Gadolinium Deposition and Chronic Toxicity

Joana Ramalho, MD[a,*], Miguel Ramalho, MD[b]

KEYWORDS

• Gadolinium • GBCAs • MR imaging • Gadolinium retention • Gadolinium storage condition • Gadolinium deposition disease

KEY POINTS

- Gadolinium is retained in body tissues; higher concentrations seem to occur in patients with renal impairment and after exposure to the less stable gadolinium-based contrast agents.
- MR imaging does not detect all the gadolinium deposits present in human tissues; bone deposition is not perceptible with MR imaging.
- MR imaging changes are seen after administration of linear agents, which may result from decreased imaging sensitivity or variations in the composition of the retained gadolinium.
- The mechanism of gadolinium uptake and deposition in brain has not yet been convincingly clarified. Recent literature suggests diffusion through the gliolymphatic system.
- Enhanced MR imaging studies should be performed using the most stable agents with a dose as low as possible.

INTRODUCTION

Gadolinium-based contrast agents (GBCAs) have been in use for almost 30 years, and have become indispensable in routine MR imaging. So far, more than 300 million doses have been administered worldwide.[1,2] Overall these agents have been considered extremely safe. Adverse events are rare, varying from 0.06% to 0.3%,[3] and most are physiologic in nature and mild in severity. GBCAs were thought to be biologically inert and were even favored in patients with renal impairment over the iodinated contrast for computed tomography scans.[4–7] In 2006, GBCAs were linked with nephrogenic systemic fibrosis (NSF) a serious, debilitating, and sometimes life-threatening condition seen in a small percentage of patients with impaired renal function after the administration of some GBCAs. NSF has been almost completely eliminated since mid 2009 by screening patients for the presence of renal disease, by performing unenhanced studies or half-dose contrast-enhanced studies in those patients, and by changing the agents used avoiding the high-risk GBCAs. The confidence in GBCAs was then restored and its widespread use continued with only a few restrictions. Since 2014, a number of publications describing a dose-dependent deposition of gadolinium in the brain, seen as high signal intensities on nonenhanced T1-weighted images in the dentate nucleus (DN) and globus pallidus (GP) have been published. Subsequent postmortem studies, using inductively coupled plasma mass spectrometry, confirmed gadolinium deposition in these areas of T1 shortening, raising new concerns regarding the safety of GBCAs. Residual gadolinium is retained not only in brain regions, but also in extracranial tissues such as liver, skin, and bone. This condition was recently called "gadolinium storage condition." The clinical significance of gadolinium retention in the brain and elsewhere in

Disclosure Statement: No disclosure.

[a] Department of Neuroradiology, Centro Hospitalar de Lisboa Central, Rua José António Serrano, 1150-199 Lisboa, Portugal; [b] Department of Radiology, Hospital Garcia de Orta, Avenida Torrado da Silva, 2805-267 Almada, Portugal

* Corresponding author. Rua José António Serrano, 1150-199 Lisboa, Portugal.
E-mail address: Joana-Ramalho@netcabo.pt

Magn Reson Imaging Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.mric.2017.06.007

the body is not known yet; however, it seems reasonable to assume that this is not desirable. Anecdotal case reports of neurologic and nonneurologic gadolinium-induced toxicity in humans have been published,[8–12] but no definite conclusions can be drawn from these data. A further problem that is only now being defined is that some patients with normal renal function experience a toxic response to gadolinium, a condition that was named "gadolinium deposition disease." In this review, we will cover gadolinium retention and potential toxicity, with a special focus on brain deposition. To better understand the biodistribution of GBCAs and their potential toxic effects, a brief review of the pharmacokinetics and stability of these agents is provided.

GADOLINIUM-BASED CONTRAST AGENTS

Gadolinium is a rare earth element in the lanthanide series with powerful paramagnetic properties. Free gadolinium ($Gd3^+$) is toxic in humans and to be used in vivo it must be chelated to organic ligands. Numerous mechanisms of gadolinium toxicity have been proposed, including calcium channel inhibition, production of reactive oxygen species, and induction of apoptosis.[13–15] Gadolinium may also increase the expression of some cytokines[16] and inhibit mitochondrial function.[17]

The chelate is a carrier molecule that must remain bound to Gd^{3+} until its excretion. Stability is the ability of the ligand to retain the Gd^{3+} ion within the complex. Based on the structure of the ligand used and its stability in vivo, as measured in human serum by Frenzel and colleagues,[18] GBCAs can be classified into 3 groups: nonionic linear, ionic linear, and macrocyclic. Macrocyclic chelates are more stable than linear chelates, and ionic linear chelates are more stable than the nonionic linear chelates. The dechelation of gadolinium from its ligand is an equilibrium process mainly defined by kinetic and thermodynamic stabilities. Thermodynamic stability is the thermodynamic equilibrium in a solution between the dissociated gadolinium ion, the ligand, and the entire contrast molecule, whereas the kinetic stability is the speed at which the dissociation equilibrium is reached. Kinetic stability is evaluated using the dissociation half-life time ($t_{1/2}$) of GBCAs under various conditions.[19]

The chemical properties of the ligand molecule determine the likelihood of dechelation. However, this process is also influenced by the environment of the molecule, including pH and temperature; the presence of competitors, which have the potential to interact with either the Gd^{3+} or the ligand; and the interaction time between the gadolinium chelates and their competitors, which is increased in patients with renal insufficiency. The gadolinium ion and the ligand do not exist as free ions because they bind to other agents rapidly. This exchange process is termed "transmetallation."[18–23] Different endogenous cations (eg, Fe^{3+}, Mg^{2+}, Cu^{2+}, Zn^{2+}, or Ca^{2+}) compete with Gd^{3+} for the ligand, and endogenous anions (eg, phosphate, carbonate, hydroxide) compete for the Gd^{3+} ions. A number of the linear GBCAs, including all nonionic compounds, contain excess chelates to reduce the amount of unchelated gadolinium in solution. The addition of excess chelate to nonionic linear chelate dramatically reduces its acute toxicity.[24–26]

In 1988, the US Food and Drug Administration approved the first GBCA for clinical use (gadopentetate dimeglumine, Magnevist, Bayer HealthCare Pharmaceuticals, Wayne, NJ). Since that time, other formulations have become available clinically and are now routinely used worldwide (**Table 1**). Most GBCAs in clinical use are nonspecific extracellular contrast agents, meaning that they passively distribute in the extracellular fluid, do not enter cells, and are cleared almost exclusively by the kidneys. There are also combined extracellular–intracellular agents, which are in part taken up by hepatocytes via specific transport mechanisms and, therefore, also named as "hepatocyte-specific agents." These agents, gadobenate dimeglumine (MultiHance, Bracco Diagnostics, Princeton, NJ) and gadoxetic acid–gadoxetate disodium (Primovist/Eovist, Bayer Schering Pharma, Berlin, Germany) when taken up by hepatocytes are excreted into the bile ducts, thus exhibiting dual elimination routes (renal and biliary).

GADOLINIUM STORAGE CONDITIONS

It has been considered that GBCAs are eliminated rapidly and almost completely after intravenous injection. However, currently, it is recognized that GBCAs may be retained, undergo dechelation, and induce gadolinium deposition in a range of tissues and organs in patients with normal renal function, a condition recently termed "gadolinium storage condition." Data from both animal and human studies have so far demonstrated that gadolinium can accumulate in skin, bone, brain, liver, kidney, muscle, and spleen.

Gadolinium Retention in Human Tissue

The deposition of gadolinium in human tissues was first described in the bones of patients with normal renal function after administration of a GBCA.[27–29] In 1 study, gadolinium was shown to be retained in bone tissue for longer than 8 years.[29] Bone accumulation has been shown to be 2.5 to 4 times greater after a nonionic linear chelate than after a