Dechelation (Transmetalation)

Consequences and Safety Concerns With the Linear Gadolinium-Based Contrast Agents, In View of Recent Health Care Rulings by the EMA (Europe), FDA (United States), and PMDA (Japan)

Val M. Runge, MD

Abstract: The issue of dechelation (transmetallation) in vivo after administration of the linear gadolinium-based contrast agents, and potential safety concerns, is considered on the basis of an extensive, focused literature review. Early indications of potential problems included the high level of excess ligand used in the formulation of 2 agents (indeed the 2 least stable thermodynamically) and interference with laboratory tests when blood was drawn from patients relatively soon after administration of these same agents. The advent of nephrogenic systemic fibrosis in the late 2000s raised additional major concerns.

The correlation in 2014 of dentate nucleus hyperintensity on precontrast T1-weighted scans with multiple prior injections of linear gadolinium chelates, in patients with normal renal function, has driven subsequent research concerning dechelation of these agents in vivo. Unexpectedly high levels of gadolinium in the bone, skin, and liver have been found long term after administration, in animal models and in humans, although the latter data are limited. Bone may serve as a long-term reservoir, with a residual excretion phase for gadolinium after intravenous injection of the linear agents due to a subsequent slow release from bone. Many different patient populations could be vulnerable and potentially later develop clinical symptoms, although at this stage there are only limited data and small retrospective uncontrolled studies. Possible vulnerable populations include children, menopausal women, patients with osteoporosis (who are predisposed to fractures and often slow to heal or heal poorly), those receiving multiple doses, those with proinflammatory conditions, moderate renal dysfunction, or an undefined genetic predisposition. Of particular concern would be nephrogenic systemic fibrosis–like symptoms—including particularly pain and skin/joint symptoms, or disease related to the incorporation of gadolinium in hydroxyapatite in bone, in small subgroups of patients with a not yet defined propensity and/or cofactor. These concerns have led to withdrawal of the linear agents from the largest clinical market, Europe, with the exception of the hepatobiliary agents for delayed liver imaging, an indication that cannot be fulfilled by the current macrocyclic gadolinium chelates (for which these concerns do not apply).

Key Words: contrast media, magnetic resonance, dentate nucleus, safety, toxicity, gadolinium-based contrast agents, brain, bone, skin

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The gadolinium-based contrast agents (GBCAs) used in magnetic resonance imaging (MRI) can be differentiated on the basis of their thermodynamic and kinetic stability in vivo, which parallels that established in vitro.[1,2] Structural differences play a major role, with the linear chelates less stable than the macrocyclic agents. The linear chelates can further be divided into 2 groups, nonionic and ionic, with the former the least thermodynamically stable.[3] Dechelation, specifically release of the gadolinium ion, can occur in vivo as a consequence with the less stable agents, and has been studied in depth in recent years as safety concerns mounted regarding the least stable GBCAs. An interplay between thermodynamic and kinetic stability governs gadolinium release, with the macrocyclic agents markedly more stable due to their kinetic stability, which the linear agents lack. Reflecting the importance of this fundamental issue, the literature is replete over the years during the history of the development of the GBCAs—including in the very first published articles—with statements such as "the general aim was to find a compound that remained stable in vivo,"[4] "the design of intravenous agents depends upon the ability to reduce the toxicity of the agent by chelating or complexing the paramagnetic metal ion…is a highly stable chelate that does not undergo metal exchange in vivo,"[5] and "the safety of the gadolinium chelates is largely based on their stability in vivo,"[6] indeed the first comes from Weinmann's original landmark article describing the development of gadopentetate dimeglumine. Gadolinium is a rare earth metal not normally found as a trace element in the human body. It is toxic to mammals when present in water-soluble salts, both acutely (mostly by blocking of calcium channels) and chronically (due to profibrotic and proinflammatory effects).[7–9] This review focuses on the issue of dechelation with the GBCAs, examining 6 key issues. Covered in sequence are excess of chelate in the formulation of the agents, interference with analytical tests, gadolinium retention and excretion, the fate of gadolinium in the body and potential toxicity, possible chronic symptoms and syndromes, the status regarding regulatory action and changes in approval in the major 3 markets in the world (Europe, the United States, and Japan), and the concern regarding possible iatrogenic disease.

Excess Ligand

High levels of excess ligand were used in the formulation of the least 2 stable GBCAs, the linear nonionic agents, to reduce dechelation, with the efficacy therein debatable.

The formulations of many, but not all, of the gadolinium chelates that have been developed for clinical use contain excess ligand.[10] The quantity of excess ligand varies widely, with 2 outliers, gadodiamide and gadoversetamide.[1] The first is formulated with 12 mg/mL excess ligand (5%)—specifically Ca-DTPA-BMA (sodium salt), and the second with 28.4 mg/mL excess (10%)—specifically Ca-DTPA-BMEA (sodium salt). The next closest agent in terms of excess ligand is gadoxetic acid disodium, which is formulated with 1.0 mg/mL excess ligand (0.5%). The other approved agents feature either low amounts (gadopentetate dimeglumine 0.4, gadoteridol 0.2, and gadobutrol 0.5 mg/mL—for these 3 agents, all equivalent to 0.1% excess ligand) or no excess ligand (gadoterate meglumine, gadobenate dimeglumine) in the formulation.

The original formulation of gadopentetate dimeglumine contained 0.2 mg/mL excess ligand, which was very early in development doubled to 0.4 mg/mL. This change reduced the dose-dependent, transient elevation in serum iron and bilirubin seen early after injection, with a maximum at 8 hours postinjection.[11] It is of historical interest to note that in the clinical trials performed for approval purposes with gadodiamide

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From the Department of Diagnostic, Interventional and Pediatric Radiology, Inselspital, University Hospital, University of Bern, Bern, Switzerland.
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Correspondence to: Val M. Runge, MD, University Hospital of Bern, Inselpital, Freiburgstrasse 10 (INO B 106), 3010 Bern, Switzerland.

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blood samples were only collected at one time point postinjection, presumably at 24 hours (and thus would not have seen this change).[12]

The development of the nonionic linear chelates was controversial due to the knowledge that these derivatives of DTPA were susceptible to dechelation, in addition to possible breakdown of the ligand itself.[13] Ironically, an argument was put forth in early development that the addition of this degree of excess ligand (5% to 10%) would enhance the intrinsic safety of such complexes, with release of gadolinium ion from the complex admitted to be responsible for toxicity and hypothesized to be a consequence of transmetallation with zinc, calcium, and copper.[14] Research published in 1995 confirmed that gadodiamide as formulated with excess ligand led to lower (but still high) residual tissue gadolinium, in experimental animals, when compared with the agent without the excess ligand, with dechelation and changes due to the presence of excess ligand explaining these results.[15] The presence of this degree of excess ligand, with gadodiamide, also improves the acute tolerance (median lethal dose). It was not however until 2008 that the addition of such large amounts of excess ligand was indeed shown to reduce dechelation in in vivo–like conditions.[1] And, although it did reduce the gradual release of dissociated "free Gd"—for the 2 nonionic linear chelates, as evaluated in human serum at pH 7.4, to approximately 20% (with 15 days incubation), this level was still more than a factor of 10 times greater than that seen with the other linear chelates. As noted in the early investigation of nephrogenic systemic fibrosis (NSF) and its etiology, it is likely that the excess ligand only confers an advantage early on after injection of any agent, since other endogenous metallic ions such as copper, zinc, and calcium in vivo can be chelated, according to their affinity for the ligand and their local concentration.[16]

Interference With Analytical Tests

Gadodiamide and gadoversetamide, after injection, interfere with blood laboratory tests, in particular the measurement of serum calcium.

It was first published in 1995[17] that gadodiamide injection interfered with the determination of serum calcium on laboratory colorimetric tests. Despite an additional report in 1999 explaining this effect as the consequence of transligation (exchange of ligand) for Gd between the ligand of gadodiamide (DTPA-BMA) and the compound used for the colorimetric test (*o*-cresolphthalein complexone or OCP),[18] clinicians remained largely unaware of this issue until 2003. In that year, an article was published demonstrating spurious decreased serum calcium measurements in patients receiving gadodiamide, with "critical" hypocalcemia in many (and more common in renal insufficiency). Inappropriate treatment with intravenous calcium was reported in 7 patients.[19] Spurious hypocalcemia was deemed by the authors to be "a potentially important cause of unnecessary and potentially dangerous medical interventions."

Care needs to be exercised, given the findings just cited, when interpreting results of laboratory tests for patients who have recently received either gadodiamide or gadoversetamide, which of all the approved MR contrast media are the 2 most frequently implicated and having the greatest effect.[9,20] With normal renal function, the elimination half-life of these agents is approximately 90 minutes. To diminish the likelihood of any interference, it is suggested to wait 24 hours between administration of these contrast agents and blood specimen collection. The waiting period for patients with renal insufficiency necessarily would be substantially longer, with the elimination half-life of these agents being much longer than 24 hours in patients with severely reduced renal function.[21]

The most prominent interference is with the measurement of calcium, angiotensin-converting enzyme, and serum iron.[19,22,23] Results depend upon the specific analytical method used. The interference seen after gadodiamide and gadoversetamide administration has been concluded to be due to the dissociation of these gadolinium chelates, with macrocyclic chelates not producing any interference with analytical methods.[24] For example, in the presence of OCP (used for the calcium colorimetric assay), it has been shown that gadodiamide disappears and the free ligand and a new complex Gd-OCP appear.[24] In the case of circulating angiotensin-converting enzyme, an effect of the added free ligand, with gadodiamide and gadoversetamide, is likely.[22] In regard to the determination of serum iron and problems therein principally with gadodiamide and gadoversetamide, the situation would most likely arise only shortly after contrast administration or in patients with renal impairment. This effect upon the measurement of serum iron has been shown to occur with all the linear agents tested, and not with macrocyclic agents.[24] Indeed, the thermodynamic stability constant of DTPA-BMA is higher with iron than for both gadolinium and calcium.

Gadolinium Retention/Excretion

A residual excretion phase, with subsequent slow release from bone, has been identified for the GBCAs, with the linear nonionic and to a lesser degree the linear ionic agents having high long-term levels in bone, skin, and liver.

Upon injection, the GBCAs are distributed in the extracellular space and eliminated (as was previously thought) unchanged by the kidneys—with additional elimination in the bile for 2 agents (Table 1). The blood elimination half-life of the agents in healthy adults is about 90 minutes.[10,25] Regulatory information (specifically, for example, the summary of product characteristics in Europe), however, does not detail the percentage retained beyond 24 hours, or the subsequent involved pathways. The presence of a long-lasting residual excretion phase was first described in 1996,[26] being further developed and exemplified in a 2016 article.[27] It is now known that macrocyclic agents undergo a much faster residual excretion from the body than linear agents. The mechanism for the long-term retention of the linear agents and their subsequent slow release from bone in vivo is likely explained by their dissociation. The existence of substantial bone deposition raises the possibility of toxicity therein, in part due to bone marrow loss or a decrease in cancellous bone but also due to the risk of Gd release in patients with increased rates of bone resorption (eg, osteoporosis patients and menopausal women).[28]

Research performed in 1995, well before the recognition of NSF and the later discovery of focal dentate nucleus accumulation, identified a separation of whole-body clearance data after 24 hours dependent on GBCA stability.[15] Formulated gadodiamide left the largest % remaining at the latest time point sampled (14 days, in mice), specifically 0.3%, followed by gadopentetate dimeglumine, 0.1%, with the 2 macrocyclic agents evaluated (gadoteridol and gadoterate meglumine) having the least residual Gd in the body. Although these differences in delayed biodistribution were identified, the study did not evaluate the form of the retained Gd. Liver and bone had the greatest detected residual Gd at the latest time point evaluated, with the residual Gd correlating (as with the whole-body data) with GBCA stability. For example, in the femur, 0.01% residual was identified with formulated gadodiamide, 0.003% with gadopentetate dimeglumine, and below the limits of detection with the 2 macrocyclic agents evaluated (gadoteridol and gadoterate meglumine).

In 2009, during the NSF era, Gd deposition in the skin was studied in experimental animals.[29] Using rats, Gd was assayed from skin biopsies obtained sequentially for a year after intravenous injection of the GBCAs. The evaluation was limited to the agents with solely renal excretion. As with the results in other organs in the earlier radiolabeled study, it was demonstrated that the Gd concentration in the skin, regardless of time point, correlated with chelate stability. In addition, in the case of the linear GBCA gadodiamide but not with a macrocyclic GBCA, the presence of dissociated and soluble Gd in skin and bone was shown by the relaxometry technique.[30] Continuing with a description of the results from the 2009 publication, the less stable

TABLE 1. GBCAs for Intravenous Injection, Characteristics, Recent Regulatory Changes

				2017 and 2018 Regulatory Changes*		
Brand Name	**Generic Name**	**Chemical Structure**	**Stability**	**Europe**	**United States**	**Japan**
Dotarem	Gadoterate meglumine	Macrocyclic	Highest			
Eovist (Primovist)	Gadoxetate disodium	Linear, ionic	Intermediate	Delayed liver imaging only		
Gadovist (Gadavist)	Gadobutrol	Macrocyclic	Highest			
Magnevist	Gadopentetate dimeglumine	Linear, ionic	Intermediate	Suspended		"For use if a macrocyclic is not appropriate"
MultiHance	Gadobenate dimeglumine	Linear, ionic	Intermediate	Delayed liver imaging only		(Never approved)
Omniscan	Gadodiamide	Linear, nonionic	Lowest	Suspended		"For use if a macrocyclic is not appropriate"
OptiMARK	Gadoversetamide	Linear, nonionic	Lowest	Expired	No longer available	(Never approved)
ProHance	Gadoteridol	Macrocyclic	Highest			

*The package inserts have also been modified after requests from the respective agencies. This applies to both macrocyclic and linear chelates. The wording is different between Europe, the United States, and Japan. The difference between macrocyclic and linear chelates is clearly made in Europe and Japan (as well as in Canada, Australia, and South Korea). Only the FDA mandated the same changes in the package inserts for both macrocyclic and linear chelates, minimizing the difference between classes. However, in the required FDA wording, it is noted that gadolinium retention is less with the macrocyclic agents.

GBCAs resulted in higher Gd concentrations, with Gd in the skin undetectable in the later time points after administration of the macrocyclic GBCAs. Not only was delayed clearance noted with the linear GBCAs, but in addition a plateau in concentration was reached by 60 days with relatively stable residual amounts thereafter. This was also subsequently shown in the brain, with demonstration that Gd is no longer in its initial molecular form there as well after injection of the linear agent gadodiamide.[31]

Of critical importance are biospeciation studies, determining the form in which gadolinium is present in tissue, which can serve to drive hypotheses and further research concerning potential acute and chronic toxicity.[1,27,31–33] According to the most common current hypothesis, GBCAs move from the bloodstream to the cerebrospinal fluid and thence into the brain. With the linear GBCAs, a portion remains intact and there is dechelation (transmetallation/transchelation) of the remainder.[32] The latter leads to soluble Gd (bound to macromolecules),[34,35] causing the high signal intensity on T1-weighted scans in the dentate nucleus, and insoluble Gd (for example as gadolinium phosphate), with weak or no effect on T1. Acute[7,36] and chronic toxicity need to be distinguished, the latter possibly leading to inflammatory reactions. The distribution and local concentration of gadolinium will differ depending upon its form and, for the soluble species, the macromolecules to which it is bound. Most speciation analysis requires a soluble sample, with appropriate controls needed to ensure that the gadolinium species remain unchanged during sample preparation.

During the NSF period, very high levels of Gd were also documented in the skin of these patients. Despite regulatory efforts since connection of that disease with administration of GBCAs, occasional patients have been diagnosed in subsequent years.[37] Elemental analysis has been used in at least one such patient for disease diagnosis. It is important to note, however, that levels in the skin of Gd in 1 patient (a case report)—who had normal renal function and dentate nucleus hyperintensity—were shown to be at or above the level demonstrated in NSF patients.[38] The question thus arises whether patients such as the individual in this case report may manifest NSF-like symptoms. For example, the patient in question had increased CD34 immunoreactivity in the subcutaneous tissue, indicating inflammation and/or tissue injury. The patient also had joint contractures; however, without joint biopsy, the association with high gadolinium levels could not be confirmed or excluded.

Recently, detailed evaluation of midterm (with regards to lifespan, and still in the washout phase of the intact chelate) Gd deposition in different organs has been performed in rats, comparing the 3 groups of agents as defined by their relative stability (from lowest to highest), the linear nonionics, linear ionics, and macrocyclic compounds.[31,32,39] At 8 weeks after repeated high doses, skin, bone, and muscle levels of Gd were greatest with formulated gadodiamide, less with gadopentetate dimeglumine, and lowest (near control values in skin and muscle) for the 2 macrocyclic compounds evaluated. This study, as with most others, measured total Gd by inductively coupled plasma mass spectrometry (ICP-MS), with no information provided about the form of the tissue Gd (dissociated or chelated, soluble or insoluble). Of note (and specifically different in comparison with skin results), deposition in the brain was similar for formulated gadodiamide and gadopentetate dimeglumine, with that for the 2 macrocyclic compounds again near control values (close to undetectable). No statistically significant difference was found between the 2 macrocyclic agents evaluated. Two additional publications show retention in the skin in rats to be below the limit of quantification or in the same range as controls for all 3 macrocyclic agents, with one of these 2 articles also providing data specifically for gadoterate meglumine in juvenile animals.[29,40] The latter confirmed in juvenile animals below the limit of quantification amounts of Gd at 60 days in bone and liver as well.

In the literature, a 2006 study compares bone deposition in humans after formulated gadodiamide and gadoteridol administration.[41] The study is limited due to the short time frame (1 week) between agent administration and bone biopsy. In this study, the nonionic linear agent left approximately 4 times more Gd in the bone as compared with the macrocyclic agent. A subsequent study showed that osteoporotic patients exposed to Gd have significantly lower Gd concentrations, raising the question whether there may be an increased risk of Gd release in subjects with increased rates of bone resorption.[28] Large at risk groups for Gd release from the bone reservoir might thus exist, including osteoporosis patients and menopausal/postmenopausal women.

Scant human autopsy data exist to compare with animal studies. The human studies are also limited to date by the lack of control for time after the last recorded GBCA administration, as well as the inability to exclude additional injections in any patient beyond that available in the medical record of the institution from which the report was generated.

Gadolinium Fate/Toxicity

Possible vulnerable patient populations include children, menopausal women, patients with osteoporosis, those with renal failure, those with systemic inflammation, and those receiving multiple doses. For NSF, fibrosis led to contractures, with collagen deposition involving nerves likely leading to the burning pain.

Gadolinium in the skin was extensively investigated during the period that NSF was discovered and linked to GBCA use. Skin biopsies were consistent with in vivo release (also described using the terms transmetallation, transligation, and dechelation) of the gadolinium ion from gadodiamide and its retention in apatite-like deposits.[42] The variable delayed onset of disease in NSF patients after gadodiamide injection and the increasing concentration of Gd in the skin over time would suggest a solubilization of the Gd species released from the hydroxyapatite crystals with subsequent binding to circulating macromolecules (this has not yet been demonstrated). As concluded by a subsequent investigation, NSF is in essence a manifestation of toxicity from gadolinium released by MRI contrast media, probably in the presence of cofactors.[8,43] It has also been shown that gadodiamide (presumably the released Gd ion) stimulates fibroblast growth (with fibrosis of the skin, joints, and internal organs defining this disease).[44] In NSF, gadolinium is detected both extracellularly and intracellularly, the latter in macrophages and fibrocytes. The acidic environment in lysosomes, after endocytosis, might promote dissociation and subsequent deposition as insoluble phosphates. Animal studies performed during this era showed (with formulated gadodiamide) that the same levels of long-term Gd skin retention were reached whether doses were given over a short or long period. However, skin lesions were more severe when doses were given over a short period.[29]

The changes in muscles, fascia, nerves, and vessels were studied in depth in affected patients during the NSF era, along with the specific gadolinium localization. In these studies, muscle was noted to be the most common organ involved after skin, with CD34-positive cellular fibrosis seen therein.[45] Muscle biopsies showed disease ranging from mild myopathic changes to severe fibrosis, correlating with the degree of muscle hardening and immobility. Atrophy, infiltration with fibrous tissue, and increased collagen deposition were seen.[46] Thickening of tendons and periarticular tissues was also noted.[47] Skin and muscle fibrosis were deemed responsible for the contractures seen in NSF. Fibrous bands of collagen were also noted, invading nerves as well as muscle fibers, causing neuropathies with both neurogenic and myopathic features.[48] A sensory-motor polyneuropathy was thought to be responsible for the burning pain so characteristic of NSF. Regarding the vessels, perivascular Gd deposition was noted, with colocalization of calcium and phosphorus.[45]

Metals in general can be taken up into bone either by active incorporation during osteoblastic mediated bone mineralization or by passive exchange into the bone lattice. Regarding Gd specifically, it is proposed that hydroxyapatite can incorporate this metal ion.[42] Of concern is that Gd incorporation into bone could negatively impact bone health, as occurs with other metals such as lead. There is the potential for inhibition of fracture healing and altering the metabolism of osteoclasts and osteoblasts responsible for bone remodeling.[49–51]

Based primarily on animal data, long-term retention of Gd in the body is thought to be highest in bone (although perhaps not with gadodiamide, where higher gadolinium concentrations have been noted in skin).[39,52] In bone, as previously noted, Gd can replace calcium in hydroxyapatite. Dissociation has been shown to occur in vivo for some linear chelates, potentially explaining their long-term retention and slow release from bone. Potential toxicity from such stores in bone warrant further investigation.[27] The release of Gd from the long-term reservoir in bone could also explain the increased skin Gd concentration observed on sequential biopsies in some NSF patients, despite the lack of further GBCA administration, as well as the delayed onset of disease seen in some NSF cases.[42,43,53,54]

The long-term reservoir of Gd in bone suggests the possibility of specific vulnerable patient populations. Postmenopausal women and pregnant or lactating women have increased bone resorption, which would predispose these patients to Gd release from bone. The same is true for osteoporosis. In children, there is increased bone formation, and this poses the risk of accumulating a larger bone reservoir of Gd. Patients exposed to multiple linear GBCA doses, whether due to chronic illness or high-risk screening, would represent a further potential group at risk, due to accumulation of larger amounts of Gd in bone. Proinflammatory events, including surgery, could predispose patients in any of these populations to further risk, in the presence of a long-term bone Gd reservoir. Proinflammatory events, along with hyperphosphatemia, were noted in the NSF period to place dialysis patients at greater risk for the development of NSF.[55]

The potential for Gd toxicity in the liver has received little attention to date. This organ likely contains, long-term following linear GBCA administration, the third largest concentration of Gd, after the bone and skin. Although not well studied, the lanthanides are known to cause liver necrosis.[7,26]

Potential Chronic Symptoms

Questions have been raised regarding possible cutaneous, musculoskeletal, and pain syndromes linked to GBCA administration in patients with normal renal function, in small and as yet undefined subgroups.

There are suggestions of small groups of normal renal function patients with chronic symptoms from Gd deposition when examining the scientific literature and the Food and Drug Administration (FDA) adverse event reporting system. In the latter, there is a clustering of adverse events around cutaneous, musculoskeletal, and pain syndromes. These symptoms overlap that seen in NSF, raising the concern and increasing the likelihood of an association with GBCA exposure. The need for the presence of a cofactor for disease development might explain the low incidence relative to the very high number of contrast administrations performed worldwide over the years. Possible cofactors for the development of disease in the setting of normal renal function include but are not limited to medication interaction (containing competing metals, such as Ca, Zn, or Cu, favoring transmetallation), elevated serum phosphate, proinflammatory conditions, and genetic variables.

A case report in 2016 describes 4 patients with normal renal function developing symptoms within hours to weeks after GBCA administration.[56] Burning/sharp pain involving the extremities was seen in all 4 and involved the trunk in 3—symptoms such as that seen in NSF. Skin thickening was seen in the late stage, also characteristic of NSF. This work was followed by a report in 25 patients with normal renal function and symptoms presumed related to GBCA administration receiving chelation therapy.[57] A large, statistically significant increase in urine Gd content was measured in this population after intravenous Ca-/Zn-DTPA therapy. Of particular note, however, was that 11 patients of the 25 experienced transient worsening of at least some symptoms, with the reasons unclear. Caution is suggested in interpretation of this study, and specifically the urine Gd content. It was not a crossover study (no placebo). No clear conclusions can be made without the data from each individual, and the agent(s) administered cannot be verified with certainty.

Current Health Care Policy in the 3 Largest GBCA Markets Worldwide

Concern regarding gadolinium release from the linear chelates, and potential complications therein, have led to the withdrawal of these agents in Europe, with the exception of the hepatobiliary agents for delayed liver imaging. In the third largest market, Japan, these agents are to be used only when macrocyclic agents are not appropriate.

In the world's largest market for the GBCAs, Europe, in November 2017, the European Commission adopted the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use recommendation—the result of a 21-month safety review—regarding the GBCAs. The whole-body marketing authorizations of the multipurpose linear GBCAs (Omniscan, Magnevist, and MultiHance) were suspended (that for Optimark was allowed to lapse earlier during the year by the manufacturer). Approval was continued, pending possible further review, for 2 special indications involving linear GBCAs-Primovist and MultiHance for delayed liver imaging and a dilute formulation/extremely low dose of Magnevist for intra-articular injection. The option to defer product suspensions for up to 12 months was granted on the basis of potential unmet medical need and lack of availability of suitable alternatives on a country basis. Austria and Denmark enacted these changes in December 2017, France in January 2018, and the United Kingdom, Germany, and Italy in February 2018.

In the United States, in December 2017, 3 months after an advisory committee meeting, further instructions were issued by the FDA, leading in May 2018 to changes in the package inserts and the availability to patients of a Medication Guide. The package inserts (prescribing information in the United States) were changed for all agents, incorporating the same standard detailed wording and explanation regarding gadolinium retention. Agents were differentiated into 3 groups on the basis of the degree of Gd retention. Rare reports of pathologic skin changes in patients with normal renal function were noted, including adverse events involving multiple organ systems. Regarding the clinical consequences of gadolinium retention in patients with normal renal function, it was noted that these have not yet been established. However, it was stated that certain patient groups might be at higher risk, specifically those requiring multiple doses over their lifetime, pregnant and pediatric patients, and patients with inflammatory conditions. Furthermore, the following guidance was given in terms of a Medication Guide that should be made available to patients:

"All MRI centers should provide a Medication Guide the first time an outpatient receives a GBCA injection or when the information is substantially changed. In general, hospital inpatients are not required to receive a Medication Guide unless the patient or caregiver requests it. A health care professional who determines that it is not in a patient's best interest to receive a Medication Guide because of significant concerns about its effects may direct that it not be provided to that patient; however, the Medication Guide should be provided to any patient who requests the information."

The Medication Guide for each agent is individualized and available on the FDA Web site (https://www.fda.gov/Drugs/DrugSafety/ucm085729.htm). The following statement was however added for all agents: "There are different GBCAs that can be used for your MRI exam. The amount of gadolinium that stays in the body is different for different gadolinium medicines. Gadolinium stays in the body more after Omniscan or Optimark than after Eovist, Magnevist, or MultiHance. Gadolinium stays in the body the least after Dotarem, Gadavist, or ProHance."

As of September 15, 2018, Optimark (one of the 2 linear nonionic gadolinium chelates) will no longer be available on the US market. Guerbet incidentally acquired the agent as part of its 2015 purchase of the contrast media and delivery systems business of Mallinckrodt Pharmaceuticals. Guerbet also allowed the approval for distribution of Optimark in Europe to expire in 2017.

As background to the recent Japanese guidance, it should be noted that only 3 linear gadolinium chelates were ever approved in Japan (Omniscan, Magnevist, and Primovist), whereas all 3 macrocyclic agents are approved. In November 2017, the decision was issued by the Japanese authorities to restrict the use of the nonspecific linear GBCAs (Omniscan and Magnevist) to patients where there is no other alternative (specifically when use of macrocyclic agents would not be appropriate). This was done to allow the use of the 2 linear agents in patients with reactions to macrocyclic agents. The Japanese decision was based on the higher accumulation in the brain of gadolinium reported with the linear agents. Although a labeling change was made for all 3 linear agents, regarding the larger amount of gadolinium remaining in the brain as compared with the macrocyclic agents, the use of Primovist was not restricted. This agent is the only hepatobiliary gadolinium chelate available in Japan, with high usage due to the prevalence of hepatocellular carcinoma.

Additional Issues

That dechelation occurs in vivo after administration of the linear GBCAs is well established. The concern is regarding possible clinical symptoms, with limited such data and investigations to date. Identification of the macromolecules that bind the Gd in the case of linear GBCAs may be the starting point for any investigation on toxicity.

A major reason that health care authorities in Europe and Japan have left available to clinicians—but generally only for delayed hepatobiliary phase imaging—the linear hepatobiliary gadolinium chelates is that these were deemed medically necessary, and without comparable macrocyclic analogues (also due to the smaller dose used, at least for gadoxetic acid disodium, and the lower likelihood for repeat injections). The scientific literature is replete with articles demonstrating the importance in terms of medical diagnosis, lesion characterization, and response to therapy provided by delayed imaging with the hepatobiliary linear gadolinium chelates.[58–60]

Renal function needs to be kept in mind in regard to the potential for long-term gadolinium deposition (and the degree thereof) after administration of the linear chelates. It is clear from the evaluation of animals receiving such agents that renal dysfunction (with the correlate in patients being mild or moderate chronic kidney disease) potentiates deposition of gadolinium not only in the cerebellum but also in the brain and bones.[61] These results are fully consistent with a prior clinical study,[62] thus stressing the translational value of most nonclinical studies.

Animal studies performed by many different research groups have definitively established that dechelation occurs after injection of the linear gadolinium chelates.[32] Evidence for such includes the hyperintensity on imaging of the dentate nucleus (and other structures, in patients receiving a high number of injections of the linear agents),[63] measurement of tissue gadolinium concentration by ICP-MS,[64] evaluation of tissue homogenates by gel permeation chromatography,[33] and evaluation of spatial tissue distribution of Gd by laser ablation coupled with ICP-MS.[39]

In the development of the gadolinium chelates, it was not thought that this group of agents would have access to the brain, other than in disease states, due to the blood-brain barrier. It is now known that at least one pathway for access to the brain, in normal individuals, exists—specifically the glymphatic system.[65] Further supporting the study of Taoka and colleagues, an additional nonclinical study revealed insoluble Gd deposits in specific areas consistent with this pathway.[66] Despite the existence of this pathway, only minute fractions (<0.001%) of the total gadolinium dose are found in the brain.[39] In addition to the demonstration of this pathway in animals, support for its existence has been shown in patients, with demonstration of dentate nucleus hyperintensity 2 to 12 years after intrathecal injection of gadopentetate dimeglumine.[67]

Although many articles have been published advocating alternatives to the gadolinium chelates, both development and—even in the case of already existing products—clinical approval is very unlikely. First and foremost, the issue of gadolinium deposition has arisen due to the existence (and widespread use, formerly) of the linear chelates, with dechelation and focal tissue deposition of gadolinium not seen in vivo with the macrocyclic agents. The safety profile of the macrocyclic agents is excellent, as shown by hundreds of millions of injections

worldwide. Additional reasons that alternative agents are very unlikely to be developed include cost, toxicity, and the time required in terms of years needed for approval. For example, even as of 2006, the cost of developing an agent for diagnostic imaging was estimated to be in the $200 million range, with the current global market only $500 million/year in sales.[68] Potential toxicity is a problem for proposed new manganese-based agents and iron particles,[69] with hypersensitivity reactions also a concern for the latter. Off-label use of other agents, for example as advocated for ferumoxytol,[70] does not take into consideration the significant risk of hypersensitivity reactions, which explains in part why such agents are not approved for clinical use as contrast media.

As an alternative to the development of iron or manganese agents for magnetic resonance, improved chelate design—possible due to the advances in chemistry in the past 30 years—could result in next-generation GBCAs with markedly higher relaxivity.[71] These agents would need to have a stability matching or improved relative to the current macrocyclic agents. Commercial development could be justified by the use of a lower gadolinium dose yet achieving the same contrast enhancement as with the current macrocyclic agents, or by keeping the dose at 0.1 mmol/kg and improving further diagnostic efficacy.[72]

The incidence of reactions to a product (and specifically that of a competitor) has often been used by the pharmaceutical industry to influence market share. Indeed, such an argument was used by 1 company in defense of its agent (with data from an article subsequently published), in a failed attempt to justify its continued approval by the EMA in 2017.[73] If one considers the gadolinium chelates that have only renal excretion (excluding the hepatobiliary agents), "to the best of current scientific knowledge, all of the gadolinium chelates… have the same incidence of severe anaphylactoid reactions." "This is also true for minor adverse reactions, the 2 most notable being nausea and hives."[74] If the incidence of hypersensitivity reactions was indeed lower with one of the gadolinium chelates, and not just a marketing argument, then the FDA and EMA approvals would carry such a specific statement. A recent investigation has specifically looked at this question, as many sites have transitioned from linear to macrocyclic agents. During transition from 1 contrast agent to another, a transient increase in frequency of hypersensitivity-like reactions can be observed, which is well described in the scientific literature as the "Weber effect." This is defined as "a transient rise in reported adverse drug reactions after the introduction of a new drug to the market, classically peaking within 2 years and declining thereafter."[75] In such a transition, an increased incidence of reactions can also be seen with the agent that is being discontinued, with these observations likely due to an increased awareness to contrast-related adverse events during the period of transition with increased attention to documenting such reactions.

The major concern with dechelation is the potential for clinical symptoms, both short and long term. Gadolinium is not a normal trace element in the body, and as one of the lanthanide metals can be in its unchelated form highly toxic. Perinatal exposure to a GBCA in mice has been shown to induce behavioral changes, more severe with a linear as opposed to a macrocyclic agent.[76] Although attention has been primarily directed toward the potential for clinical symptoms due to deposition in critical brain nuclei, such as the dentate nucleus, the potential for symptoms due to bone, skin, and liver deposition also exists. In a single case report, previously discussed, in a patient with normal renal function who received a very high number of injections of predominantly linear gadolinium chelates, skin samples demonstrated a very high level of gadolinium deposition, similar to reported levels seen in patients with renal failure and NSF.[38]

A re-evaluation of the NSF data in 2018 shows a profound effect of the year of market introduction and market share, among other issues, on the assessment of risk (by agent) that was made in the late 2000s.[77] In the concluding sentence, it is noted that comparative risk assessments should be primarily based on objective product parameters, including specifically and foremost chelate stability. As was hypothesized in 2007, the etiology of NSF was eventually shown to be caused by the instability of a gadolinium chelate and dechelation in vivo.[16] It should be noted that NSF-like symptoms of extremity and torso pain have been described, as previously discussed, in a small number of patients with normal renal function after gadolinium chelate injection.[56] Unfortunately, all such reports to date are anecdotal. Evidence of dechelation in patients with symptoms is, however, clear due to the existence of a published clinical trial with chelation therapy, also previously discussed.[57] Urinary gadolinium content increased significantly in these patients after administration of Ca-/Zn-DTPA, with improvement in symptoms for 13 of 25 patients, although symptoms were worse in 2. The mixed results, together with a transient worsening of some symptoms in 11 patients, may reflect the extensive bone reservoir of gadolinium.

CONCLUSIONS

The gadolinium chelates (also known as the GBCAs) are well established today as the contrast media for magnetic resonance, with an excellent overall safety profile. These agents are critical for disease diagnosis and indeed to clinical medicine worldwide.

Recent findings have again emphasized that within the group of previously approved agents there is a range of stability, with this being one key aspect for safety in man. A relatively recent clinical imaging finding, specifically hyperintensity of the dentate nucleus on unenhanced scans after multiple doses of the linear gadolinium chelates, has driven subsequent key research in this area. Many in-depth, well-performed, scientific investigations have now been completed in this area, clarifying mechanisms and consequences. It is now known that administration of the linear gadolinium chelates to patients, despite normal renal function, leads to long-term deposition of gadolinium in the skin, bone, liver, and brain (with that in the brain occurring with a focal, specific distribution). Deposition in the bone also serves as a potential reservoir for later release. Dechelation occurs in vivo with the linear agents, leading to this tissue gadolinium deposition and raising safety concerns.

In 2016, the question was raised whether clinical practice with the less stable gadolinium chelates, specifically those that offer no additional clinical benefit when compared with the approved macrocyclic agents, would continue due to these issues.[78] Today, the linear agents (excluding hepatobiliary applications) have either been withdrawn or face continued reduction in market share in the world's 3 largest markets (Table 1). This is the result of both regulatory actions and patient/physician pressure. Unfortunately, outside of the industrialized countries, knowledge concerning these issues can be poor, leading to continued use of high-risk agents.[79] It is interesting in retrospect, but also somewhat disappointing, to consider that the knowledge of the greater stability of the macrocyclic chelates was well established by 1989, and indeed earlier to dedicated researchers in the field, and that it was suggested at that time that the macrocyclic agents should replace the linear chelates due to the improved safety margin.[13]

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