Commentary on T1-Weighted Hypersignal in the Deep Cerebellar Nuclei After Repeated Administrations of Gadolinium-Based Contrast Agents in Healthy Rats

Difference Between Linear and Macrocyclic Agents

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In this landmark article by Robert et al, an animal model is presented for the T1 signal hyperintensity in the deep cerebellar nuclei, including specifically the dentate nucleus, after intravenous administration of the linear gadolinium-based contrast agent gadodiamide (Omniscan) in normal renal function.[1] This change was further demonstrated to correlate with higher gadolinium concentration in the brain, as determined by inductively coupled plasma mass spectrometry. No abnormality was noted after administration of a macrocyclic agent, gadoterate meglumine (Dotarem). The study provides a scientific basis for previous clinical observations, together with a platform for rigorous further investigation. In-depth study, using this model or similar models, of all of the approved gadolinium-based contrast agents (GBCAs) is warranted.

Including the current research, there are 8 published articles to date examining this critical topic. The first two appeared in 2014, demonstrating in patients with normal renal function the progressive increase of T1 signal intensity of the dentate nucleus on unenhanced magnetic resonance (MR) images with increasing cumulative dose of gadodiamide.[2,3] Subsequent clinical studies by the same 2 groups appeared in 2015, together with an additional publication from Germany, confirming the finding to be associated with prior gadodiamide administration, identifying that this also occurs with the linear GBCA gadopentetate dimeglumine (Magnevist) and demonstrating the lack of any abnormality in patients who had received the macrocyclic agent gadoterate meglumine.[4–6] Additional studies on tissue from deceased patients in 2015 identified gadolinium deposition in neuronal tissue (in patients with prior administration of gadodiamide or gadopentetate dimeglumine) and in the larger study in a dose-dependent relationship correlating with signal intensity changes on precontrast T1-weighted scans, without detectable levels in controls.[7,8] Of critical importance is that this phenomenon is observed in the setting of relatively normal renal function.

This topic and its evolution bring to mind that of nephrogenic systemic fibrosis (NSF). The initial article by Thomas Grobner[9] in 2006 alerted the community to the correlation between NSF and administration of gadodiamide and was followed in 2007 by an article suggesting in vivo dechelation as the root cause.[10] By 2008, it had been established that "the risk of NSF is unexpectedly and unacceptably high (18%) in patients with stage 5 chronic kidney disease (CKD5) exposed to gadodiamide".[11] In 2008 and 2009, research emerged using an animal model, confirming the correlation between disease development and chelate stability, with gadolinium deposition noted in tissues.[12–14] These and other studies led to the current clinical guidelines, as reflected by the ninth version of the Contrast Media Guidelines from the Contrast Media Safety Committee of the European Society of Urogenital Radiology. In summary, gadodiamide (Omniscan), gadopentetate dimeglumine (Magnevist), and gadoversetamide (Optimark) are contraindicated in patients with CKD stages 4 and 5, acute renal failure, pregnant women, and neonates. Caution is suggested in patients with CKD stage 3 and in children younger than 1 year. Estimated glomerular filtration rate measurement and clinical assessment of patients before contrast administration are mandatory. These 3 agents are considered to have the highest risk of NSF (and the recommendations being specific to this group). In distinction, the 3 macrocyclic agents—gadobutrol (Gadovist, Gadavist), gadoterate meglumine (Dotarem), and gadoteridol (Prohance)—are considered to have the lowest risk of NSF.

Stability in vivo of the gadolinium chelates is fundamental to the safety basis of this class of contrast media. This has been emphasized throughout the evolution of the field,[15] indeed since the very first public presentation of results using a paramagnetic metal chelate.[16] High thermodynamic and kinetic

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stability was identified in the literature as a critical feature as early as 1983,[17] with the importance of in vivo stability reiterated in 1984 at the American Society of Neuroradiology in presentation of the first research demonstrating potential clinical utility.[18] By the early 1990s, the higher in vivo stability of the macrocyclic agents, with transmetallation occurring only very slowly, was well known with approval of Dotarem in 1989 in France and Prohance in 1992 in the United States.[19] This safety basis has been re-emphasized in many review articles, two of which are cited.[20,21] Statements of note from 2000 should be reiterated[20]: "The safety of the gadolinium chelates is largely based on their stability in vivo. The chelates were designed to bind the gadolinium ion extremely tightly, thus ensuring nearly complete renal excretion of the intact chelate" and "A major safety concern in the development of this class of agents is the possible release of free gadolinium in vivo."

The field of medicine has radically changed in the past 30 years. Our clinical colleagues heavily rely on imaging, and specifically MR and computed tomography, for disease diagnosis, management, and treatment monitoring. Yet, my greatest concern in 1982, at the beginning of my career, was that the area I had picked as my focus, MR imaging, had already peaked in its development. Little did I know that I would be the individual to first suggest publicly the use of paramagnetic metal ion chelates as intravenous contrast media, with today approximately 30 million doses given each year and more than 300 million administrations since clinical approval of the first agent, Magnevist, in 1987. In the meantime, we have seen consolidation of the pharmaceutical industry, development of group purchasing organizations, and an intense focus on profitability and blockbuster drugs, all of which could be considered to be negative developments with regard to what should be a physician's focus, the safety of any administered agent. Adding to this is another huge negative factor, specifically that the cost of developing an agent for diagnostic imaging has exploded to more than 200 million dollars, representing a significant brake on new development.[22] Improvements in the approval process (streamlining and lowering costs) and reinvestment by the pharmaceutical industry to develop new agents should be strongly encouraged. Chemistry is far advanced today in comparison to 30 years ago when both the linear and macrocyclic gadolinium chelates were conceptualized, making possible substantial improvements in design, stability (safety), and relaxivity (efficacy).

The gadolinium chelates (the GBCAs) are critical to disease diagnosis by MR, indeed to clinical medicine worldwide, and have proven to be overall a very safe class of contrast media. However, the article of reference in this issue of *Investigative Radiology* should serve as a call for further research as well as re-evaluation by the pharmaceutical regulatory agencies worldwide. All of the currently approved GBCAs should be evaluated by the methods used in the article by Robert et al, or by a similar approach. This could lead, and if so appropriately, to the reassessment of the approval status of the least stable agents. As physicians, let us remember, above all, to do no harm.

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