumine, gadobenate dimeglumine and gadoxetate) and macrocyclic agents (gadobutrol, gadoteridol and gadoterate dimeglumine). The safety and tolerability of these agents is generally good with small differences in the incidence of some side effects, possibly influenced by differences in protein binding. The less stable non-ionic linear agents, which are more likely to release free Gd, have been associated with higher NSF risk in patients with renal failure. The efficacy of the agents to enhance image contrast is determined by both relaxivity and concentration. The two agents with the highest relaxivity are gadobenate dimeglumine and gadobutrol, but only gadobutrol combines this high relaxivity with a high concentration of Gd in the formulated product together with highest stability as a macrocyclic compound.

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