MR Contrast Agents

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MRI Contrast Mechanisms

- Contrast agents can be principally divided into T1 and T2 agents.

- Paramagnetic contrast agents (e.g. gadolinium based contrast agents or GBCA) are most commonly employed as T1 contrast agents due to a predominant shortening of the T1 relaxation time:
  - GBCA reduce both T1 and T2, with T1 relaxivity ~ T2 relaxivity
  - This shortened T1 relaxation time results in increased signal intensity on a T1 weighted image (positive enhancement).

- T2 contrast agents consist mainly of iron oxide particles, which feature substantially higher magnetic moments than paramagnetic contrast agents, with magnetic susceptibility effects dominating:
  - They have much greater T2 relaxivity than T1 relaxivity, resulting in decreased SI on T2 weighted images.
Fig. 7-1. One of first phantoms investigated at NMR research facilities of Siemens (UB Med., Erlangen, FRG). Aqueous solutions containing different concentrations of paramagnetic substances were studied by means of resistive NMR imager running at 0.12 T. Solutions of two high concentrations produced black "holes" in phantom (T2 effect).

**FIGURE 1.** $T_1$ relaxivity (mmol$^{-1}$ s$^{-1}$) of paramagnetic elements at 20 MHz.
The clinical safety of a gadolinium chelate is to a large extent dependent upon the stability of the chelate in vivo.
Linear Gd Chelates

Gd-DTPA

Gd-DTPA-BMA

Gd-DTPA-BMEA

Gd-BOPTA

Gd-EOB-DTPA

MS-325

Extracellular Non-ionic

Hepatobiliary Ionic

Blood pool Ionic
THE RELATIONSHIP BETWEEN THERMODYNAMICS AND THE TOXICITY OF GADOLINIUM COMPLEXES

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The suitability of gadolinium complexes as magnetic resonance imaging contrast agents depends on a number of factors. A thermodynamic relationship to toxicity exists if one assumes that the chemotoxicity of the intact complex is minimal but that the toxicity of the components of the complex (free metal and uncomplexed ligands) is substantial. Release of Gd\(^{3+}\) from the complex is responsible for the toxicity associated with gadolinium complexes; this release appears to be a consequence of Zn\(^{2+}\), Ca\(^{2+}\), and Ca\(^{2+}\) transmetalation in vivo. This hypothesis is supported by acute toxicity experiments, which demonstrate that despite a 50-fold range of LD\(_{50}\) values for four Gd complexes, all become lethally toxic when they release precisely the same quantity of Gd\(^{3+}\), and by subchronic rodent toxicity experiments, which demonstrate a set of gross and microscopic findings similar to those known to be caused by Zn\(^{2+}\) deficiency. Finally, this hypothesis predicts that subtle changes in formulation can further enhance the intrinsic safety of these complexes.

Keywords: Thermodynamics; Toxicity; Gadolinium; Contrast.

INTRODUCTION

The evaluation of paramagnetic complexes as contrast agents for magnetic resonance imaging has focused upon the safety and efficacy of these agents. Safety has been evaluated by acute toxicity (LD\(_{50}\), sub-vivo toxicity, however, does not hold for GdDTPA-BMA, GdDTPA, GdDTPA-BP and GdEDTA. A more complete thermodynamic evaluation is needed to ascertain in vivo stability and to explain the observed toxicity of these complexes.

In addition to demetalation, the diamide derivatives of DTPA may suffer other decomposition reactions both in vitro and in vivo. One obvious possibility is hydrolysis of the amide bond.
Macro cyclic Gd Chelates

- Higher in vivo stability, with less release of Gd
- Markedly improved safety profile (relative to nephrogenic systemic fibrosis)
- No FDA or EMA restrictions
Thermodynamic Stability

TABLE 1. Overview of the GBCAs Investigated and Their Published Thermodynamic ($K_{\text{therm}}$) and Conditional Stability Constants at Physiological pH 7.4 ($K_{\text{cond}, 7.4}$)

<table>
<thead>
<tr>
<th>Class</th>
<th>Net Charge</th>
<th>Trade Name</th>
<th>Manufacturer</th>
<th>Short Names</th>
<th>Excess Ligand</th>
<th>Log $K_{\text{therm}}$</th>
<th>Log $K_{\text{cond}, 7.4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>Nonionic</td>
<td>Omniscan</td>
<td>GE Healthcare, Braunschweig, Germany</td>
<td>Gadodiamide Gd-DTPA-BMA</td>
<td>5%</td>
<td>16.9</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>Nonionic</td>
<td>Optimark</td>
<td>Mallinckrodt Inc., St. Louis</td>
<td>Gadoversetamid Gd-DTPA-BMEA</td>
<td>10%</td>
<td>16.8</td>
<td>15.0</td>
</tr>
<tr>
<td>Ionic</td>
<td></td>
<td>Magnevist</td>
<td>Bayer Schering Pharma, Berlin, Germany</td>
<td>Gadopentetate Gd-DTPA</td>
<td>0.1%</td>
<td>22.5</td>
<td>18.4</td>
</tr>
<tr>
<td>Ionic</td>
<td></td>
<td>Multihance</td>
<td>Bracco Altana, Konstanz, Germany</td>
<td>Gadobenate Gd-BOPTA</td>
<td>0%</td>
<td>22.6</td>
<td>18.4</td>
</tr>
<tr>
<td>Ionic</td>
<td></td>
<td>Primovist</td>
<td>Bayer Schering Pharma</td>
<td>Gadoxetate Gd-EOB-DTPA</td>
<td>0.5%</td>
<td>23.5</td>
<td>18.7</td>
</tr>
<tr>
<td>Ionic</td>
<td></td>
<td>Vasovist</td>
<td>Bayer Schering Pharma</td>
<td>Gadofosveset</td>
<td>0.1%</td>
<td>22.1</td>
<td>18.9</td>
</tr>
<tr>
<td>Macrocyclic</td>
<td>Nonionic</td>
<td>Gadovist</td>
<td>Bayer Schering Pharma</td>
<td>Gadobutrol Gd-BT-DO3A</td>
<td>0.1%</td>
<td>21.8</td>
<td>15.5</td>
</tr>
<tr>
<td>Macrocyclic</td>
<td>Nonionic</td>
<td>Prohance</td>
<td>Bracco Altana</td>
<td>Gadoteridol Gd-HP-DO3A</td>
<td>0.1%</td>
<td>23.8</td>
<td>17.2</td>
</tr>
<tr>
<td>Macrocyclic</td>
<td>Ionic</td>
<td>Dotarem</td>
<td>Guerbet, Roissy, France</td>
<td>Gadoterate Gd-DOTA</td>
<td>0%</td>
<td>25.6</td>
<td>19.3</td>
</tr>
</tbody>
</table>

The amounts of excess ligand in the marketed formulations are expressed in percentages of the molar concentration of the Gd complex.
Kinetic Stability

The agents can be differentiated on the basis of thermodynamic and kinetic stability, with the latter the overriding factor (slow dissociation is desired).
Allergic Reactions

“to the best of current scientific knowledge, all of the gadolinium chelates approved clinically for use in the United States ... have the same incidence of severe anaphylactoid reactions”

“this is also true for minor adverse reactions, the two most notable being nausea and hives”

“let us not add to the problem ... by permitting unsubstantiated rumors to circulate ... but continue to promote science”

Radiology 2011, Morgan, 28,078 patients, ProHance, comparable AEs to other agents
The more stable an agent is, the less gadolinium is left in the body after injection - data is from animal studies with radiolabeled gadolinium chelate.
Nephrogenic Systemic Fibrosis (NSF)

- NSF is an uncommon but serious acquired systemic skin disorder affecting patients with renal insufficiency, specifically patients on dialysis or approaching dialysis – caused by Gd release from the less stable MR CM.

- Systemic manifestations include involvement of the muscles, liver, and lungs; with patients often reporting pruritus and sharp pain over skin lesions.

- Fibrosing effects can progress rapidly, leading to limb contractures and decreased mobility; the disease can be fatal (< 5%).
Retired Cleveland Businessman Sues Tyco International for Rare Disease Caused by its MRI Drug, Optimark Through Law Firm of Spangenberg, Shibley & Liber

GE Healthcare sued over MRI agent

A Jacksonville man’s lawsuit alleges a GE product gave him an incurable illness.

By URVAKSH KARKARIA, The Times-Union

A Jacksonville retiree has sued GE Healthcare for an incurable illness he claimed he contracted after being injected by one of the company’s imaging products.

O’Hara Wells Jr., filed the lawsuit against GE after contracting a skin and joint disease known as Nephrogenic Systemic Fibrosis that has left him physically deformed and in a wheelchair. Wells’ attorney say their client got the disease within weeks of being injected with GE’s Omniscan, a contrast agent, during an MRI procedure at Mayo Clinic Jacksonville in August.

GE’s Own Safety Team Urged Company to Restrict MRI Drug

by Jeff Gerth
ProPublica, April 15, 2010, 5:50 p.m.

GE Healthcare ignored the advice of its own safety experts to “proactively” restrict the use of its imaging drug, Omniscan, after reports in Europe linked the drug to a potentially crippling disease, according to a newly unsealed order in a lawsuit against the company.
The Impact of NSF

The present study demonstrates that the risk of NSF is unexpectedly and unacceptably high (18%) in CKD5 patients exposed to gadodiamide.” (18 of 102 patients)

Accordingly, the use of gadodiamide and gadopentate dimeglumine for renal failure patients was banned in Europe in spring 2007. The same two compounds should only be used cautiously in patients with moderate renal dysfunction.”
Update on the Etiology of NSF


“In summary, our data suggest that NSF-like skin lesions in rats were induced by an acute reaction to Gd, indicated by the rapid but transient upregulation of several cytokines involved in fibrotic processes. Without cofactors such as high cytokine expression, the NSF-like lesions were not maintained.”
Current situation in Europe (NSF)

EMA uses 3 classes – FDA 1 class (prior to late 2010)

High risk
  Optimark, Omniscan, Magnevist

Moderate risk
  Primovist, Vasovist, MultiHance

Low risk
  Dotarem, Gadovist, ProHance
Relaxivity Theory

- Successful water proton relaxation enhancement depends on the ability of a paramagnetic metal ion, via its magnetic moment, to influence the protons of water molecules in fluid or tissues.

- Key to a strong effect is that the number of unpaired electrons matches the number of d or f orbitals they exist within, and that the ions are highly labile, exchanging water molecules rapidly.

- The non-particulate MRI contrast agents approved clinically to date all include, as the active component, a paramagnetic ion, specifically Gd$^{3+}$ or Mn$^{2+}$, with these ions having either 5 (Mn$^{2+}$) or 7 (Gd$^{3+}$) unpaired electrons, creating a strong net magnetic moment resulting in efficient T1 and/or T2 relaxivities.

utmb Health
Manganese

- In phase I, facial flushing and warmth were observed in 35 of 40 subjects, dose dependent increases in heart rate and blood pressure were also seen.
- Subsequent clinical trials were conducted with lower doses and slower IV injection.
- Mn DPDP dechelates in vivo.
- The instability of the complex raised concerns regarding potential toxicity from free Mn (known to accumulate in brain and leading to a parkinsonism-like syndrome).
- Skeletal abnormalities were seen in fetal rats (teratogen).

Withdrawn!
Dysprosium

- Due to a very short electron spin relaxation time, Dy has a negligible T1 effect.
- The magnetic moment is 7.6 for Gd vs 10.6 for Dy, with $\Delta R_2$ proportional to the ratio of the squared magnetic moments.
- First-pass brain MR studies are improved both by use of higher concentration Gd chelate formulations (1.0 versus 0.5 mol/L) and by substitution of the Dy ion.

No Dy agent has ever been approved for clinical use.
Relaxivity Theory (inner sphere)

- Measured relaxivities are composites of two interactions between paramagnetic contrast agents and water protons: inner sphere and outer sphere relaxation.

- Inner sphere relaxation refers to the interaction between water protons and the metal while the water molecule is chemically bound to the metal ion.

- The more water molecules that can bind with the paramagnetic ion simultaneously and rapidly exchange with the surrounding bulk fluid, the greater is the contrast agent’s influence on relaxation enhancement – but in practice, the clinical GBCA have only one coordinated water molecule.
Relaxivity Theory (outer sphere)

- Outer sphere relaxation results from an interaction between non-bonded water molecules and the paramagnetic species.
- Outer sphere effects are less effective than inner sphere effects at inducing proton relaxation enhancement on a per metal ion-water molecule basis because the water protons are further from the metal ion.
- But the fact that there are many more water molecules involved makes total inner and outer sphere relaxivities about equal for clinical Gd chelates.
Supratentorial Brain Neoplasms

A&B  Oligoastrocytoma
C&D  Glioblastoma multiforme
Metastatic Brain Disease

Multiple intracranial metastases
Multiple Sclerosis (active disease)
Postoperative Lumbar Spine

Recurrent disk herniation

Department of Radiology
Infections

Disk space, vertebral body, and epidural infection

Department of Radiology
Primary Neoplasms

Ependymoma

Department of Radiology
Conclusion

- The dominant contrast media today for MR are the gadolinium chelates
- These can be differentiated on the basis of stability (safety) and effective enhancement (relaxivity and formulation)
- Relaxivity is dependent upon inner and outer sphere interactions and correlation time phenomenon

Runge VM, et al. The developmental history of the gadolinium chelates as IV contrast media for MR. Invest Radiol 2011; 46:807

UTMB, Galveston