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Review Article

Hyperintensity in the Dentate Nucleus on Nonenhanced T1-Weighted Magnetic Resonance Imaging Suggests Dechelation of Contrast Agents

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ABSTRACT

With the exception of renal failure patients, gadolinium-based contrast agents (GBCAs) for magnetic resonance imaging (MRI) have a high tolerance and acceptability in patients needing to undergo an enhanced MRI. Now that enhanced MRIs are becoming increasingly popular and nephrogenic systemic fibrosis cases are becoming a rarity, a common belief is that these GBCAs are essentially "biologically inert" materials. However, recent reports have emerged querying the link between these GBCAs and hyperintensity in the dentate nucleus on unenhanced T1-weighted MRI in some patients. This review article outlines the basic chemistry and characteristics of currently approved GBCAs, summarizes the described research findings of gadolinium deposition in the dentate nucleus, and identifies areas for future research.

RÉSUMÉ

Sauf dans le cas des patients souffrant d'insuffisance rénale, les agents de contraste à base de gadolinium (GBCA) pour l'imagerie par résonance magnétique (IRM) présentent un degré élevé de tolérance et d'acceptabilité parles patients qui doivent passer un examen d'IRM avec injection d'un agent de contraste. Maintenant que les IRM avec injection d'un agent de contraste gagnent en popularité et que les cas de fibrose néphrogénique systémique deviennent très rares, il semble s'être établi une croyance commune à l'effet que les GBCA sont essentiellement « biologiquement inertes ». Cependant, de récents rapports s'interrogent sur le lien entre les GBCA et l'hyperintensité du noyau dentelé dans l'IRM en pondération sans agent de contraste chez certains patients. Cet article examine la chimie et les caractéristiques de base des agents de contraste à base de gadolinium actuellement approuvés, résume les résultats de recherche décrits sur le dépôt de gadolinium dans le noyau dentelé et recense des secteurs de recherche potentiels.

Keywords: Magnetic resonance imaging; MRI; CEMRI; dentate nucleus; MRI safety; gadolinium contrast

Introduction

In 1988, the first intravenous gadolinium (Gd)-based contrast agent (GBCA) for magnetic resonance imaging (MRI) was introduced for clinical use. Since then, numerous agents have been developed, all with tremendous growth and utility around the world. In 2012, an average of 50 in every 1,000 people received MRI worldwide, and it is estimated that nearly half of these studies were contrast-enhanced (CEMRI) [1]. Because MRI is such a new modality, clinical advances and technical applications are expected to continue to grow along with the demand of imaging into the foreseeable future. Although all GBCAs contain a toxic heavy metal, these agents have proven to be a great complement to non-CEMRI and are also very well tolerated by the general public [2]. This has led many to believe that GBCAs are essentially "biologically inert," an impression which, after the discovery of the association between certain GBCAs and potentially fatal nephrogenic systemic fibrosis (NSF), is evidently false. Although NSF is a rarity in current clinical practice, a new finding in the dentate nucleus of patients who have had multiple CEMRIs is resurrecting a fear that GBCAs are not as harmless as once believed.

Gd-Based Contrast Agents

In MRI, the relaxation mechanisms are what determine image contrast; therefore, tissues with long relaxation times do not appear the same as those with short relaxation times. The contrast agents used in MRI are based on the ability of the agent to affect the local magnetic field and thus the T1 and/or T2 relaxation times of tissues. Although contrast media in MRI consist of agents with varying magnetic susceptibilities, GBCAs are the most common [3]. As an element, Gd is a heavy

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metal, and therefore ferromagnetic. However, when used as a contrast agent, Gd is bound or chelated to other chemicals to decrease toxicity and make it safe for human use. Gd chelates are paramagnetic and create a low, positive effect on the local magnetic field at body temperature. As a result, GBCAs (also known as T1 agents) shorten T1 relaxation and create bright lesions on T1-weighted imaging, making them easier to depict from normal surrounding tissue on MRI [3].

Approved MR Contrast Agents

To date, Health Canada and the Food and Drug Administration has approved eight intravenous GBCAs. In 1988, Magnevist (gadopentetate dimeglumine) was the first GBCA to be approved for human use. Shortly after, three comparable "first-generation" GBCAs were approved: Omniscan (gadodiamide), ProHance (gadoteridol), and OptiMARK (gadoversetamide). A "second-generation" GBCA known as MultiHance (gadobenate dimeglumine), with slightly different characteristics was approved in 2004 [2]. Gadovist (gadobutrol), Ablavar (gadofosveset trisodium), and Primovist/Eovist (gadoxetate disodium) are the three most recently approved agents, and to date do not have as widespread usage as the other agents. A ninth agent, Dotarem (gadoteric acid), is approved by the Food and Drug Administration and currently pending approval by Health Canada.

Ideal MR Contrast Characteristics

The GBCAs currently in use at most clinical centres are what are considered "ideal agents." These agents must be able to effectively lower the T1 and/or T2 in tissues using low (μM or mM) concentrations that are tolerable with the patient [2]. Because the relaxivity (r_1 and r_2) is fundamental to reducing the T1 and/or T2, an agent with a *high relaxivity* will be more effective at decreasing the T1 and/or T2 than an agent with a lower relaxivity at the same concentration. A high relaxivity is therefore ideal because it can be used to lower the dose or increase signal at equivalent doses to allow for an improved detection or definition of lesions [2]. As discussed, GBCAs contain chelating agents (tiny, water-soluble units) that are bound to transitional (heavy) metal Gd ions (Gd^{+3}) to form a stable complex that mitigates the substantial natural toxicity of the free metal ion and essentially makes GBCAs safe for human use. It is therefore imperative that clinically used GBCAs have a *high stability*, and thus, a *low toxicity*. A low toxicity is required because it reduces the incidence of acute side effects, such as allergic and/or anaphylactoid reactions and alterations in normal serum parameters. To maintain a low toxicity, GBCAs must be composed and chelated in a way that minimizes Gd dissociation from the chelate during the typical 2- to 3-year shelf-life and, more vitally, decreases dissociation in vivo [2].

Finally, it is important that all GBCAs have a *rapid and substantial clearance* and an *iso-osmolality and low viscosity*. No Gd chelate is completely resistant to dissociation, where the free metal ions dissociate and deposit into specific tissues. A rapid clearance is therefore essential to preventing this dissociation and deposition from occurring [2]. In an attempt to improve dose tolerance and formulation flexibility, an iso-osmolality and low viscosity is sought. This is especially useful when using rapid bolus administrations by use of the power injector. An iso-osmolality agent is also associated with a decreased likeliness of serious adverse reactions, such as local tissue necrosis, in cases where a large volume of contrast is inadvertently extravasated during injection [2].

Molecular Structures of MR Agents

According to their chemical structures, there are four distinct divisions of GBCAs. The chelating ligands are either cyclic (better known as macrocyclic) or linear, in which the Gd chelates are either charged (ionic) or electrically neutral (nonionic). The four types are: ionic linear, nonionic linear, ionic macrocyclic, and nonionic macrocyclic [4]. Approved GBCAs including Magnevist, Primovist/Eovist, MultiHance, and Ablavar are ionic linear; Omniscan and OptiMARK are non-ionic linear; and Dotarem is ionic macrocyclic; whereas ProHance and Gadovist are nonionic macrocyclic (Table 1). For the purpose of this article, it is important to understand three realities of GBCAs: (1) Gd in its pure state is a toxic heavy metal, adequate for human use only because of chelating agents, (2) dissociated Gd is not able to be excreted from the human body, and (3) despite the strongest chelation bonds being used in clinical practice, no Gd chelate is completely resistant to Gd dissociation [2, 4]. What many do not know is that depending on their molecular structure, certain agents are more prone to dissociation than others.

Ionic linear agents are all composed of five monodentate (one binding atom) carboxylic oxygen atoms and three amino nitrogen atoms. Nonionic linear agents include three amino nitrogen atoms and are slightly different from the ionic linear agents because they are composed of three instead of five monodentate ionic carboxylic oxygen atoms and two nonionic monodentate carbonylic oxygen atoms bound to Gd^{3+} [4]. Importantly, in comparison with the carboxylic atoms, the two nonionic amide carbonylic atoms attach to Gd^{3+} more weakly. In turn, this weak attachment reduces the stability of the nonionic linear GBCAs in comparison with their ionic linear relatives. Thus, there is increased likeliness of dechelation of these agents in vivo [4].

Macrocyclic agents stem from a 12-member macrocyclic polyamino ring. Dotarem, an ionic macrocyclic agent, has

Table 1
Linear Versus Macrocyclic Gadolinium-Based Contrast Agents

Linear		Macrocyclic	
Ionic	Nonionic	Ionic	Nonionic
Magnevist	Omniscan	Dotarem	ProHance
Primovist/Eovist	OptiMARK		Gadovist
MultiHance			
Ablavar			