Radiology

Nephrogenic Systemic Fibrosis: A Chemical Perspective[1]

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Recent concern regarding an association between use of gadolinium-based magnetic resonance (MR) imaging contrast agents and nephrogenic systemic fibrosis (NSF) has called into question the long-standing notion that patients with renal insufficiency could receive these agents with negligible risk. A growing number of reviews and editorials (1–5) and clinical studies (6–9) have either attempted to describe the degree of association between NSF and contrast agent administration or described more mechanistic studies (10,11) aimed at defining the relationship(s) between the physicochemical properties of individual agents and their relative propensity to cause NSF. The ultimate goal of these investigations is to understand the origins of NSF in order to create rational, safe, and evidence-based guidelines for using gadolinium-based contrast agents in clinical practice. We believe that it is important for radiologists to have an appreciation of the relevant chemical properties of MR contrast agents for considerations of the association between NSF and MR contrast media. To begin, we offer a brief review of MR contrast media.

The use of MR contrast agents has been motivated by the ability to increase the sensitivity and specificity of MR diagnoses. Diagnostic improvement is possible when the contrast between tissues or spaces is augmented. In MR imaging, contrast manipulation with pharmaceutical agents is achieved indirectly by altering the local magnetic environment. This alteration affects the T1 and T2 relaxation times as a consequence of interactions between the unpaired electrons of a metallic ion and the hydrogen nuclei of water molecules. It is the presence of unpaired electrons in the 3d (transition metals) or 4f (lanthanide) orbitals from which the property of paramagnetism that underlies contrast augmentation derives. This property is inherent to a number of metal ions, making them attractive as MR contrast agents. The lanthanides, the set of chemically related elements with atomic numbers from 57 to 71 and properties similar to those of lanthanum, have unpaired electrons and deserve special mention since one of these, gadolinium, is the primary element from which MR contrast media are developed.

Paramagnetic MR contrast media generally consist of a metal ion bonded to an organic moiety (ligand) to form a metal chelate complex. This complex is essential for biologic use, since naked metal ions are highly toxic. The successful development of an MR magnetopharmaceutical agent relies on the ability of a complex to alter the MR signal favorably, distribute differentially in tissue, and demonstrate an acceptable safety profile. Recent observations of associations between NSF and use of gadolinium-based contrast media present a challenge to the safety profile.

There is still no definitive answer to the question of how the administration of gadolinium-based contrast agents in patients with impaired renal function results in NSF. However, persuasive pieces of evidence derived from a combination of in vitro and in vivo animal data and clinical studies are beginning to emerge. These pieces of evidence can be connected to form the basis for establishing a hypothesis about the causal relationship between administration of gadolinium-based contrast agents and development of NSF. For example, High et al (11) stated recently in a research article describing the results of assays to assess gadolinium concentrations in tissue samples from patients with NSF, "Ultimately, it is our hypothesis that in vivo transmetallation (displacement of Gd^{3+} from the chelating agent) is in-

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volved in the mechanism of tissue accumulation."

It has been known for many years that free Gd^{3+} is toxic (12). The fact that free Gd^{3+} is toxic is reported almost universally in all of the discussion sections of articles describing NSF. The authors of most of these articles then proceed to discuss the likelihood that the approved contrast agent dissociates to deposit free Gd^{3+} in terms of thermodynamic stability constants, conditional stability constants, and/or selective stability constants. The thermodynamic stability constant is the in vitro measure of affinity between a Gd^{3+} ion and each organic ligand that comprises the metal-ligand complex or chelate. The conditional stability constant is also an in vitro measure of the affinity between Gd^{3+} and each organic ligand measured at a pH of 7.4 under nearly physiologic conditions (13). The selective stability constant is a reflection of how effectively naturally occurring endogenous cations, such as Zn^{2+}, Cu^{2+}, and Ca^{2+}, compete with Gd^{3+} to bind to the organic ligand (13–15).

While these parameters are important in that they reflect the thermodynamic stability of these gadolinium chelates, which in turn allows an estimate of free noncomplexed Gd^{3+} at equilibrium under a variety of conditions (both in vitro and in vivo), they do not provide the full story as to why some organic ligands are more likely than others to release more Gd^{3+}. The missing component in most of the discussions published to date is the question of how fast dissociation approaches equilibrium in vivo. This question is based on chemical kinetics—not thermodynamics—a topic largely overlooked in current discussions of the physicochemical properties of these chelates.

Lanthanide chemists have long recognized that in addition to having favorable thermodynamic stabilities, these chelates must also be kinetically inert—that is, their rates of formation and dissociation must be slow. The basis for distinguishing between thermodynamic and kinetic stability is illustrated in Figure 1. The thermodynamic stability constant is determined on the basis of the enthalpy of formation value and the entropy of formation value (16,17). The enthalpy value reflects the relative energy of the product(s) with respect to the starting materials, and as illustrated in Figure 1, the product has a lower enthalpy than does the starting materials. The relationship of the entropy of formation with the thermodynamic stability constant is a bit more complex and cannot be depicted in Figure 1. It is critical to emphasize that the rates of formation—that is, how quickly these chelates form and how rapidly they reach equilibrium—are determined by another factor—the E_a, as shown in Figure 1. The E_a parameter is the potential energy that must be overcome for the reaction to proceed. The rate of dissociation serves as an important parameter for comparing contrast agents in the context of the free gadolinium hypothesis—that the deposition of free Gd^{3+} in tissue induces NSF. The E_a is determined on the basis of a potential energy barrier that is higher than that for formation (the reverse reaction illustrated in Fig 1). Most lanthanide chelates have large E_a values for both formation and dissociation. That is, they have very slow rates of formation and dissociation (18).

Thus, the thermodynamic stability constant determines the concentrations of gadolinium chelate, free chelate, and free gadolinium chelate at equilibrium, while rates of formation and dissociation, which are dictated by E_a, determine how rapidly these compounds reach equilibrium. In principle, it is possible for a chelate to have a relatively low stability constant and a high E_a value; this phenomenon results in a "kinetically trapped" chelate that does not dissociate on any relevant time scale.

The biologic relevance of the kinetic properties of relevant contrast agents has also been studied. In 1992, Wedeking et al (19) examined the chemical properties of a number of gadolinium chelates, including their stability constants, ionic charge, lipophilicity, and size. They found that the thermodynamic and conditional stability constants could give only partial indications of which chelate was likely to induce residual Gd^{3+} deposition in mice. These authors found a very strong correlation between the dissociation rates of chelates in acid and the long-term deposition of Gd^{3+} in rat tissues such as liver and bone (femur). The nonchemist may be puzzled as to why the dissociation rates were measured in 0.1 mol/L acid, a condition that seems decidedly nonphysiologic. The major reason is that at a neutral pH, these rates of dissociation are simply too slow to measure. However, as will be discussed, the measured rates of dissociation can be extrapolated to a neutral pH.

The acid dissociation rates for the five Food and Drug Administration–approved intravenous gadolinium-based contrast agents and the two gadolinium-based contrast agents used in Europe are given in the Table. Although to our knowledge, the dissociation rate for gadobenate dimeglumine has not been reported, it is likely similar to those reported for the other substituted pentetic acid–like chelates. Although the dissociation rates at a physiologic pH are substantially slower than the rates given in the Table, the relative rates shown here likely reflect the relative rates of dissociation at a physiologic pH. From

Figure 1

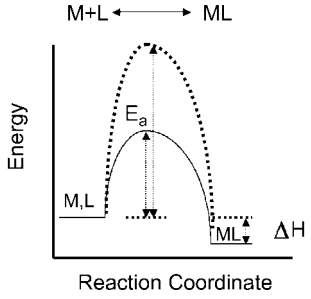

Figure 1: Energy diagram illustrates formation of a chelate *(ML)* created by combining two chemicals—free Gd^{3+} *(M)*, which is a metal ion, and an organic ligand *(L)*. The energy of activation (E_a) is shown for two different hypothetical ligands. One ligand (dotted curve) has a much greater E_a compared with the other ligand (solid curve). ΔH = enthalpy of formation.

Thermodynamic Stability Constants and Acid Dissociation Rates for Gadolinium-based MR Contrast Agents

Generic Name of Contrast Agent	Chemical Abbreviation	Brand Name*	Amine Backbone Structure	Stability Constant	Dissociation Rate in 0.1 mol/L HCl (sec^{-1})
Gadoversetamide	Gd-DTPA-BMEA	OptiMark (Mallinckrodt, St Louis, Mo)	Linear	16.8	$>2.2 \times 10^{-2}$
Gadodiamide	Gd-DTPA-BMA	Omniscan (GE Healthcare, Princeton, NJ)	Linear	16.8	$>2 \times 10^{-2}$
Gadopentetate dimeglumine	Gd-DTPA	Magnevist (Bayer Healthcare Pharmaceuticals, Wayne, NJ)	Linear	22.2	1.2×10^{-3}
Gadobenate dimeglumine	Gd-BOPTA	MultiHance (Bracco Diagnostics, Princeton, NJ)	Linear	22.6	Not reported
Gadobutrol	Gd-DO3A-butriol	Gadovist (Schering, Berlin, Germany)	Macrocyclic	21.0	2.8×10^{-6}†
Gadoteridol	Gd-HP-DO3A	ProHance (Bracco Diagnostics, Princeton, NJ)	Macrocyclic	23.8	6.4×10^{-5}
Gadoterate meglumine	Gd-DOTA	Dotarem (Guerbet, Aulnay-sous-Bois, France)	Macrocyclic	25.6	8.4×10^{-7}‡

* Manufacturer name and location are in parentheses.

† Value estimated from data in Toth et al study (20).

‡ Source.—Reference 21.

these data, it is clear that the dissociation rates for gadoteridol and gadoterate meglumine, both of which are derived from macrocyclic ligands, are much slower than those for the other contrast agents. Examples of the chemical structures of linear and macrocyclic gadolinium chelates are shown in Figure 2.

Figure 2

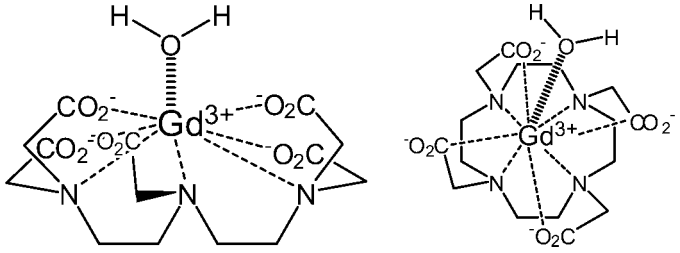

Figure 2: Chemical structures of gadopentetate dimeglumine (left), a linear chelate, and gadoterate meglumine (right), a macrocyclic chelate.

To extrapolate the acid dissociation data to a neutral pH, it is important to understand the mechanisms of dissociation of these chelates, the mechanisms of dissociation for linear chelates being slightly different from those for macrocyclic ligands. For the linear chelates, the rates of dissociation obey acid-catalyzed behavior (18) (and thus should become appreciably slower at a neutral pH) and first involve monoprotonation and diprotonation of the gadolinium chelate followed by dissociation of the Gd^{3+} ion. Thus, all complexes experiencing acidotic pH in tissue can be expected to dissociate more rapidly. Although some evidence indicates that competing cations can facilitate this dissociation, these effects are most relevant to the linear chelates. Overall, the rates of dissociation of Gd^{3+} from macrocyclic ligands are several orders of magnitude slower than their dissociation from linear systems. Competition for binding of endogenous ions to the ligand does not occur to any appreciable extent until the Gd^{3+} ion fully leaves.

For the macrocyclic ligands, dissociation is initiated by protonation at one of the acetate side arms and involves "uncaging" of the gadolinium from the macrocyclic ring while the proton is transferred from the acetate to a nitrogen atom in the macrocyclic cavity. The kinetic intermediate along this reaction pathway then corresponds to the Gd^{3+} ion sitting above the macrocyclic ring weakly complexed by the acetates. Once the nitrogen(s) becomes protonated, the Gd^{3+} ion has more difficulty falling back into the cavity and hence a greater chance of dissociating completely from the organic ligand.

On the basis of these considerations, the rates of transmetallation by endogenous ions should reflect only the rate-limiting step—that is, the rate of dissociation of the Gd^{3+} ion from each chelate. Thus, measured transmetallation rates should be surrogates for rates of dissociation of Gd^{3+} from these chelates. Laurent et al (22,23) determined the rates of transmetallation by zinc(II) for six approved gadolinium-based contrast agents at a neutral pH. After 5000 minutes (3.5 days), no appreciable transmetallation was observed for the macrocyclic chelates (gadoterate me-

glumine, gadoteridol, and gadobutrol), whereas the linear chelates (gadopentetate dimeglumine, gadodiamide, and gadobenate dimeglumine) showed more rapid transmetallation.

These data suggest that these transmetallation study findings directly reflect the different kinetic stabilities of the chelates at a neutral pH and support the earlier conclusions of Wedeking et al (19), who found no detectable free Gd^{3+} in the livers and femurs of mice after intravenous administration of a macrocyclic chelate. More recently, it was shown that levels of Gd^{3+} in bone were markedly lower (2.5–4.0 times, depending on the analytic method used) (24,25) in patients who had received gadoteridol (a macrocyclic agent) than in those who had received gadodiamide (a linear agent).

Given these chemical and biologic factors, we suggest that discussions of the relative safety of gadolinium-based contrast agents include strong consideration of their kinetic inertness. Although pertinent related data are relatively sparse, chemical and physical considerations clearly indicate that if other factors are equal, macrocyclic agents are far less likely to dissociate and hence release free Gd^{3+} in vivo. If the free gadolinium hypothesis is correct—that is, if the deposition of free Gd^{3+} in tissue induces NSF—then the risk of NSF should be minimized with use of macrocyclic agents. This suggestion is based on thermodynamic considerations alone (2,5). However, a comparison of the thermodynamic stability constants and dissociation rates reveals further differences between the linear and macrocyclic agents that can help guide the selection of contrast agents when they are being administered to high-risk patients. That is, if one relies on the free gadolinium hypothesis as a cause of NSF, then a macrocyclic agent rather than one of the currently available linear agents with a high thermodynamic stability constant should be selected, despite the relaxivity considerations and dose reduction implications. It will be interesting to see whether this prediction will ultimately be supported by clinical experience and scientific data.

Clearly, more clinical and mechanistic studies are necessary to determine the precise relationships between gadolinium-based contrast agent administration and NSF. The impressive safety record of these agents prior to the reports of associated NSF may have lulled the MR imaging community into a false sense of security regarding the use of these agents—especially high-dose concentrations or multiple doses—in patients with impaired renal function. As with any pharmaceutical agent, careful risk-benefit analysis should be performed before the administration of any contrast agent is considered. In this context, it may be just as dangerous (for the patient) to focus only on the risks associated with an agent while ignoring the benefits. For years, radiologists have carefully weighed the risk of anaphylaxis against the benefits of performing contrast material–enhanced examinations. We support caution and the establishment of conservative guidelines for administering gadolinium-based contrast agents in patients with impaired renal function. We also encourage investigators to consider the points outlined herein, which include suggested explanations for the causal relationship between the administration of these contrast agents and the development of NSF.

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