Mechanism of Gadolinium-Based Contrast Agents Retention

Subjects: Chemistry, Inorganic & Nuclear
Contributor: Zoltan Kovacs

The extracellular class of gadolinium-based contrast agents (GBCAs) is an essential tool for clinical diagnosis and disease management. The differences observed in tissue gadolinium retention and deposition associated with GBCAs administration is the direct consequence of the differing thermodynamic stability and kinetic inertness of GBCAs.

Keywords: gadolinium-based contrast agents ; thermodynamic stability ; kinetic inertness ; gadolinium deposition

1. Introduction

Gadolinium-based contrast agents (GBCAs), the most widely used MRI contrast agents, have been instrumental in research and clinical applications including disease diagnosis and monitoring. GBCAs are generally extracellular fluid agents and rapidly equilibrate in the extracellular space. GBCAs are eliminated by renal filtration with a half-life of approximately 90 minutes in healthy individuals. However, in patients with renal failure, a longer than normal elimination half-life were noticed. In 2000, GBCAs was linked to NSF, a devastating systemic disease characterized by the formation of scar tissue (fibrosis). Reports of GBCA-linked NSF led to safety related labeling changes with class warning and contraindications in patients with poor renal function. These safety measures eliminated NSF altogether.

Although longer than normal, elimination half-life was noticed early on in patients with renal failure; this had not raised any concerns until about a decade later. The first published report describing nephrogenic systemic fibrosis (NSF) appeared in 2000 [1]. NSF is a devastating systemic disease characterized by the formation of scar tissue (fibrosis). Connection between kidney failure and contrast-enhanced MRI in the etiology of NSF was made in 2006 [2][3]. Reports of GBCA-linked NSF led to safety-related labeling changes with class warning and contraindications in patients with poor renal function. These safety measures eliminated NSF altogether. However, the safety of GBCAs came under close scrutiny again in 2014, when high MRI signal intensity on unenhanced T_1-weighted brain images of patients who had repeated exposure to GBCAs was described [4]. This observation was confirmed in numerous subsequent studies [5][6][7][8] and the presence of gadolinium deposition was confirmed using inductive coupled plasma mass spectroscopy (ICP-MS). These reports led to a new class warning for all GBCAs and restriction of the use/suspension of the authorization of some linear GBCAs by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). In their statements, the FDA and the International Society of Magnetic Resonance in Medicine (ISMRM) [9] stressed other than in NSF, that there is currently no evidence that gadolinium deposition in the brain and other tissues has caused any harm to patients.

2. How does the structure influence the tissue gadolinum deposition?

In the design of contrast agents for MRI, Gd^{3+} is enclosed in a ligand to form a complex that is expected to remain chelated in the body and be excreted intact. All ligands used as components of approved GBCAs are based on two octadentate polyaminocarboxylate type chelators: DOTA (macrocyclic) and DTPA (linear). The in vivo behavior of GBCAs is predicted by physical properties such as thermodynamic and kinetic stabilities gathered from in vitro and in vivo distribution data. The thermodynamic stability of the complex is characterized by the thermodynamic stability constant, which is the equilibrium constant for the reaction between the metal ion and the fully deprotonated ligand. The thermodynamic stability constant is inadequate by itself to predict the in vivo behavior of GBCAs. Kinetic inertness is characterized by the experimentally observed rate constant of dissociation, k_{obs} or the corresponding half-life ($t_{1/2}$). Kinetic inertness is a better predictor of in vivo stability.

Upon entering the body, GBCAs are exposed to endogenous metal ions (Cu^{2+}, Zn^{2+}), proteins, and biologically available anions such as phosphates and carbonates, all of which have the potential to assist in gadolinium complex dissociation. To minimize the dissociation, gadolinium complexes must be kinetically inert under this condition. The pharmacokinetics and physiological profiles of GBCA are related to the chemical structures of the GBCA, specifically linear or macrocyclic.

The linear GBCA's have flexible chelators whereas the macrocyclic agents have rigid caged structures. The higher flexibility of the linear agents result in more rapid dissociation of gadolinium from the chelate and a higher likelihood of transmetallation than the macrocyclic agents. The kinetic stability of the FDA approved macrocyclic chelates is far superior to that of the linear chelates. The higher kinetic inertness of DOTA based complexes is largely due to the more rigid macrocyclic backbone of DOTA in comparison to the flexible open DTPA derivatives. The significantly higher kinetic inertness of macrocyclic GBCAs as compared to the linear GBCAs undoubtedly contributes to the lower retention of macrocyclic GBCAs in tissues.

3. Linear GBCAs deposit significantly higher amounts of gadolinium in tissues than the macrocylic agents

It was previously thought that GBCAs do not cross the blood brain barrier and are cleared from the brain via venous drainage. From preclinical studies, we now know that regardless of the chemical structure, all GBCA's enter the rat brain intact. Evidence seems to indicate that while all GBCAs enter intact, macrocyclic GBCAs are subsequently cleared from the brain without appreciable dissociation, while linear agents are more likely to dissociate and leave behind residual gadolinium. There have been a number of studies looking into the amount and chemical form of the retained gadolinium in human tissues and preclinical animal models. Across these studies, one can draw the conclusion that the amount of retained gadolinium was much higher in animals exposed to linear agents compared to those exposed to macrocyclic ones. This is in good agreement with the results of human studies. The deposited linear agents could be found in various forms: insoluble inorganic salts, intact chelate, and a soluble Gd-macromolecular fraction.

4. Conclusion

There are no rigorous clinical studies suggesting a long-term health consequence due to gadolinium deposition/retention. The importance of developing compounds that are kinetically and thermodynamically stable for in vivo application is evident from studies of NSF and Gd tissue deposition. GBCAs were developed to answer a clinical need: to enable a timely and accurate disease diagnosis for better patient care. For a patient with a medical condition requiring evaluation with contrast-enhanced MRI, like the tens of millions of patients who have received gadolinium contrast safely for years, the risk/benefit ratio currently strongly favors contrast administration.

References

1. Cowper, S.E.; Robin, H.S.; Steinberg, S.M.; Su, L.D.; Gupta, S.; LeBoit, P.E. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet 2000, 356, 1000–1001.
2. Grobner, T. Gadolinium—A specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis? Nephrol. Dial. Transplant. 2006, 21, 1104–1108.
3. Marckmann, P.; Skov, L.; Rossen, K.; Dupont, A.; Damholt, M.B.; Heaf, J.G.; Thomsen, H.S. Nephrogenic systemic fibrosis: Suspected causative role of gadodiamide used for contrast-enhanced magnetic resonance imaging. J. Am. Soc. Nephrol. 2006, 17, 2359–2362.
4. Kanda, T.; Ishii, K.; Kawaguchi, H.; Kitajima, K.; Takenaka, D. High signal intensity in the dentate nucleus and globus pallidus on unenhanced T1-weighted MR images: Relationship with increasing cumulative dose of a gadolinium-based contrast material. Radiology 2014, 270, 834–841.
5. Errante, Y.; Cirimele, V.; Mallio, C.A.; Di Lazzaro, V.; Zobel, B.B.; Quattrocchi, C.C. Progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance images is associated with cumulative doses of intravenously administered gadodiamide in patients with normal renal function, suggesting dechelation. Investig. Radiol. 2014, 49, 685–690.
6. Radbruch, A.; Weberling, L.D.; Kieslich, P.J.; Eidel, O.; Burth, S.; Kickingereder, P.; Heiland, S.; Wick, W.; Schlemmer, H.P.; Bendszus, M. Gadolinium retention in the dentate nucleus and globus pallidus is dependent on the class of contrast agent. Radiology 2015, 275, 783–791.
7. McDonald, R.J.; McDonald, J.S.; Kallmes, D.F.; Jentoft, M.E.; Murray, D.L.; Thielen, K.R.; Williamson, E.E.; Eckel, L.J. Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging. Radiology 2015, 275, 772–782.
8. Ramalho, J.; Castillo, M.; AlObaidy, M.; Nunes, R.H.; Ramalho, M.; Dale, B.M.; Semelka, R.C. High Signal Intensity in Globus Pallidus and Dentate Nucleus on Unenhanced T1-weighted MR Images: Evaluation of Two Linear Gadolinium-based Contrast Agents. Radiology 2015, 276, 836–844.

9. Gulani, V.; Calamante, F.; Shellock, F.G.; Kanal, E.; Reeder, S.B.; International Society for Magnetic Resonance in Medicine. Gadolinium deposition in the brain: Summary of evidence and recommendations. Lancet Neurol. 2017, 16, 564–570.