Advocating the Development of Next-Generation High-Relaxivity Gadolinium Chelates for Clinical Magnetic Resonance

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Abstract: The question of improved relaxivity, and potential efficacy therein, for a next-generation of magnetic resonance gadolinium chelates with extracellular distribution and renal excretion, which could also be viewed from the perspective of dose, is addressed on the basis of historical development, animal experimentation, and human trials. There was no systematic evaluation that preceded the choice of 0.1 mmol/kg as the standard dose for human imaging with the gadolinium chelates. In part, this dose was chosen owing to bloodwork abnormalities seen in phase I and phase II studies. Animal investigations and early clinical trials demonstrated improved lesion detectability at higher doses in the brain, liver, and heart. By designing an agent with substantially improved relaxivity, higher enhancement equivalent to that provided with the conventional gadolinium agents at high dose could be achieved, translating to improved diagnosis and, thus, clinical care. Implicit in the development of such high-relaxivity agents would be stability equivalent to or exceeding that of the currently approved macrocyclic agents, given current concern regarding dechelation and gadolinium deposition in the brain, skin, and bone with the linear agents that were initially approved. Development of such next-generation agents with a substantial improvement in relaxivity, in comparison with the current group of approved agents, with a 2-fold increase likely achievable, could lead to improved lesion enhancement, characterization, diagnosis, and, thus, clinical efficacy.

Key Words: gadolinium, relaxivity, contrast media, magnetic resonance imaging

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The developmental history of contrast media for magnetic resonance (MR) has spanned more than 30 years.[1] It is important to note that many of the agents that were initially approved for clinical use have now either been withdrawn or are no longer available. This reflects in part the difficulty in development of agents for MR and the marked evolution of the field with the unpredictability therein concerning need for specific types of contrast media. Three oral contrast agents were approved in the early years of MR, 1 based on dilution of a conventional gadolinium (Gd) chelate (developed for intravenous [IV] administration),[2] the second an oral iron preparation,[3] and the third a manganese chloride–based agent.[4] Timewise, these were the first agents to be discontinued from the market, with low utilization a major reason. Non–Gd-based agents for IV administration were developed for liver imaging, with 3 approved, 3 large iron particles,[5,6] and a manganese-based chelate.[7] As with the oral contrast media, with time, these agents were discontinued and are no longer clinically available. Within this latter group, there were concerns about possible toxicity, and the incidence of mild immediate allergic type reactions was higher than with the Gd chelates. The next agent temporally to leave the clinical market was the single blood-pool Gd chelate that was eventually approved.[8] Although there was initially great interest in development of blood-pool agents for MR, with time, the market and need for such became quite limited. This occurred in part because of the technological success of contrast-enhanced (CE) MR angiography (MRA), which was enabled by the development of short-echo-time (TE), high-resolution 3-dimensional (3D) gradient echo imaging techniques, which could be utilized for imaging the bolus of a conventional extracellular Gd chelate within both the arterial and venous systems.[9] These developments left the 6 conventional, extracellular, renally excreted Gd chelates that had been approved, together with 2 Gd chelates that have hepatobiliary in addition to renal excretion (Table 1). These 8 agents, however, fall into 3 distinct groups by chemical structure and the stability, specifically the macrocyclic chelates, the linear ionic chelates, and the nonionic linear chelates (listed in order from highest to lowest stability both in vitro and in vivo). Owing to the establishment of a causal relationship between administration of less thermodynamically/kinetically stable Gd chelates and occurrence of nephrogenic systemic fibrosis (NSF),[10–12] and subsequently that of dechelation with deposition of Gd (no longer bound to the original chelate) in specific areas of the brain,[13–17] as well as in the skin and bone, the attention of the regulatory authorities worldwide has been attracted, with the European authorities ruling to leave only the 3 macrocyclic Gd chelates on the clinical market with a whole-body indication.[18] Reflecting upon these developments, it is important to note that the Gd chelates are critical to medical diagnosis today and overall have a very high safety profile.

Chemical synthesis and the ability to evaluate molecules, both in terms of potential safety and relative to their contrast effect (relaxivity), is much advanced today in comparison to the 1980s and early 1990s, when the clinical agents that are available today were conceived. After the development of that group of agents, the cost in terms of approval for a new agent dramatically increased.[19] This factor, together with the subsequent consolidation of the diagnostic pharmaceutical industry and the maturation of the market, led to lower interest in development of next-generation contrast media. Today, there is renewed interest in this area, specifically in development for clinical use of high-relaxivity Gd chelates (with a relaxivity approximately twice that of the agents currently approved for whole body use)—as indicated by 1 ongoing clinical trial and multiple patent filings, detailed subsequently. This review provides a background for the development of such agents and overviews briefly the current status. It advocates what is felt to be a critical new area of development, with the potential to both substantially improve patient safety as well as to offer diagnostic possibilities not available with the current agents. Three major topics are addressed—the question of dose, imaging technique, and influencing relaxivity. Within the last section, the relaxivities of the currently approved agents are first considered, followed in order by a discussion of blood pool, fibrin binding and non–protein binding, and low- to intermediate-molecular-weight agents (Table 2). Today, research is focused on this last group, which seems to hold the most promising candidates for next-generation high-relaxivity Gd chelates.

QUESTION OF DOSE

The dose used today for contrast enhancement with the Gd chelates is considered on the basis of the developmental history, animal evaluations, and clinical trials. The reason for this discussion is that one way the next-generation high-relaxivity Gd chelates could be

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TABLE 1. Approved* Gd-Based MR Contrast Agents

Type	Chemical Name	Generic Name (INN)	Trade Name	Manufacturer
Macrocyclic	Gd-DO3A-butrol	Gadobutrol	Gadovist/Gadavist	Bayer HealthCare
	Gd-DOTA	Gadoterate meglumine	Dotarem	Guerbet
	Gd-HP-DO3A	Gadoteridol	ProHance	Bracco
Linear ionic	Gd-DTPA	Gadopentetate dimeglumine	Magnevist	Bayer HealthCare
	Gd-BOPTA	Gadobenate dimeglumine	MultiHance	Bracco
	Gd-EOB-DTPA	Gadoxetic acid disodium	Primovist/Eovist	Bayer HealthCare
Linear nonionic	Gd-DTPA-BMA	Gadodiamide	Omniscan	GE-Healthcare
	Gd-DTPA-BMEA	Gadoversetamide	OptiMARK	Guerbet

* In November 2017, the European Commission adopted the decision of the European Medicines Agency to suspend the marketing authorizations for intravenous use for Omniscan, Optimark, and Magnevist and to restrict the use of MultiHance to liver scans only, with EU member states having 2 months to 1 year to implement this decision.

Gd indicates gadolinium; MR magnetic resonance; INN, International Nonproprietary Names.

viewed is for use to achieve an enhancement effect similar to that possible with high doses of the current agents. The latter (use of high dose) is limited today, due both to safety concerns as well as cost.

Initial clinical trials with the first agent developed, gadopentetate dimeglumine, were performed at 0.1 mmol/kg, in part as a result of laboratory findings in phase I and with no attempt to systematically study dose efficacy. Phase I with gadopentetate dimeglumine evaluated doses from 0.05 to 0.25 mmol/kg. In this limited evaluation, an increase in serum iron and bilirubin was noted for subjects receiving a dose higher than 0.1 mmol/kg, leading to the choice of 0.1 mmol/kg for subsequent phase II clinical trials. As the patient population evaluated was expanded, an increase in serum iron and bilirubin was also seen at this dose, although of lower magnitude.[20,21] The agent was subsequently reformulated with twice the amount of excess chelate initially included (0.4 mg/mL).

Two articles published in 1992[22,23] conclusively demonstrated improved visualization of brain metastases at doses higher than 0.1 mmol/kg. In both studies, which compared 0.3 with 0.1 mmol/kg, higher dose enabled visualization of lesions not seen at standard dose. In the study by Yuh, 46 new lesions were detected in 19 of 27 patients. In 1994, the overall experience from this multicenter phase III trial of gadoteridol was published.[24] A total of 49 patients were included in the analysis. Of these, multiple lesions were demonstrated in 5 patients with high dose who had examinations at standard dose demonstrating only 1 lesion. Also, 1 or more lesions were demonstrated at high dose in 2 patients who had a normal examination at standard dose. Imaging results at high dose would have presumably changed treatment for both groups. Discussing this in greater detail, if only 1 metastasis is detected, in the appropriate clinical setting and with a favorable lesion location treatment is by surgical resection. With more than 1 metastasis, and less than a certain number (variable by site, typically <5-10), stereotactic radiosurgery is performed. With disseminated brain metastases, whole brain radiation therapy is indicated. It has also been shown that it is more than just the number of brain metastases that influences survival. With stereotactic radiosurgery, for example, the presence of brainstem metastases and high cumulative supratentorial tumor volume adversely affect patient survival, with detection and assessment therein important to determine patient prognosis.[25]

The 2 studies cited in the previous paragraph, published in 1992, as well as that published in 1994 were all performed using an injection of 0.1 mmol/kg followed 30 minutes later by a supplemental injection of 0.2 mmol/kg. It was established that the observed results were not a result of delayed enhancement by observing the time course of enhancement between the 2 injections. However, a more difficult study to perform, comparing dose in the same patient with brain metastatic disease but on 2 different examinations (separated by more than 24 hours and less than 7 days, with no intervening therapy), was subsequently performed to validate these results (Fig. 1).[26] In that study, with 15 patients, 40 metastatic brain lesions were detected using a dose of 0.3 mmol/kg, with only 33 seen on the examination with 0.1 mmol/kg. Region of interest analysis demonstrated that lesion contrast increased from 54% at standard dose to 92% at 0.3 mmol/kg. Summarizing from this and other subsequent work (specifically comparing 0.1 and 0.2 mmol/kg gadobutrol),[27] it has been well demonstrated on MR imaging that a dose of 0.1 mmol/kg does not demonstrate all brain metastases, in particular smaller lesions.

TABLE 2. Advanced Design Gd-based MR Contrast Agents

Type (Subtype)	Name	Furthest Pursued Development
Blood pool		
Protein binding	Gadofosveset trisodium	Clinically approved
	Gadocoletic acid trisodium	Phase II
	BRU 52	Preclinical
Non–protein binding	Gadomer-17	Phase II
	P792 (gadomelitol)	Phase I
Fibrin binding	EP-2104R	Phase II
Non–protein binding, low to intermediate molecular weight	P846	Preclinical
	P03277	Phase II (in progress)

Gd indicates gadolinium; MR, magnetic resonance.

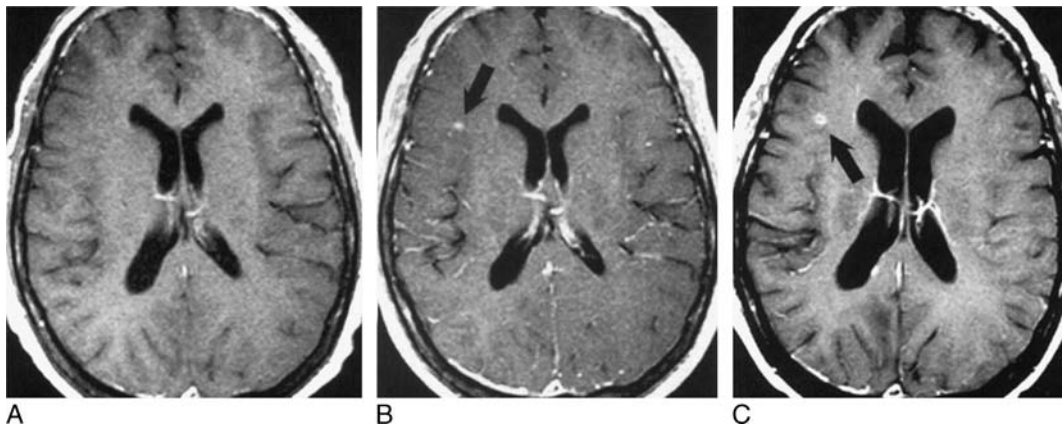


FIGURE 1. Visualization of a brain metastasis with a dose of 0.3 mmol/kg (B, arrow), not detected at 0.1 mmol/kg (A), using a conventional extracellular, renally excreted, gadolinium chelate, specifically gadoteridol. In this case of metastatic lung carcinoma, evaluating the entire examination, 2 metastatic lesions were detected at 0.1 mmol/kg in comparison with 7 at 0.3 mmol/kg. The right frontal metastasis is further confirmed on a follow-up study (C) performed with 0.1 mmol/kg, which demonstrated an increase in lesion size despite interval whole brain radiation therapy. Adapted with permission.[26]

Earlier work, published from 1987 to 1990,[28–30] had already demonstrated improved enhancement of lesions with higher doses, the first 2 studies focusing on a dose of 0.2 mmol/kg and the third encompassing doses from 0.05 to 0.3 mmol/kg. These describe the dose effect on T1-weighted images, and with it, it is important to consider also the effect on T2* in first-pass brain studies. Results published in 1990 and 1993,[31,32] the earlier being a patient study (evaluating 0.1 and 0.2 mmol/kg) and the latter in experimental animals (evaluating up to 0.5 mmol/kg, in the cat), concluded that the first-pass effect was dose dependent, with improved efficacy at higher doses.

In 1994, attention was drawn to the need for further studies addressing the appropriate choice of dose for IV Gd chelate administration.[33] The results of clinical trials at that time suggested improved efficacy for high-dose contrast administration in multiple organs and disease states, including specifically the brain, heart, and liver. Animal studies showed efficacy for doses of 0.5 (cat, brain first pass)[32] and 0.6 (rabbit, breath-hold liver imaging) mmol/kg,[34] although this work did not consider the effect of body surface area on dose. Whether animal imaging studies of contrast dose should be corrected for body surface area is not clear, although it is classically done for toxicology. It is also justified in the case of recent nonclinical studies regarding the question of Gd deposition in the brain after IV Gd chelate administration (eg, in rats, where a single daily dose of 0.6 mmol Gd/kg equates to 0.1 mmol Gd/kg in humans).[17]

Regarding the previously cited work, data for the effect of body surface area concerning the cat are scarce, whereas a conversion factor of 3.1 is commonly quoted for the rabbit,[35] with the human equivalent dose in the quoted work thus being 0.2 mmol/kg. For liver evaluation in humans, there exist phase II data for dynamic scans with gadobenate dimeglumine, published in 2000 (this was a dose ranging study, with patients receiving 1 of 4 doses—0.025, 0.05, 0.1, or 0.2 mmol/kg), which showed a statistically significant improvement in enhancement of normal liver with higher doses, including specifically the comparison of 0.2 versus 0.1 mmol/kg (Fig. 2).[36] A study comparing double-dose gadobutrol with single-dose gadopentetate dimeglumine later in 2008 confirmed these findings, if the small relaxivity differences between the agents are disregarded. Specifically, there was an increase in normal liver signal-to-noise ratio (SNR) with a dose of 0.2 mmol/kg on dynamic imaging, with the study further demonstrating improved lesion-liver contrast-to-noise ratio (CNR).[37] Cardiac imaging is one of the few areas that continues to employ routinely a dose higher than 0.1 mmol/kg of an extracellular, renally excreted Gd chelate. For visualization and definition of myocardial infarcts on delayed imaging, a dose of 0.2 mmol/kg is most commonly used today.[38] It

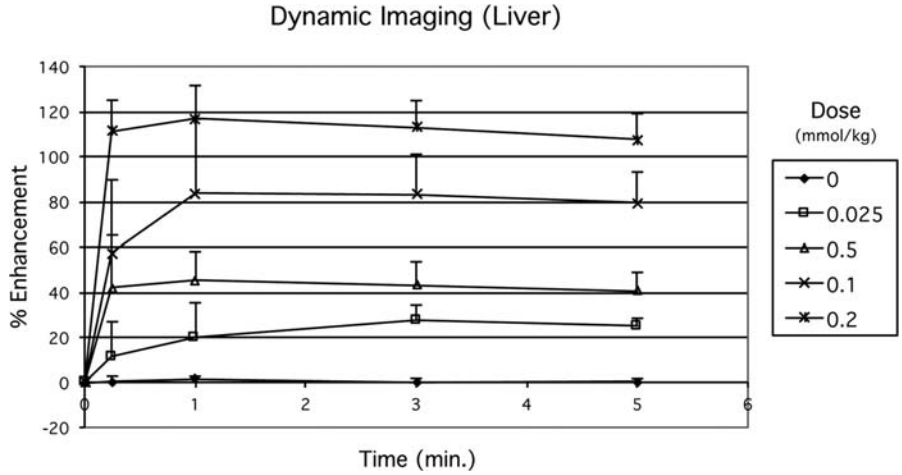


FIGURE 2. Normal liver enhancement, dynamic temporal time course, from phase II clinical evaluation of gadobenate dimeglumine. Enhancement of normal liver scales with dose up to the highest level evaluated, 0.2 mmol/kg. Reprinted with permission.[36]

should be noted, regardless, that, in some countries (eg, in the United States), price (and the lack of reimbursement therein) has markedly restricted the use of doses higher than 0.1 mmol/kg for the Gd chelates, particularly in recent years.

Of additional note, most research to date has focused on the evaluation of dose in neoplastic disease. Infection is an additional major disease category, with little data in the literature concerning contrast dose on MR and detectability therein. For example, it is known that MR is relatively insensitive for the detection of meningitis. Research using a dog model of early meningitis in the brain, performed in 1995, demonstrated improved detectability of meningeal enhancement as contrast dose was increased.[39] Enhancement of meningeal inflammation was seen with the magnitude therein and the sensitivity of the technique ranking by contrast dose with 0.8 > 0.3 > 0.1 mmol/kg. Using a conversion factor of 1.8 for the dog (to determine human equivalent doses on the basis of the body surface area), this equates to evaluation of 0.44 versus 0.17 versus 0.06 mmol/kg. Given that early meningitis is typically not visualized in patients with a dose of 0.1 mmol/kg, it is likely that the lowest dose evaluated in these experiments mimics closely the clinical situation—with only 2 of 5 animals having an abnormal postcontrast scan at this dose despite an imaging protocol that maximized contrast detectability.

The discovery of NSF and subsequently Gd deposition in the brain, skin, and bone in patients with normal renal function, after administration of linear Gd chelates, has impacted the clinical view of high dose, even with the macrocyclic agents, owing to the role of dose with the linear agents in both settings. Unfortunately, use of gadodiamide and gadopentetate dimeglumine at extremely high doses (up to and exceeding 0.3 mmol/kg) in renal failure patients in the early days of CE-MRA, and the NSF cases seen in this group, likely contributed today to this reluctance to inject doses above 0.1 mmol/kg regardless of agent.[40]

IMAGING TECHNIQUE

Both the time following contrast administration and the specific pulse technique used for visualization on MR are critical for maximizing detection of contrast enhancement. However, both factors are often overlooked. In the very first study demonstrating contrast enhancement with a Gd chelate in a brain lesion on MR, the existence of a temporal time course of enhancement was noted, with greater enhancement on delayed scans.[41] This was known from compute tomography and confirmed in many subsequent MR studies, including the landmark study comparing gadopentetate dimeglumine and gadobenate dimeglumine (with higher relaxivity) for brain lesion enhancement.[42] Lesion-to-brain contrast increases rapidly in the first few minutes after contrast administration and continues to increase at a slower pace thereafter up to at least 10 minutes after injection. This factor is often ignored in clinical practice today with the necessity to complete the examination as rapidly as possible to ensure high patient throughput. Delayed scans would ensure better lesion enhancement in the brain and have been advocated as a supplement to standard postcontrast scans for improved detection of brain metastases.[43] Alternatively, this result could be achieved by the use of a next-generation, higher-relaxivity agent. Although the factor of timing postcontrast for brain lesions has been relatively well studied (as well as that for the imaging of myocardial scar),[44] in other areas of the body, such as the musculoskeletal system, a temporal time course likely also exists but has never been evaluated.

The specific pulse sequence and the settings therein are also very important for visualization of contrast enhancement, with a wide variety of T1-weighted sequences available. For example, at 3 T, if a very rapid scan of the brain is desired, a 2D short-TE gradient echo sequence can be used. If high-resolution imaging is desired, the most commonly used sequence is 3D magnetization prepared rapid gradient-echo, which is also gradient echo in type. With sequence parameters as commonly used, unfortunately, gradient echo techniques are inferior to spin echo techniques for detection of contrast enhancement using a Gd chelate. For example, a short TE 2D gradient echo technique—which is often used at 3 T for postcontrast imaging of the brain—is inferior to a 2D fast spin echo scan, when TE, repetition time, and flip angle are chosen as commonly used, with voxel size held constant.[45] Similarly, for high-resolution 3D imaging, the most appropriate choice to maximize visualization of lesion enhancement would be a spin echo–based technique, such as Sampling Perfection with Application optimized Contrasts using different flip angle Evolution. The latter, however, is not commonly used in clinical practice, despite definitive studies demonstrating improved lesion enhancement and detection.[46] That Sampling Perfection with Application optimized Contrasts using different flip angle Evolution or similar sequences are not used routinely for brain imaging is likely because of neuroradiologists' preference for a scan with high gray-white matter contrast, specifically magnetization prepared rapid gradient-echo. Looking at other areas of the body, little work has ever been performed to optimize the postcontrast imaging sequence for the detection of contrast enhancement.

Other approaches have also been studied for maximizing the detection of a Gd chelate on MR, including specifically the use of additional radiofrequency pulses. Application of a magnetization transfer pulse was demonstrated early in the development of clinical MR to improve the visualization of contrast enhancement in the brain.[47,48] magnetization transfer (MT) pulses suppress the signal intensity of tissue, thus improving the detectability of contrast enhancement (against a lower-signal-intensity background). The disadvantages of an MT pulse include a slight prolongation of imaging time, higher specific absorption rate, decreased signal intensity from nonenhancing tissue, and an increase in motion artifacts. MT is rarely used today for postcontrast imaging, reflecting these factors and in particular the image degradation from motion. Fluid-attenuated inversion recovery can also be used to provide improved contrast enhancement in comparison with standard T1-weighted imaging techniques.[49] As with MT, this technique suffers from accentuated motion artifacts, as well as longer scan time and lower SNR in comparison with conventional techniques. Thus, postcontrast fluid-attenuated inversion recovery also never achieved widespread clinical use or acceptance.

Not to be ignored is the impact that personal preference (of the clinic's radiologist) for imaging sequence, which is highly variable, has upon everyday clinical practice. A second important factor is the time constraint (in terms of chosen imaging scans to be run) to achieve a profit, as opposed to a monetary loss, for the operation of the clinic. These factors take the choice of imaging technique largely out of the control of a company attempting to develop a next-generation agent and could thus negatively affect development and acceptance of such.

Intertwined with the choice of pulse sequence (imaging technique), in terms of influence on the signal intensity produced by a Gd chelate, is its relaxivity, in vivo concentration, formulated concentration, and used field strength. Higher T1 relaxivity always comes with higher T2 relaxivity, the latter also influencing signal intensity. Field strength strongly influences relaxivity, although the end result in terms of enhancement can be surprising, due to the increase in tissue T1 with field strength.

INFLUENCING RELAXIVITY

Relaxivities of Current Agents

With the exception of the 2 agents with partial hepatobiliary excretion (gadoxetate disodium and gadobenate dimeglumine), the T1 relaxivities of the Gd chelates approved worldwide today are closely clustered. Two major studies have evaluated in vitro T1 relaxivity of these agents, the first in 2005 at both 1.5 and 3 T, using bovine plasma and canine whole blood.[50] It should be noted that relaxivity can differ between species, and so these results cannot be completely extrapolated to humans.[51] The second extended these results, reporting relaxivities

at 1.5, 3, and 7 T, and importantly evaluated the agents for the first time in human whole blood.[52] At 1.5 T, the range in relaxivities in this group is from 3.9 to 4.6 s^{-1} mM^{-1}, and at 3 T, from 3.4 to 4.5. It is to be noted that for each agent, the specific T1 relaxivity decreases from 1.5 to 3 to 7 T. However, because the T1 of tissue is prolonged at higher field strengths, the enhancement effect has been shown to increase from 1.5 to 3 T, despite the decrease in relaxivity.[45] From lowest to highest relaxivity, for all approved agents, the ranking in terms of T1 relaxivity from the 2015 publication of Shen et al (irrespective of field strength) is gadoxetate disodium > gadobenate dimeglumine > the remaining Gd chelates (gadobutrol, gadodiamide, gadoversetamide, gadoteridol, gadopentetate dimeglumine, and gadoterate meglumine)—which all have very close, if not indistinguishable, relaxivities. Although small differences in degree of lesion enhancement have been shown between agents, for example, in brain imaging for gadobenate dimeglumine as compared with gadoterate meglumine (2 agents at the extremes of the range of relaxivities),[53] no agent has ever been approved by either the Food and Drug Administration or the European Medicines Agency in a half dose (0.05 mmol/kg) indication (excluding liver imaging), confirming the close clustering of relaxivities and, thus, enhancement effect of the approved agents.

Blood-Pool Agents

In the history of the development of the Gd chelates, extracellular agents were first developed, followed by agents with hepatobiliary excretion. Subsequently, a large effort was expended for the development of potential blood-pool agents. The first such agent conceptualized was gadofosveset trisodium[8] (also known by its commercial names, Vasovist and Ablavar). Clinical approval was eventually sought for only 1 agent in this class, that being gadofosveset trisodium. Today, this agent is no longer available in either Europe or the United States.

Clinical trials were performed with gadofosveset trisodium starting the late 1990s[54,55] and extending to the following decade. These trials included evaluation of the carotid arteries, aorta, iliac arteries, and peripheral vasculature.[56–59] Although efficacy was demonstrated, the potential application of the agent was limited by the concurrent rapid development of CE-MRA using the extracellular Gd chelates already clinically available. Contrast-enhanced MRA was first conceptualized by Revel in the early 1990s.[60] Although gadofosveset trisodium offered the possibility of delayed blood-pool imaging, in addition to first-pass imaging, this proved not to be of sufficient benefit to keep the agent on the market. This occurred despite efforts to promote its use, using the blood-pool features for which the class of agents was developed—to enable imaging that otherwise might not be possible. For example, high-resolution delayed imaging was performed in investigation of atherosclerotic disease in both the carotid arteries and lower extremities, showing improvements relative to first-pass imaging.[61,62]

Gadofosveset trisodium and other similar agents, for example, gadocoletic acid trisodium,[63] which did not progress to clinical approval, function by binding to human serum albumin in plasma. This prolongs the half-life of the agent in the body, retains the agent for at least some time period within the blood pool, and increases its T1 relaxivity. The latter occurs primarily because of the increase in the rotational correlation time (slower tumbling) when bound to albumin.[64] In vitro, in human plasma, the relaxivity of gadofosveset trisodium is markedly higher than that of the extracellular distributed Gd chelates, for example, at 0.5 T 53.5 versus 4.7 $mmol^{-1}$ L s^{-1} for gadopentetate dimeglumine.[55] However, it should be noted that in vitro measurements of relaxivity in plasma, at a fixed concentration of Gd, are not necessarily an accurate reflection of the efficiency of a Gd chelate in vivo, especially for those molecules that bind to albumin, such as gadofosveset. In vivo, the proportion of free and bound forms of albumin-binding Gd chelates varies according to the pharmacokinetic profile, with the relaxivities of the albumin-bound and the free contrast agent very different (much lower for the latter). This has led to the concept of "dynamic relaxivity."[65]

A single research paper exists investigating the dependency of brain tumor enhancement on level of protein binding (Fig. 3).[66] Agents with weak (gadobenate dimeglumine), 50% (BRU 52), and 90% (B22956/1, gadocoletic acid trisodium) protein binding were compared with a conventional non–protein-binding extracellular agent, gadopentetate dimeglumine. Both of the protein-binding agents provided a substantial improvement in lesion enhancement as compared with the Gd chelates available clinically today. A major hypothesis of the study was whether an agent with intermediate protein binding might indeed provide substantially greater lesion enhancement than with either stronger or weaker protein binding. However, both agents with substantial protein binding (50% vs 90%) proved to have comparable lesion enhancement—by comparison to the controls used, in the immediate postinjection timeframe.

Non–protein-binding Gd chelates have also been evaluated as potential blood-pool agents. Gadomer-17, a paramagnetic complex with 24 Gd atoms bound to a dendrimeric backbone, was developed as a blood-pool agent and evaluated in the late 1990s and early 2000s. This compound has a high T1 relaxivity per Gd atom owing to the increase in rotational correlation time. Because of size, after IV injection, it does not quickly diffuse into the extravascular space, and although large enough—to slow this diffusion—it is also small enough to be excreted by glomerular filtration.[67] Although extensively evaluated in animal studies, only 2 small clinical studies were ever performed.[68,69]

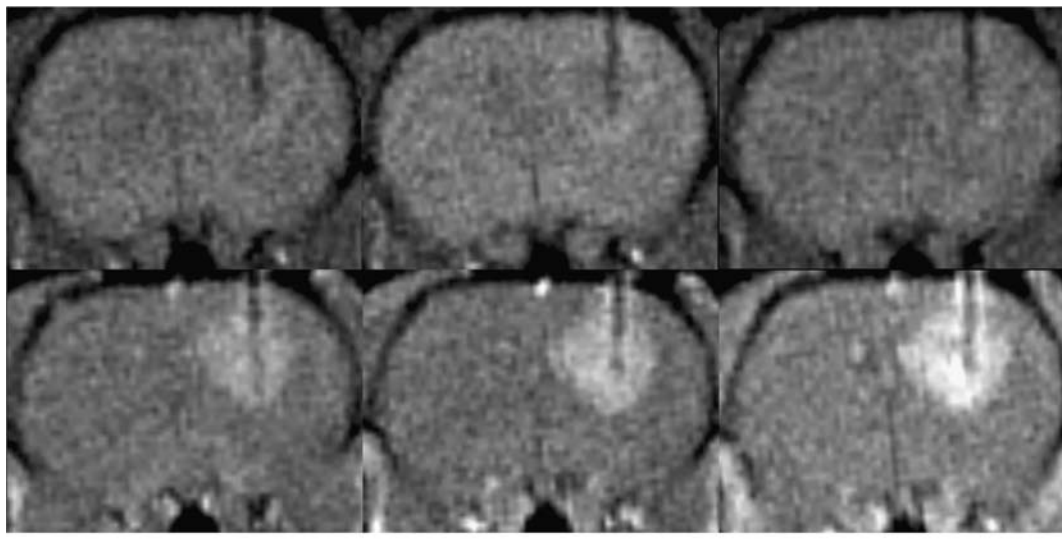
P792 (gadomelitol) is a large-molecular-weight, high-relaxivity agent based on a Gd-DOTA skeleton. The hydrodynamic molecular volume is approximately 125 times that of Gd-DOTA. The increased molecular weight leads to slowing of the rotational movement and a marked increase in T1 relaxivity, which at 0.5 T is 39 as compared with 3.5 $mmol^{-1}$ L s^{-1} for Gd-DOTA.[70] The agent was evaluated in phase I, in which distribution and clearance were shown to be consistent with a rapid clearance blood-pool agent.[71] One substantial difference between this type of agent and the albumin binders is that the relaxivity does not change during the bolus and postbolus timeframes. In the bolus and immediate postbolus phase, the relaxivity of agents that bind to albumin, for example, gadobenate dimeglumine and gadofosveset, varies. This occurs because of the change in quantity of bound and free forms.[65] In CE-MRA, with the non–protein-binding blood-pool agents, high-quality early and equilibrium phase MRA images have been demonstrated.[72]

Fibrin Binding

A single fibrin binding agent, EP-2104R, was developed by EPIX Pharmaceuticals, Inc subsequent to its initial albumin binding agent, gadofosveset trisodium.[73,74] Although developed as a fibrin specific agent, EP-2104R is a high-relaxivity agent, in addition to being a tetramer (the peptide at its core is derivatized at both the C- and N-termini with Gd-DOTA-like moieties). Its relaxivity per Gd ion is roughly twice that of comparable extracellular Gd chelates (10.5 vs 4.1 $mmol^{-1}$ L s^{-1} when measured under similar conditions and 17.4 when bound to fibrin).[75] Imaging at 1.5 T, contrast enhancement (as assessed in a brain tumor model) was demonstrated to be more than double (Fig. 4), with a prolonged temporal enhancement course. It is important to note that the increased signal intensity seen in vivo is likely a result not just of the greater relaxivity but also of the fibrin binding and thus reduced motion of the molecule. Utility was demonstrated in swine for targeted imaging of thrombi, specifically in the pulmonary arteries,[73] and for coronary thrombosis,[76] and as well for the identification of tumor associated fibrin.[77] Before development was halted, likely on the basis of commercial considerations, at least 1 phase II study was performed,[78] demonstrating in man enhancement and on that basis greater conspicuity of both venous and arterial thrombi.

Non–Protein Binding, Low to Intermediate Molecular Weight

P846 is an intermediate sized, non–protein binding, macromolecular organic Gd chelate, with approximately half the molecular weight of P792 (3.5 vs 6.5 kDa). It consists of a single Gd ion within



Contrast Enhancement (CE) of the Evaluated Rat Brain Tumors for Both Study Groups, Comparing Agents with Differences in Protein Binding

		Level of Protein Binding	Tumor Contrast Enhancement (Mean ± SD)
Group A (N=5)			
	Gadobenate dimeglumine	Weak	7.8 ± 2.7
	Gadopentetate dimeglumine	None	6.4 ± 1.9
	B22956/1	90%	15.0 ± 5.3
Group B (N=6)			
	Gadobenate dimeglumine	Weak	13.6 ± 2.5
	Gadopentetate dimeglumine	None	11.2 ± 0.5
	BRU 52	50%	21.7 ± 1.4

FIGURE 3. Comparison of enhancement with gadolinium chelates differing in the degree of protein binding (rat brain tumor model). In part I, precontrast images are in the top row, and immediate postcontrast images are in the bottom row. Part I depicts results (presented in the order noted) with gadopentetate dimeglumine, gadobenate dimeglumine, and B22956/1— the latter a linear gadolinium chelate linked to a deoxycholic acid derivative, with strong specific protein binding (approximately 90%). Part II provides results with all evaluated agents, including gadopentetate dimeglumine, gadobenate dimeglumine, B22956/1, and BRU 52—the latter a low-molecular-weight macrocyclic gadolinium chelate with intermediate protein binding properties (approximately 50%). The contrast dose was 0.1 mmol/kg in all instances. Reprinted with permission.[66]

a macrocyclic 3-armed chelate. As noted with other agents previously discussed, increasing the molecular weight and volume leads to a reduction in rotational rate, producing increased time for interaction with water protons and higher relaxivity. Unlike P792, P846 is not considered to be a blood-pool agent, with the intermediate molecular weight allowing for extravasation and accumulation in tumor tissue. Although considered a low diffusable agent, there is marked increased crossing of the disrupted blood-brain barrier with P846 as compared to P792,

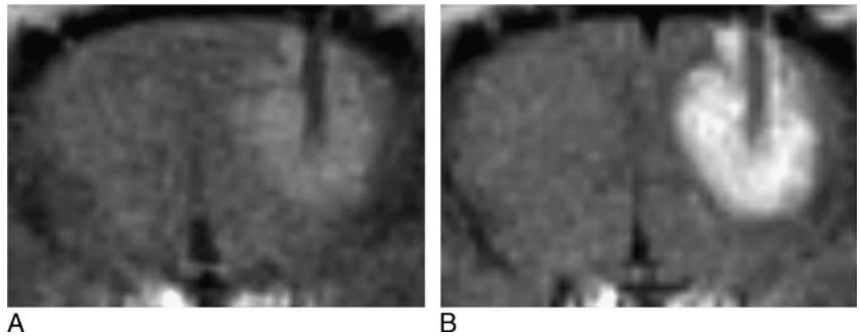


FIGURE 4. Markedly improved lesion enhancement by the use of a fibrin specific binding gadolinium chelate peptide tetramer (B), with results compared with that using gadopentetate dimeglumine (A) in a rat brain tumor model. Both scans are postcontrast at 5 minutes after injection, with CNR near double using the fibrin binding agent (despite the use of one-fourth the dose on a gadolinium ion basis). Reprinted with permission.[75]

likely owing to its smaller size and differences in 3D molecular structure. In evaluation of a rat brain tumor model, a dose of 0.025 mmol/kg produced comparable lesion enhancement when compared with a dose of 0.1 mmol/kg of a conventional, clinically approved, extracellular Gd chelate (Fig. 5).[79]

P03277 is a low-molecular-weight (0.97 kDa) single Gd-based contrast agent from Guerbet with a dedicated 3D design to increase the hydrodynamic size of the complex (patent number EP 1931 673 B1, page 8, example 2).[80] As noted previously, this reduces the molecular tumbling rate, leading to improved interaction with water protons and thus increased T1 relaxivity (with R_1 at 1.5 T being 12.8 and at 3 T 11.6 $mmol^{-1}$ L s^{-1}).[80] In addition, water access to the Gd ion is improved, with a hydration number of 1.7. The approved conventional low-molecular-weight complexes of Gd all have a hydration number of 1. There is no interaction with serum albumin or other plasma proteins. A phase II study is currently being conducted for central nervous system imaging (ClinicalTrials.gov Identifier: NCT02633501), looking at lesions with disruption of the blood-brain barrier and evaluating 4 doses—specifically 0.025, 0.05, 0.1, and 0.2 mmol/kg in comparison to a standard dose, 0.1 mmol/kg, of gadobenate dimeglumine. The conventional clinically approved Gd-based agents, as well as the macromolecular contrast agents and the agents with plasma protein interaction, have a marked deterioration in T1 relaxivity with an increase in field strength from 1.5 to 3 to 7 T. Although also seen with P03277, it is moderate in degree, with this agent maintaining notably high T1 relaxivity at ultrahigh field strengths. Bayer seems also to be in the early stages of investigating new high-relaxivity extracellular Gd chelates (specifically agents based on low-molecular-weight core polyamines).[81] Bracco is investigating as well agents within this class (non–protein binding, low to intermediate molecular weight), introducing recently at a congress another series of relatively high-relaxivity agents.[82]

One potential application already cited in the literature would be the ability to use lower doses of Gd at 1.5 and 3 T. However, any new Gd agent with higher relaxivity—to receive regulatory approval—would likely have to deposit an equal or less amount of Gd in the body compared with the currently approved macrocycles. Otherwise, there would be no benefit of going to a lower dose if the amount of Gd deposited is the same or higher than with the macrocyclic agents. Unexplored is the potential for improved diagnosis both in the brain and in body imaging due to the enhanced relaxivity with the use of a more conventional dose of 0.1 mmol/kg. Given earlier high-dose studies with the currently approved conventional Gd chelates, there is great potential in many, if not all, organ systems for the use of an agent like P03277 at a dose of 0.1 mmol/kg. This is likely even more so the case given that the selection of standard dose, 0.1 mmol/kg, for the agents approved today was not made on the basis of efficacy but because of concerns regarding toxicity, as previously discussed. An additional reason for major interest in high-relaxivity contrast agent without protein binding is that these agents are associated with constant relaxivity. This can open the way to quantitative MR imaging, specifically with no uncertainty between level of binding and local contrast agent concentration.

The financial hurdles to industry, however, for the development of agents within this category (and indeed for any new MR agents) are substantial. These only start with development costs. Likely far more challenging will be the level of reimbursement for the cost of a single dose, in an environment where the payment is already fixed and may be as well bundled with other costs including the scanner, technologist, and physician.

Looking more in depth at these obstacles, the following issues can prevent or deter market access of new, innovative contrast agents.[19,83] This can occur even if the compound has excellent proofs of concept and seems to actually save lives, as was the case with ferumoxtran-10 for lymph mode imaging in prostate cancer.[84] The single use of a contrast agent for an imaging examination, as compared with, in many cases, the long-term (months or even years) use of therapeutic agents means that the financial return for contrast agents is often much smaller. Implementation of a "first-in-class" MR contrast agent in routine practice is likely to require the development of dedicated image analysis software and MR sequences for all types of MR machines, which may impact clinical

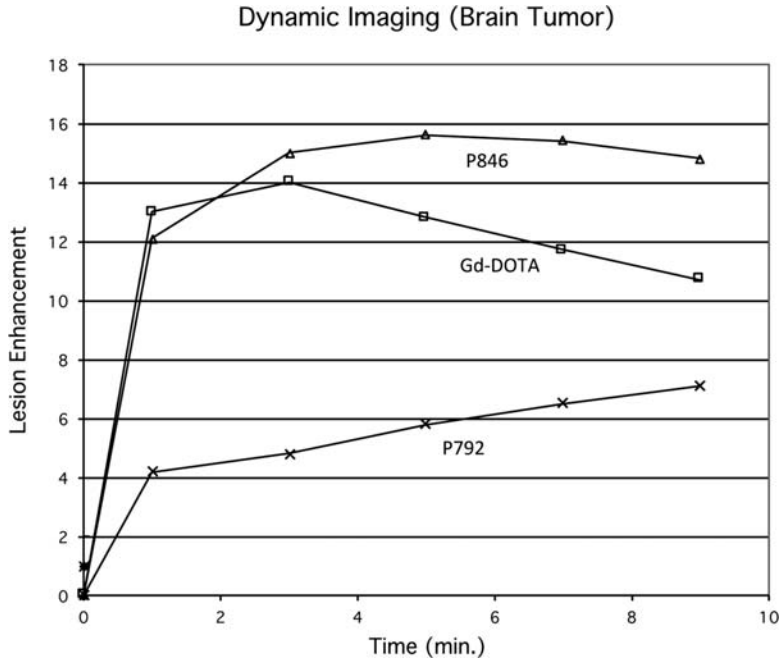


FIGURE 5. Comparison of enhancement with gadolinium chelates differing in molecular weight (rat brain tumor model). P792 is a high-relaxivity blood-pool agent, specifically a monomeric macromolecular organic gadolinium chelate, non–albumin binding, with rapid clearance. P846 is an intermediate sized high-relaxivity gadolinium-based contrast agent with rapid renal clearance. Gd-DOTA was administered at a dose of 0.1 mmol/kg body weight, P792 at 0.05 mmol/kg, and P846 at 0.025 mmol/kg. Adapted with permission.[79]

development studies and subsequent market access. Training of clinicians and radiographers relative to innovative agents is important and sometimes neglected, even by developers. Particularly from the pharmaceutical industry's perspective, an important obstacle is the projected volume of contrast usage. Until a new agent is approved for imaging, its application can be only off-label, and there will be the issues of reimbursement, insurance, and the fact that the physicians themselves bear the responsibility and liability for safety. Contrast agent developers are concerned with the huge risk of refusal from the health authorities and no obvious guarantee that, if marketed, the radiologists will adopt new contrast media. In the case of a "disruptive" imaging method associated with an innovative contrast agent, it can be anticipated that a substantial impact to the health care system will follow (patient flow management, guidelines, training) that may also impact the use of the new agent and, thus, its chances of success. Manufacturing issues under good manufacturing practices, for example, in the case of nanoparticles, is often forgotten in the case of academic researchers who launch a new business. Heterogeneity in the use of contrast agents between countries may depend on the type and nature of reimbursement. And finally, in the modern health care world, high pressure on sales prices imposed by payers (for example, governments) may discourage companies from developing new compounds.

CONCLUSION

In summary, there were limited data from human trials concerning optimum dose before the Gd-based agents were first approved. Early animal and human investigations support a higher dose (or equivalently higher relaxivity) for improved disease detection and evaluation. Gadoterate meglumine and gadoteridol remain approved clinically for up to 0.3 mmol/kg, however, with limited such use.

Next-generation Gd chelates with markedly higher relaxivity could be realized by improved chelate design, enabling in clinical use higher SNR and CNR. If used at the doses used today for conventional agents, improved clinical efficacy would be a likely result, as detailed in the "Question of Dose" section. Commercial viability could be justified on the basis of either lowering the Gd ion dose (yet achieving the same improvement in SNR and CNR) or by keeping dose on this basis constant and improving lesion/tissue enhancement.

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