Viability of Gadolinium-Based Contrast Agents in Magnetic Resonance Imaging

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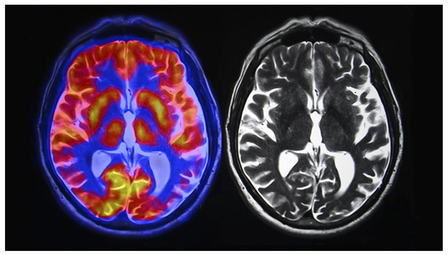
Paramagnetism in Medical Imaging

Like other lanthanides, gadolinium does not exist naturally within the human body. However, the heavy metal has unique paramagnetic properties which predispose its unmatched ability to enhance the picture created by MRI.

Under normal circumstances, the hydrogen nuclei present throughout the body spin around unique, randomly aligned axes. However, when subjected to an external magnetic field within an MRI scanner, the axes line up. Application of additional energy in the form of a radio wave causes the protons to resonate, and the time required for them to relax, or return to their original resting state, is measured. Different body tissues display different relaxation times, and this cycle of differential excitation and relaxation is what creates an internal image that can reveal a wide range of abnormalities. Gadolinium has seven unpaired electrons in its 4f orbital, each with a local magnetic field. It is not directly seen on an MRI, but facilitates the relaxation of surrounding protons, thereby increasing the contrast of the image by brightening the areas of the body where it has accumulated. Nine different Gd-based contrast dyes are approved for use in the United States, the most popular of which include Omniscan and Magnevist.



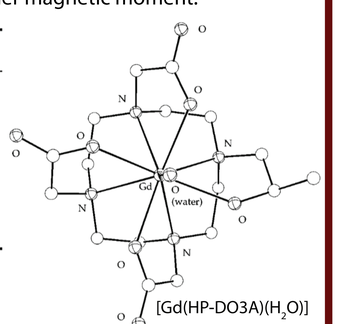
The Ideal Contrast Agent?

Gadolinium is distinctly paramagnetic for a number of reasons:

- It is one of four elements that can be magnetized at room temperature, with a ferromagnetic Curie point of 20°C.
- Gd donates its $6s^2$ and $5d^1$ electrons for bonding, leaving its seven 4f electrons intact and unpaired even when bound in a stable complex.
- It has a magnetic moment of 7.9 B.M., higher than other transition metal ions used as contrast agents: $_{24}Cr^{3+}$, $_{25}Mn^{2+}$, $_{26}Fe^{3+}$, and $_{29}Cu^{2+}$
- Gadolinium complexes have a higher degree of symmetry and therefore greater ability to slow proton relaxation rates than those made with other lanthanides like dysprosium, despite the fact that Dy^{3+} has higher magnetic moment.

	Ion	Configuration 3d	Configuration 4f	Magnetic moment
Transition metal ion	$^{24}Cr^{3+}$	↿ ↿ ↿ – –		3.88
	$^{25}Mn^{2+}$	↿ ↿ ↿ ↿ ↿		5.92
	$^{26}Fe^{3+}$	↿ ↿ ↿ ↿ ↿		5.92
	$^{29}Cu^{2+}$	↿⇂ ↿⇂ ↿⇂ ↿⇂ ↿⇂		1.73
Lanthanide metal ion	$^{63}Eu^{3+}$	↿⇂ ↿ ↿ ↿ ↿ ↿ ↿	↿ ↿ ↿ ↿ ↿ ↿ ↿	3.4
	$^{64}Gd^{3+}$	↿⇂ ↿⇂ ↿⇂ ↿⇂ ↿⇂ ↿⇂ ↿⇂	↿ ↿ ↿ ↿ ↿ ↿ ↿	7.94
	$^{66}Dy^{3+}$	↿⇂ ↿⇂ ↿⇂ ↿⇂ ↿⇂ ↿⇂ ↿⇂	↿⇂ ↿ ↿ ↿ ↿ ↿ ↿	10.65

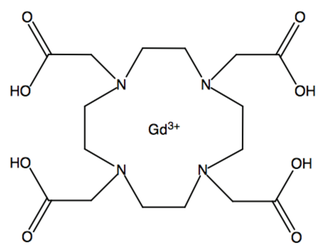
Gadolinium(III) has a ground state term symbol of ^8S and displays the longest electronic relaxation times among 3d metal ions.



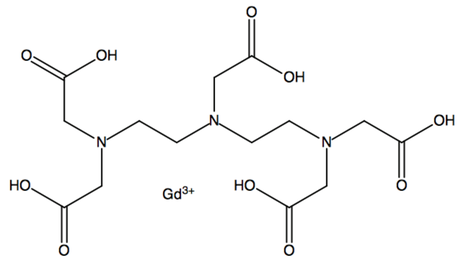
[Gd(HP-DO3A)(H_2O)]

Toxicity and Chelation

Free Gd^{3+} is toxic and must be chelated in order to be safely delivered through the human body. The process of chelation involves covalent bonding of the heavy metal ion to stable organic ligands such as DOTA, DPTA, and their derivatives, essentially encasing the ion and preventing harmful biological interactions. These agents are hydrophilic and therefore do not pass the blood-brain barrier.

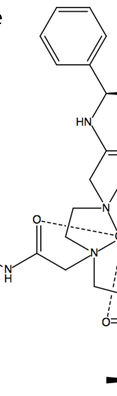


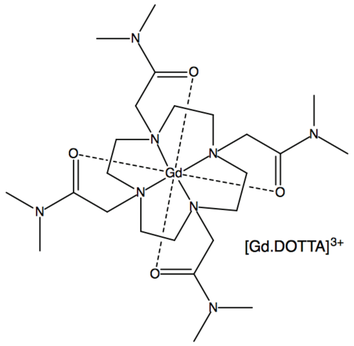
Gd-DOTA
Dotarem, ProHance, Gadovist



Gd-DPTA
Magnevist, Omniscan, MultiHance

Both cyclic and linear eight-coordinated complexes are possible, but the cyclic configuration offers more effective protection and binding strength.

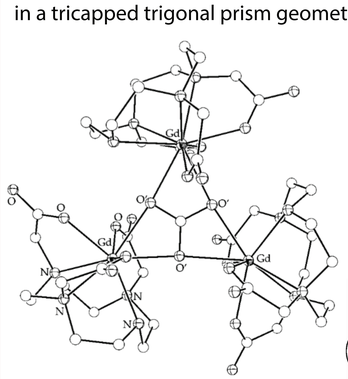




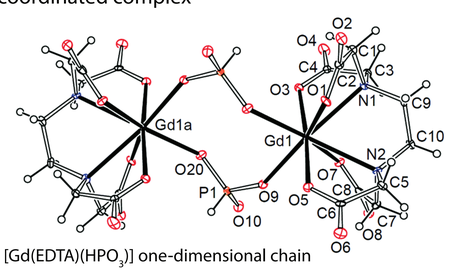
[Gd.DOTTA]$^{3+}$

Gadobenz

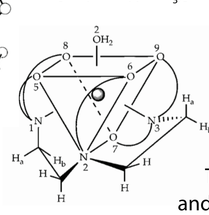
Gd(III) has a coordination number of eight and adopts a bicapped trigonal prism configuration, but also can readily accept another molecule to form a nonacoordinated complex in a tricapped trigonal prism geometry.



{[Gd(DO3A)]$_3$[CO_3]}$^{2-}$



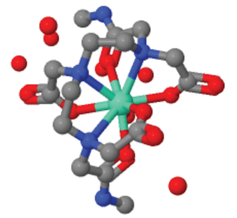
[Gd(EDTA)(HPO_3)] one-dimensional chain

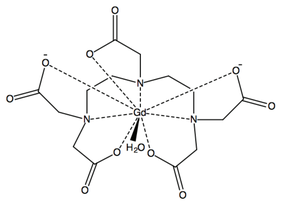


Trigonal tricapped geometry is adopted by many lanthanide chelates, yielding two "wrapping isomers" that interchange rapidly. This creates a pseudo mirror plane and increases proton relaxation rates.

Retention and Related Risks

Contrast dyes are eliminated through the kidneys with an approximate half-life of 1.5 hours. In patients with pre-existing renal problems, the half life of can be extended up to 30 hours. Accumulation of the metal complex in the body is linked to nephrogenic systemic fibrosis, a condition characterized by uncontrollable formation of scar tissue and ectopic ossification, or formation of new bone in tissues which do not normally ossify. It has also been shown to worsen symptoms in patients with MS.



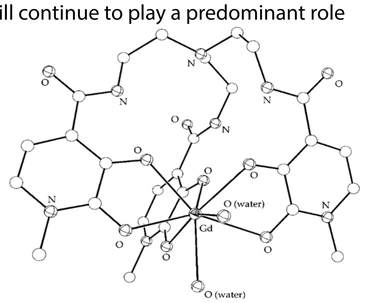


GBCA	Approval Date	Indication	Chemical Structure, Charge
Magnevist (Gadopentate)	1988	CNS/ body	Chain, ionic
Prohance (Gadoteridol)	1992	CNS	Macrocyclic
Omniscan (Gadodiamide)	1993	CNS/ body	Chain, non ionic
Optimark (Gadoversetamide)	1993	CNS/ liver	Chain, non ionic
Multihance (Gadobenate)	2004	CNS	Chain, ionic
Eovist (Gadoxetate)	2008	Liver	Chain, ionic
Ablavar (Gadofosveset)	2008	MRA Aortoiliac	Chain, ionic

120 million GBCA doses have been administered to date. Omniscan (gadodiamide, shown at left), is the most widely used GBCA in the United States. It has also been targeted in the greatest number of lawsuits relating to NSF, most likely because of its linear, non-ionic formulation.

Conclusion

60 million MRI diagnoses are conducted worldwide each year, and almost a third are enhanced with gadolinium-based contrast dyes. For the vast majority of these procedures, there is no harm associated with gadolinium retention. As such, these supplementary agents still remain viable for use in medical imaging. For patients with pre-existing renal and neurological deficiencies, alternative MRI contrast agents are currently being developed in order to completely eradicate the risks of Gd^{3+} accumulation. One promising substitute is produced from iron oxide nanoparticles, and other lanthanide metals comprise a group of GBCA's known as PARACEST agents. However, gadolinium will continue to play a predominant role in medical imaging for the foreseeable future due to its unique paramagnetism and symmetry.



Acknowledgments

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