Compare and Contrast: Defining the Value of Diagnostic Imaging Agents for MRI

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Purpose: Contrast agents for magnetic resonance imaging (MRI) are typically based on chelated gadolinium (Gd) and share an identical mechanism of action. However, differences in the molecular structures of the chelating ligands result in marked differences in contrast efficacy and potential risks to patient safety. Because pharmacists are increasingly involved in the selection and acquisition of MRI contrast agents, it is important that the benefits and potential risks are clearly understood so that informed decisions can be made on which agents to include on the formulary. This review summarizes the properties of the currently available MRI contrast agents and discusses the benefits and potential drawbacks of each.

Summary: MRI contrast agent efficacy, i.e., the extent to which a contrast agent improves detection and differentiation of pathologic from normal tissue, is a reflection of the local Gd concentration in a tissue and the r1 (and r2) relaxivity of the agent. Most of the traditional Gd-based contrast agents (GBCAs) have very similar r1 relaxivity values and thus have similar contrast efficacy when administered at equivalent dose. More recent GBCAs have considerably higher r1 relaxivities meaning that equivalent or better contrast efficacy can be achieved with much lower doses. This means that patients are exposed to less Gd and less Gd enters the environment.

Conclusion: Given safety profiles that are at least as good as those of traditional GBCAs, recently approved lower dose, high relaxivity GBCAs are advantageous to patients in terms of reduced Gd exposure and offer a more sustainable alternative to older GBCAs.

Introduction

Medical imaging is fundamental for the detection and diagnosis of disease and pathologic processes. Imaging modalities such as Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) permit the physician to detect and diagnose a myriad of pathologic processes such as cancer, cardiovascular disease, traumatic injury, etc. and are invaluable for treatment planning and for subsequent patient follow-up. Whereas CT utilizes x-ray information from different angles to create detailed cross-sectional images of the patient's body, a drawback is the need for ionizing radiation and the possible risk of radiation-induced cancer (1). MRI, in contrast, uses a powerful magnetic field and radio frequency waves to generate detailed images and is free of ionizing radiation (2). Although the diagnostic benefits of CT and MRI are largely interchangeable in many situations, CT scans are relatively fast, usually completed within seconds, making them more suitable for emergencies or urgent situations. CT is invariably a first-choice modality to image bone fractures and look for internal bleeding or blood clots, as well as spine and brain injuries in an emergency setting. In contrast, MRI benefits from superior soft-tissue contrast permitting better differentiation between fat, water, muscle, and other soft tissues and is invariably the preferred option for trauma injuries and for CNS and spine imaging in a non-emergency setting. Moreover, since MRI does not require ionizing radiation, it is potentially a preferred option for pregnant women, children, patients who require multiple repeat examinations for screening or follow-up, and individuals who have already undergone significant radiation exposure from prior CT examinations (3).

Common to both modalities is the need for dedicated contrast material to enhance the visualization and differentiation of pathologic from normal tissue. Whereas CT typically utilizes iodinated contrast material in which iodine atoms limit or block the x-rays' ability to pass through the tissue (4), MRI may require paramagnetic contrast agents whose mechanism of action is very different, involving direct influence on the paramagnetic properties of water molecules in the tissues and organs into which they distribute (5, 6). Currently, some 30–45% of all MRI examinations are contrast enhanced, depending on the anatomical area and specific imaging indica-

tion (7). Thus, while contrast agents for CT may differ in terms of molecular structure and formulation characteristics (e.g., iodine concentration: mgI/mL, viscosity etc.) the effectiveness of these agents for diagnostic CT (i.e., image quality) is directly related to the number of iodine atoms in the tissue of interest during scan acquisition. Thus, if a given volume (e.g. 100 mL) of iodinated contrast agent at a given iodine concentration (e.g. 300 mgI/mL) is administered at a given flow rate (e.g. 4 mL/s), the image quality and degree of attenuation on a CT scan will be similar, regardless of the make or manufacturer of the agent. For this reason very little developmental evolution in iodinated contrast agents for CT has occurred in recent years, and the choice of which to purchase rests primarily on differences in formulation characteristics (e.g., iodinated contrast agents containing higher iodine concentrations such as 400 mgI/mL permit reductions of both iodine dose and volume administered), safety and price.

In comparison, contrast agents for MRI differ markedly from one another, such that two agents with identical gadolinium concentrations in the formulation, which are administered under identical conditions at the same dose (mmol Gd/kg bodyweight), can impact contrast enhancement and diagnostic performance to a markedly different extent. In much the same way that different therapeutic drugs for a given condition can vary in terms of therapeutic potency, so too can contrast agents for MRI. In the case of MRI contrast agents, a more potent agent will provide similar contrast enhancement and diagnostic performance at a lower dose than if a less potent agent were used. This is a reflection of the contrast efficacy of the agent. Clearly, a lower dose will result in reduced patient exposure to the agent and potentially provide benefits in terms of improved safety, lower overall costs and reduced environmental exposure without loss of diagnostic performance, thereby time providing a more sustainable alternative to contrast agents administered at higher dose.

KEY POINTS

- Pharmacists play a crucial role in the selection of MRI contrast agents for hospital and clinic formularies.
- The potency (relaxivity) of gadolinium-based contrast agents (GBCAs) differs significantly, impacting diagnostic quality and the required dose.
- High-relaxivity GBCAs allow for a 50% reduction in the gadolinium dose without compromising diagnostic efficacy, which improves patient safety and reduces environmental impact.

Increasingly, the hospital pharmacist is involved in drug selection and purchasing decisions (8). An understanding of MRI contrast agents, of their role in MR image acquisition, and of the differences between them is critical to allowing informed decisions to be made. This review addresses the latest developments in MRI contrast agent evolution, focusing on the benefits of greater contrast agent potency and on the value that such agents bring to clinical practice.

The fundamentals of MR image acquisition and contrast enhancement

The MRI scanner is a large, cylindrical tube-shaped machine that creates a strong magnetic field in and around the patient. This magnetic field, measured in Teslas (T; typically 1.5T or 3T), causes the protons in the body to align in the same direction, with the magnetic field. In order to create MR images, a radiofrequency current is pulsed through the patient. This stimulates the aligned protons, causing them to spin out of equilibrium and strain against the pull of the static magnetic field. When the radiofrequency current is then turned off the protons realign with the magnetic field. The energy released during this realignment of the protons is detected by sensors in the MRI scanner and converted into images of the part of the body being examined. The time it takes for the protons to realign with the magnetic field is referred to as the T1 (or longitudinal) relaxation time, and this varies with the tissues and organs being examined (6). A second time measurement often used when referring to MRI is the T2 (or transverse) relaxation time which reflects the decay of magnetization in the transverse rather than the longitudinal plane, caused by dephasing of the different spins. The T2 relaxation time is essentially the time it takes for the transverse magnetization vector to decay to 1/e or 37% of its initial magnitude (6). MRI contrast agents work by shortening both the T1 and T2 relaxation times, although their principal effect at currently approved doses is on the T1 relaxation time for which they are often referred to as T1 agents (6). In shortening the T1 relaxation time they increase the speed at which protons realign with the magnetic field of the scanner once the radiofrequency current is turned off. The faster the protons realign, the brighter the image and the better the differentiation between different body tissues (e.g., between diseased and normal tissue). The extent to which MR contrast agents shorten the T1 (and T2) relaxation time, and hence the effectiveness of a specific contrast agent in clinical practice, depends on the local concentration of the agent in a given tissue and on the relaxivity values (r1 and r2; i.e., specific properties of the contrast agent molecule that defines the extent to which the T1 and T2 relaxation times can be shortened) of the MR contrast agent being used (9, 10). The combination of local Gd concentration in a tissue and r1 (and r2) relaxivity defines the “contrast efficacy” of the agent. Given identical local concentrations of contrast agent for agents administered at similar doses, differences in contrast enhancement and hence the ability to better visualize and diagnose lesions, depends entirely on the relaxivity (primarily r1 relaxivity) of the agent being used (9, 10). Contrast agents with greater r1 relaxivity

will shorten the T1 relaxation rate to a greater extent at a given identical concentration, thereby resulting in greater contrast enhancement and potentially better differentiation of diseased from normal tissue. This, in turn, will improve the quality of the imaging examination and thus positively impact the overall diagnostic potential.

Contrast agents for MRI

Relaxivity and potency

Currently approved T1 enhancing agents are based on the paramagnetic ion gadolinium (Gd3+). Although T1 agents have also been developed based on manganese (Mn2+) and iron (Fe3+) (11, 12), Gd3+ with 7 unpaired electrons, represents the most effective and appropriate paramagnetic species for the development of T1 enhancing agents (6). Today, nearly all contrast-enhanced MR exams are performed with an MRI contrast agent based on gadolinium. However, because gadolinium is a heavy metal which, in free form or as a simple salt, is highly toxic to humans (13), the Gd3+ ion is complexed with an organic ligand to drastically reduce toxicity and make it tolerable for use in humans (13). These organic ligands have either an acyclic (linear) molecular structure or a macrocyclic molecular structure (14, 15) (Fig. 1).

The first gadolinium-based contrast agent (GBCA) proposed and subsequently approved by the FDA for clinical use in humans was gadopentetate dimeglumine (Magnevist®, Bayer) (16). This GBCA has an r1 relaxivity of approximately 4.1 L.mmol-1.s-1 at 1.5T and 3.7 L.mmol-1.s-1 at 3.0T when measured in biological medium (17) (Table 1). Since then, numerous other GBCAs have been developed most of which (i.e., gadodiamide, gadoterate meglumine, gadoteridol and gadobutrol) have r1 relaxivity values of between 3.6 and 5.2 L.mmol-1.s-1 at 1.5T and between 3.5 and 5.0 L.mmol-1.s-1 at 3.0T, i.e., within 40% of the r1 relaxivity of gadopentetate (Table 1). The similar r1 relaxivity values of these GBCAs means that their ability to shorten T1 relaxation times on T1-weighted imaging during the MRI scan is roughly similar, meaning that contrast enhancement and image quality should be similar for these GBCAs when administered at equivalent dose under identical conditions (18, 19). Gadobenate dimeglumine and, more recently gadopiclenol, have markedly higher r1 relaxivity values at both 1.5T and 3.0T meaning that T1 relaxation times are shortened to a much greater extent, resulting in greater contrast enhancement, better image quality and, potentially, better diagnostic performance. Numerous intra-individual crossover studies in which patients undergo two identical MRI examinations in which only the GBCA is changed from one exam to the other (thereby eliminating all variability due to variations in patient demographics and clinical condition, disease type and extent, lesion morphologic features etc.) have shown that the higher r1 relaxivity of gadobenate dimeglumine results in significantly better imaging performance across a range of clinical indications when compared at equivalent dose with GBCAs that have standard relaxivity (20-27).

In the case of gadopiclenol, its r1 relaxivity is roughly 3 times greater than that of gadopentetate dimeglumine meaning that the impact on contrast enhancement is considerable. Intra-individual crossover studies have shown that an equivalent 0.1 mmol/kg dose of gadopiclenol provides superior imaging performance even compared to gadobenate dimeglumine at 0.1 mmol/kg (28) while a half-dose (0.05 mmol/kg) provides similar or superior imaging performance when compared to the lower relaxivity GBCA, gadobutrol at twice the dose (0.1 mmol/kg) (29, 30). As a consequence, gadopiclenol is approved at half the dose of other available GBCAs (i.e., 0.05 mmol/kg bodyweight compared to 0.1 mmol/kg bodyweight) (31, 32) meaning that patients receive a fully diagnostic MRI exam despite receiving just half the amount of Gd (550.375 mg Gd compared to 1100.75 mg Gd for a 70 kg patient administered an approved dose of 0.1 mmol/kg; Table 1).

Quantification of the impact of r1 relaxivity on imaging performance has come from a recent comprehensive review of intra-individual crossover comparisons of different GBCAs for different approved indications (10). The conclusion of the review was that at equivalent approved doses (e.g., 0.1 mmol/kg bodyweight) a difference in relaxivity between two GBCAs of ≥40% is sufficient to elicit tangible differences in diagnostic imaging performance. Conversely, differences in relaxivity between two GBCAs of <40% are insufficient to elicit noticeable differences and thus agents with differences in relaxivity of <40% are effectively superimposable in terms of diagnostic utility. Based on these findings, no, or minimal, differences in imaging performance can be expected for examinations involving the use of equivalent doses of gadopentetate dimeglumine, gadodiamide, gadoterate meglumine, gadoteridol or gadobutrol with the sole exception of gadobutrol when compared to gadoterate dimeglumine (10). Conversely, superior imaging performance can be expected for the higher relaxivity agent gadobenate dimeglumine when compared to each of these "standard" relaxivity GBCAs given that the difference in r1 relaxivity is >40% (Table 1; Fig. 2). Finally, superior imaging performance can be expected for gadopiclenol compared to the "standard" relaxivity GBCAs despite the lower (0.05 mmol/kg) approved dose for this agent (Fig. 3), while similar or better imaging performance may be expected when compared to a full 0.1 mmol/kg dose of gadobenate dimeglumine (Fig. 4).

A pragmatic and more immediate approach to comparing GBCAs in terms of contrast efficacy takes into account both the r1 relaxiv-

ity of the agent and the labelled (approved) dose (as a surrogate measure of the local tissue Gd concentration) (Table 2). This simple calculation supports the observations from clinical studies (28-30) that the contrast efficacy of gadopiclenol at 0.05 mmol/kg is roughly similar to that of gadobenate dimeglumine at 0.1 mmol/kg and similar or superior to that of 0.1 mmol/kg doses of GBCAs with standard relaxivity. Another GBCA with high relaxivity, which is currently in development, is gadoquatrane, a tetrameric, macrocyclic agent with four Gd atoms in the molecule (33, 34). This agent has r1 relaxivity values of 11.8 L.mmol-1.s-1 at 1.5T and 10.5 L.mmol-1.s-1 at 3.0T (33) and is undergoing development for clinical use at a dose of 0.04 mmol/kg (34). Using the same contrast efficacy calculation, gadoquatrane at 0.04 mmol/kg may be expected to demonstrate similar contrast efficacy to the standard relaxivity GBCAs at 0.1 mmol/kg but lower efficacy than that of gadobenate dimeglumine at 0.1 mmol/kg and gadopiclenol at 0.05 mmol/kg.

Gadopiclenol has the highest r1 relaxivity of all currently approved GBCAs and can be considered the most potent GBCA available, offering similar or better diagnostic performance at half the dose of Gd.

Safety

The GBCAs listed in Table 1 all have excellent safety profiles in terms of acute adverse events (i.e., adverse events that occur within the first 60 minutes following exposure to the imaging agent). As per the ACR Contrast Media Manual (35), reporting rates for acute AEs to GBCAs administered intravenously at approved clinical doses range from 0.07% to 2.4%. A recent report detailing the rate of acute AEs to gadopiclenol after its first year of clinical use in the USA revealed an extremely low rate of spontaneous AE reports (36). Just 32 patients out of roughly 882,550 estimated patients exposed reported acute nonserious AEs (corresponding to a reporting rate of 0.0036%, i.e., one case for every 27,580 estimated exposures) while no serious AEs were reported at all. This reporting rate compares very favorably with rates reported for gadoterate meglumine (37) and gadobutrol (38) in similar post-marketing studies.

Unfortunately, while GBCAs are relatively safe in terms of acute AEs, in 2006 an association was made between GBCA administration and a serious and often fatal disease termed Nephrogenic Systemic Fibrosis (NSF) in patients with severe renal impairment (39). Subsequent research determined that almost all cases of NSF occurred following the cumulative administration of the simple linear GBCAs gadopentetate dimeglumine and, more commonly, gadodiamide (plus a third long discontinued simple linear GBCA gadoversetamide [OptiMARK]) (40). The suspected causative feature of these GBCAs was the comparative instability of the open-chain, linear organic ligand that bound the Gd ion which allowed the release of Gd from the Gd-ligand complex during the extended residence time of the GBCA in the bodies of patients with severe renal insufficiency (14, 15). In comparison, the macrocyclic ligands form a cage-like structure that tightly binds the Gd ion, rendering these agents more stable and less susceptible to releasing Gd. Similarly, gadobenate dimeglumine and gadoxetate disodium [Primovist/Eovist], ostensibly linear GBCAs, have aromatic substituents on the ligand molecules which increases steric hindrance thereby preventing release of Gd. In addition, a fraction of the administered dose of gadobenate dimeglumine and gadoxetate disodium is eliminated through the hepatobiliary route such that elimination of these GBCAs occurs even in patients with end-stage renal disease (41, 42). A consequence of NSF was that the American College of Radiology (ACR) classified GBCAs according to the risk of NSF (35, 40). The simple linear agents gadopentetate dimeglumine, gadodiamide and gadoversetamide are classified into group I (agents associated with the greatest number of NSF cases) while the macrocyclic GBCAs gadoteridol, gadoterate meglumine, gadobutrol, and gadopiclenol, plus the substituted linear GBCAs gadobenate dimeglumine and gadoxetate disodium, are all classified into group II (agents associated with few, if any, unconfounded cases of NSF) (35).

Although the macrocyclic GBCAs are all extremely stable, there are differences between them. In terms of kinetic stability, i.e., the propensity of GBCAs to release Gd, gadoterate meglumine has a half-life (t1/2) of approximately 4 days under extremely acidic conditions (pH 1.2) at 37°C. In comparison, gadobutrol and gadoteridol have half-lives of 18 h and 4 h, respectively, while gadopiclenol has by far the highest kinetic stability of all (t1/2 of approximately 20 days at pH 1.2 at 37°C) (17). Under the physiologic conditions of the body (pH 7.4), the half-lives of these GBCAs would extend to many dozens of years implying negligible dissociation and release of Gd (15).

Although contraindication of the simple linear GBCAs in patients with severe renal insufficiency and strict regulatory guidelines on the use of other GBCAs in these patients essentially eliminated NSF as a possible risk associated with contrast-enhanced MRI (43, 44), a second major concern to impact GBCA selection and usage was the demonstration of Gd retention in the brains and body organs of patients with normal renal function who had undergone repeat contrast-enhanced MRI

examinations (45). This effectively marked the end of the simple linear GBCAs in the USA, Europe and other areas of the world, such that the only agents available today for general purpose contrast-enhanced MRI examinations are the macrocyclic GBCAs and gadobenate dimeglumine (Fig. 1) while gadoxetate disodium (and gadobenate dimeglumine in Europe) is available specifically for liver imaging.

To note, is that while Gd retention is known to occur to a greater or lesser extent with all GBCAs, to date, after more than 10 years of intense research and reporting, no clinical effects from retained Gd have yet been demonstrated (35).

Selecting a GBCA for routine clinical use

Based on diagnostic efficacy alone, the most potent GBCA (i.e., the GBCA with the highest r1 relaxivity) would seem to offer the greatest value for imaging departments. However, decisions over which GBCA to purchase invariably take into account many factors beyond contrast efficacy alone, such as the safety of the agent and its price, in addition to less tangible factors such as manufacturer support and education. Moreover, the distribution (i.e., extracellular vs. hepatobiliary), approved indications and intended application of the agent are also important criteria to bear in mind when selecting a GBCA.

At the patient level, the ACR guidelines note that multiple factors need to be considered when selecting a GBCA, including diagnostic efficacy, relaxivity, rate of adverse reactions, dosing/concentration, and propensity to be retained in more sensitive organs such as the brain (35).

In practical terms, the value of a GBCA can be defined as:

$$Value = \frac{\text{Quality}}{\text{Price}}$$

where quality refers to both the potency and safety profile of the agent plus other less tangible factors.

Based on this equation, a GBCA which is only averagely efficacious (e.g., a GBCA with "standard" relaxivity) or which has only a mediocre safety profile would represent relatively poor quality, thus offering poor overall value, particularly if there is no mitigation in terms of reduced cost. Moreover, choosing a GBCA with relatively low relaxivity often represents a false economy in that the lower relaxivity agent may need to be given at a higher dose (with associated higher costs) to achieve adequate diagnostic performance (46, 47). Conversely, a more potent GBCA with greater contrast efficacy which offers tangible benefits in terms of diagnostic performance and/or Gd dose reduction possibilities could be considered of higher quality offering better overall value, particularly if associated with a good safety profile without substantial differences in overall cost compared to other GBCAs.

Of the currently available GBCAs, gadopiclenol possesses many of the attributes of a very high quality GBCA. Firstly, its high relaxivity permits Gd dose reduction without loss of diagnostic performance (29, 30). On the one hand, this means that patients are exposed to just half the amount of Gd during each contrast-enhanced MR examination. This may be particularly important in pediatric patients, vulnerable patients, or in patients that undergo regular screening (e.g., young women at high risk of breast cancer or patients with multiple sclerosis) or multiple follow-up contrast-enhanced MRI exams (e.g., oncologic patients). On the other, hand, it also means that half the amount of Gd enters the environment following each contrast-enhanced MR examination. The impact of Gd and other imaging agents on the environment is of increasing relevance and concern (48-50) and the use of high relaxivity GBCAs at reduced dose has been proposed as a means of improving sustainability and the envionmental Gd footprint (7). Secondly, gadopiclenol has an excellent safety profile with just one acute non-serious AE reported for every 27,580 estimated exposures during its first year of clinical use (36). Moreover, its macrocyclic molecular structure and classification as a group II agent by the ACR (35) implies negligible or no risk of NSF while the reduced administered dose implies lower levels of retained Gd compared to that seen with other GBCAs. Finally, gadopiclenol is the GBCA with the largest number of approved indications in the USA, covering both the brain and body organs (31, 32, 51). This potentially means that fewer agents need to be included in the formulary to address all clinical indications.

Potential increased downstream costs of not achieving a fully diagnostic exam

The potential costs of an MR imaging study that fails to deliver a correct diagnosis are multifaceted and affects both the patient and the healthcare system (52). Patients may incur additional expense due to the need for repeat imaging or alternative diagnostic tests. Incomplete diagnoses can delay appropriate treatment, potentially leading to disease progression and to an increase in the overall cost of care, as more advanced disease stages often require more intensive and expensive treatments. Additionally, the psychological impact on patients cannot be overlooked; uncertainty and prolonged diagnostic processes can cause significant stress and anxiety, affecting overall well-being and potentially leading to decreased patient satisfaction and trust in the healthcare system. From a healthcare system perspective, a non-diagnostic MR imaging study may result in additional costs related to the inefficient use of an expensive resource, and repeated tests. Rescheduling a patient adds to the strain of a limited resource with possible

effects on waiting times and patient access.

Clearly, selection of the MR imaging agent that offers the greatest opportunity for a fully diagnostic exam will help to minimize or eliminate possible increased downstream costs. In so doing, a fully diagnostic exam will benefit the patient, the imaging center, and the healthcare system as a whole.

Switching Contrast agents/Recommendations for Pharmacists

A new GBCA introduced into a hospital pharmacy must be at least as safe and at least as efficacious as the previous agent used. Concerning price, it is important not to make direct comparisons with other available GBCAs on a cost per mL basis. The volume administered to achieve the approved dose depends on the concentration of Gd in the formulation and the approved dose itself. Thus, if the Gd concentration in a GBCA formulation is twice that of another GBCA (e.g., in the case of gadobutrol) and the approved dose is the same (i.e., 0.1 mmol/kg), then half the volume of GBCA should be administered. Likewise, if the approved dose is half that of another GBCA and the Gd concentration in the formulation is the same (e.g., in the case of gadopiclenol), then, again, half the volume of GBCA should be administered. In both cases care should be taken when comparing and adjudicating the cost of the GBCA to determine the overall cost on a per exam basis, and to bear in mind the differences in GBCA volumes and vial sizes.

Finally, it is important to make a controlled transition to a new GBCA. In this regard different hospitals and imaging centers may adopt different approaches to introducing a new GBCA. At some centers reassurance of the safety and efficacy of a new GBCA can come from an initial onsite assessment of image quality and safety conducted in conjunction with the radiology department, prior to its inclusion on the hospital formulary. Once assured of the safety and efficacy of the new GBCA, a clean transition is made with a precise cut-off date for transition from the old GBCA to the new, with the old GBCA removed from the pharmacy and from all imaging departments before the cut-off date. Benefits of this approach are that the risk of incorrect dosing potentially leading to non-diagnostic exams is reduced and that easier one-time calibration of software associated with GBCA usage (i.e., ordering the exam, barcode scanning etc.) is facilitated. Conversely, other centers, particularly first or early adopters of a new GBCA, may prefer to retain the old GBCA on the formulary for a given period of time in case of allergic reactions or other unforeseen issues with the new GBCA. Because allergic reactions are extremely rare, they may not present during pre-introductory testing or in the first weeks or months after introduction and so having the previous GBCA available will allow the diagnostic study to proceed if there are concerns over the new product.

Conclusion

Recent years have seen increased scrutiny of GBCAs with attention focused on safety and the GBCA dose administered to patients. Hospital pharmacists are increasingly involved in decisions over which GBCA a hospital or imaging center should purchase and utilize. As a result, pharmacists need to be aware of the differences between GBCAs and on how differences in GBCA potency can potentially impact the diagnostic quality of a given MRI examination. A GBCA can be considered of high value if it has a safety profile at least as good as other available GBCAs while at the same time allowing fully diagnostic MRI examinations at reduced Gd dose without dramatic differences in price. In reducing patient exposure to Gd and, as a result, the amount of Gd entering the environment, such GBCAs offer a more sustainable and economically more viable option for contrast-enhanced MRI.

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Table 1. Characteristics of gadolinium-based contrast agents

Scientific name		Gadopentetate dimeglumine	Gadodiamide	Gadoterate meglumine	Gadoteridol	Gadobutrol	Gadobenate dimeglumine	Gadopiclenol
Brand name		Magnevist®	Omniscan™	Dotarem® / Clariscan™	ProHance®	Gadovist® / Gadavist® / Pixxoscan™	MultiHance®	Vueway® / Elucirem®
Manufacturer		Bayer	GE	Guerbet / GE	Bracco	Bayer / GE	Bracco	Bracco / Guerbet
Molecular structure		Simple Linear	Simple Linear	Macrocyclic	Macrocyclic	Macrocyclic	Substituted Linear	Macrocyclic
Relaxivity*	1.5T	4.1	4.3 (+5%)	3.6 (-12%)	4.1 (0)	5.2 (+27%)	6.3 (+54%)	12.8 (+212%)
	3.0T	3.7	4.0 (+8%)	3.5 (-5%)	3.7 (0)	5.0 (+35%)	5.5 (+49%)	11.6 (+214%)
Gd Concentration in formulation		0.5 M	0.5 M	0.5 M	0.5 M	1.0 M	0.5 M	0.5 M
Approved dose** (mmol/kg)		0.1	0.1	0.1	0.1	0.1	0.1	0.05
Dose volume (mL) for 70 kg patient		14	14	14	14	7	14	7
Total Gd (mmol) administered		7	7	7	7	7	7	3.5
Total Gd (mg) administered		1100.75	1100.75	1100.75	1100.75	1100.75	1100.75	550.375

Relaxivity values taken from Robic et al. (17).
Numbers in parentheses represent difference in relaxivity from gadopentetate, the first approved GBCA, taken as a reference
* r1 relaxivity ($L.mmol^{-1}.s^{-1}$) in biological medium at 37 °C
** for extra-hepatic indications
n.b. Not included is Gadoxetate disodium (Eovist® / Primovist®), a liver-specific GBCA not approved for extra-hepatic indications.

Table 2. Comparative GBCA contrast efficacy (r1 relaxivity × labelled dose [mmol Gd/kg])

GBCA	Dose	1.5T		3.0T	
		r1 relaxivity	Contrast efficacy	r1 relaxivity	Contrast efficacy
Gadopentetate dimeglumine	0.1	4.1	0.41	3.7	0.37
Gadodiamide	0.1	4.3	0.43	4.0	0.4
Gadoterate meglumine	0.1	3.6	0.36	3.5	0.35
Gadoteridol	0.1	4.1	0.41	3.7	0.37
Gadobutrol	0.1	5.2	0.52	5.0	0.5
Gadobenate dimeglumine	0.1	6.3	0.63	5.5	0.55
Gadopiclenol	0.05	12.8	0.64	11.6	0.58
Gadoquatrane	0.04*	11.8**	0.47	10.5**	0.42

* Taken from Frenzel et al [ref 34]

** Taken from Lorhke et al [ref. 33]

Figure 1. Molecular structures of general purpose GBCAs
A: gadopentetate ion (Magnevist®); B: gadodiamide (Omniscan™); C: gadoterate ion (Dotarem®/Clariscan™); D: gadoteridol (ProHance®); E: gadobutrol (Gadovist®/Gadavist®/Pixxoscan™); F: gadobenate ion (MultiHance®); G: gadopiclenol (Vueway®/Elucirem®). Gadopentetate and gadodiamide (A, B; no longer commercially available in the USA) have simple linear (acyclic) structures while gadoterate, gadoteridol, gadobutrol and gadopiclenol (C, D, E, G) have macrocyclic structures. Gadobenate (F) has a benzyloxymethyl substituent on its molecule and can be considered a substituted linear contrast agent. Gadopentate, gadodiamide, gadoterate, gadoteridol and gadobutrol display similar r1 relaxivity values. Contrast enhancement on T1-weighted MR images is threfore similar, resulting in MR images of comparable image and diagnostic quality (with the possible exception of gadobutrol compared to gadoterate [see text]). The benzyloxymethyl substituent results in gadobenate (F) having higher relaxivity while specific unique features of the gadopiclenol molecule (G) results in this contrast agent having the highest relaxivity of all. Reasons for the higher relaxivity of gadobenate and gadopclenol are presented in detail in refs 9 and 10, respectively (Kanal 2014; Kanal 2024).

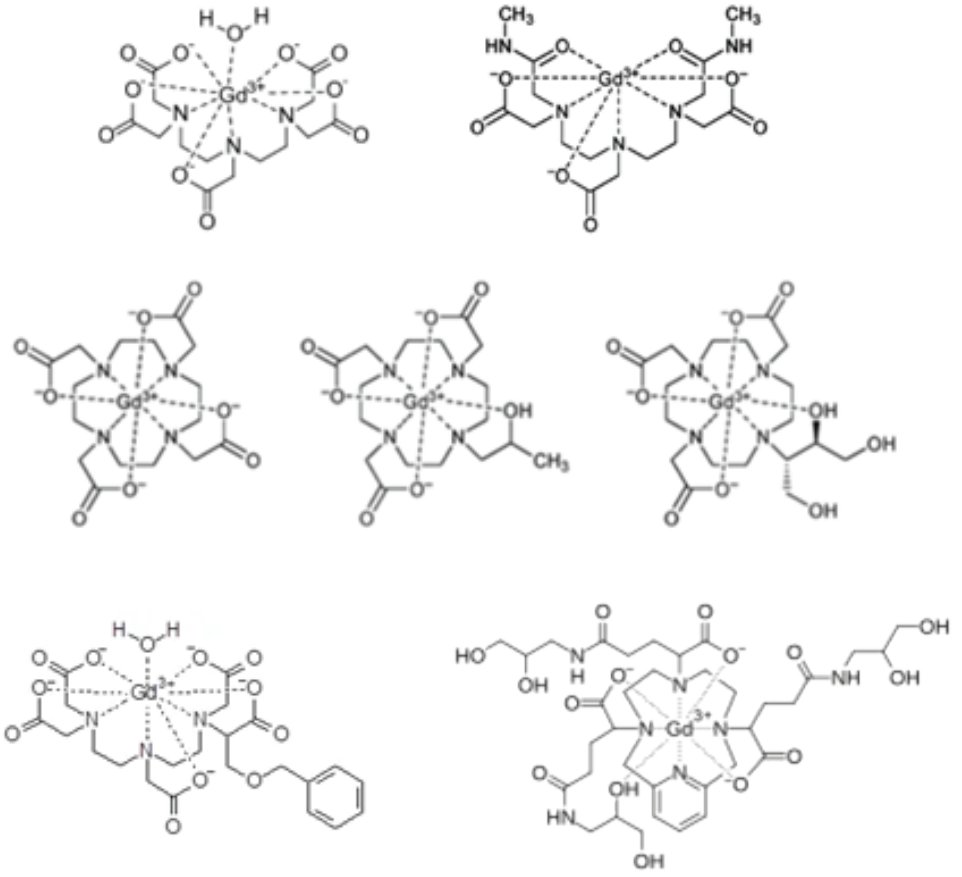

Figure 2. A 62-year-old patient with metastasis in the Sellar region of the brain parenchyma. A) image acquired after administration of gadobenate (MultiHance) at 0.1 mmol/kg bodyweight; B) image acquired after administration of gadoterate (Dotarem) at 0.1 mmol/kg bodyweight. The metastasis (arrow) is clearly evident after administration of MultiHance but is poorly seen after the same dose of Dotarem because of the lower relaxivity od this GBCA.

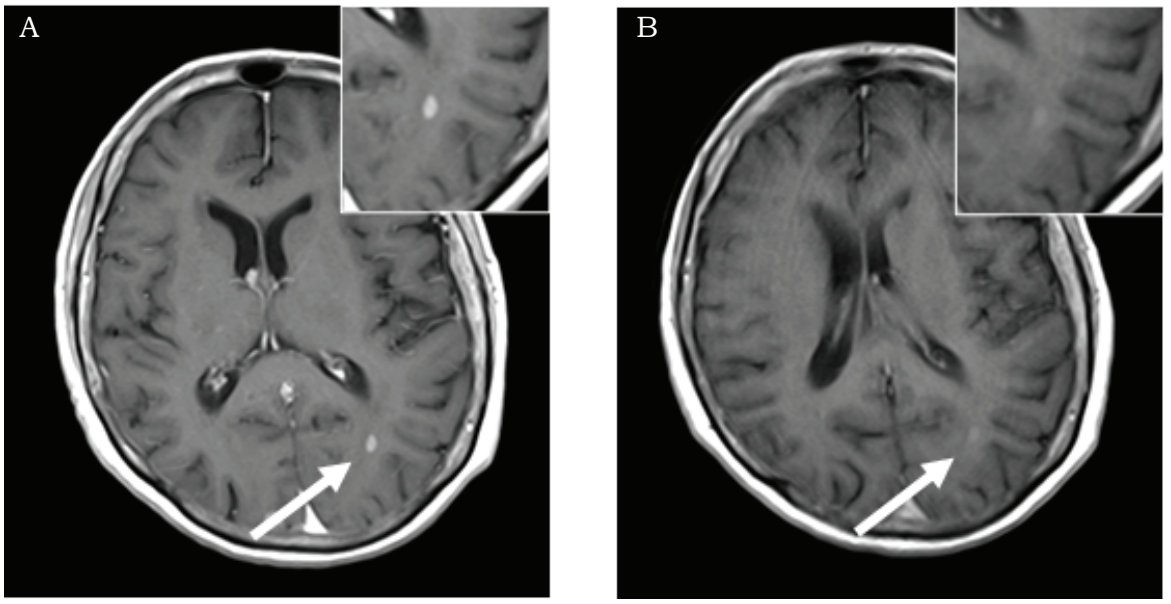

Figure 3. A 76-year-old patient with multiple metastases from lung cancer. A) image acquired after administration of gadopiclenol (Vueway) at 0.05 mmol/kg bodyweight; B) image acquired after administration of gadobutrol (Gadavist) at twice the dose (0.1 mmol/kg bodyweight). A large metastasis in the frontal lobe (red arrow) and a smaller metastasis in the basal ganglion (white arrow) show greater enhancement and are more easily seen with 0.05 mmol/kg gadopiclenol despite half the amount of administered gadolinium.

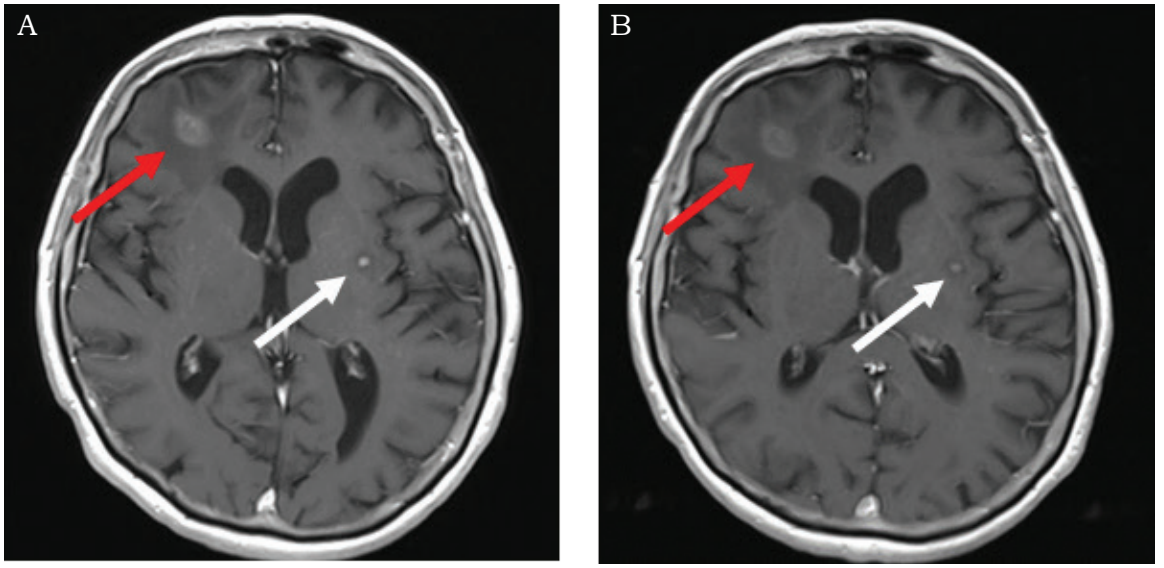

Figure 4. A 76-year-old patient with metastasis. A) image acquired after administration of gadopiclenol (Vueway) at 0.05 mmol/kg bodyweight; B) image acquired after administration of gadobenate (MultiHance) at twice the dose (0.1 mmol/kg bodyweight). Similar enhancement and definition of lesion borders is achieved with 0.05 mmol/kg gadopiclenol despite half the amount of administered gadolinium.