EDITORIAL

https://doi.org/10.1590/1806-9282.20220643

The benefits and side effects of gadolinium-based contrast agents in multiple sclerosis patients

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Gadolinium offers extra insight into our body's condition. But, is it safe?

Gadolinium-based contrast agents (GBCAs) were safely delivered to millions of patients throughout the world since 1988, and their usage has definitely benefitted many individuals by allowing doctors to detect neurological disorders earlier and more accurately. GBCAs frequently have minor side effects. Injection-site discomfort, nausea, itching, rash, headaches, and dizziness are the most prevalent adverse effects. Patients with significant renal issues are more likely to experience serious, but uncommon side effects, including gadolinium poisoning and nephrogenic systemic fibrosis[1].

One of the biggest radiological concerns in recent years is the safety of GBCAs used in magnetic resonance imaging (MRI). As a study showed that gadolinium deposited in the brain and remained there, radiologists began to question the safety of gadolinium[2]. Results showed that the high signal intensity in patients' brains is correlated with the number of GBCAs administrated. The new findings have sparked a major debate in radiology about the safety of these agents. For all GBCAs of MRI, the Food and Drug Administration (FDA) mandates a new class warning and additional safety precautions in terms of gadolinium staying in the patients' bodies, including the brain, for months to years after taking these medications[3].

It is known that patients with renal insufficiency cannot filter the gadolinium from their body, so it is included as a FDA warning label on the contrast packaging. However, there was less evidence showing patient safety issues in those with normal renal function. Boxed warnings are also mentioned for recognized hypersensitivity relationships that can arise in individuals, especially in those with allergic diseases. Using GBCA in MRI has been questioned in recent years as evidence has emerged linking gadolinium to nephrogenic systemic fibrosis (NSF) and gadolinium deposition. Although most gadolinium is removed by urine after an MRI scan, a minimal amount stays and can accumulate over time, according to research published in 2017. This is an important concern for people who need to have MRI scans on a frequent basis[1]. Linear and macrocyclic agents are the two types of GBCAs depending on their chemical forms. Several studies indicated that the linear agents remain more in the brain than macrocyclic agents. However, new research has revealed that all treatments, including macrocyclic, leave some gadolinium in the brain. While gadolinium accumulation in the brain has been the focus of attention in recent years, the authors claimed that, in animal tests, 100 times more gadolinium was found to be retained in the skin and bones than in the brain[4]. The patients with multiple sclerosis (MS) should have brain MRIs both during relapse and remission (every few months) to assess disease activity. In the individuals with MS, the dentate nucleus (DN) T1 hyperintensity was detected[5].

However, certain studies on the effects of various kinds of GBCA administrations on gadolinium accumulation in MS patients have yielded conflicting results. In these investigations, some researchers[6] found that repeated macrocyclic GBCAs administrations enhanced DN-to-pons signal intensity ratios, while others[4] found that numerous doses of macrocyclic chelates administrations did not affect brain signal intensity variations in MS patients. To date, no specific clinical evidence was reported for complications associated with the deposition of GBCAs in the patients' brains. However, it is possible that based on the deposition of GBCAs in different areas of the brain, some symptoms, such as neurological and motor disorders, may occur in patients, which requires further studies. Gadolinium deposition in the humans appears to be linked to a wide range of diseases. One of the studies observed the difference in gadolinium deposition between patients

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Conflicts of interest: the authors declare there is no conflicts of interest. Funding: none.
Received on June 17, 2022. Accepted on June 18, 2022.

with neuromyelitis optica spectrum disorder (NMOSD) and those with MS and found that patients with MS were more prone to gadolinium accumulation compared to patients with NMOSD. The authors hypothesized that changes in disease pathophysiology and gadolinium structure could influence gadolinium deposition[7]. There are certain potential biases in examining and evaluating the health/clinical consequences of gadolinium deposition[8]. The bulk of clinical investigations on GBCAs were unable to examine direct acute toxicity and diagnostic effectiveness of the agents, and hence the long-term health impacts, according to the research. Despite no neurological symptoms or parenchymal damage being associated with gadolinium deposition in the retrospective studies published to date, it seems necessary to have a selective approach in MS patients requiring contrast-enhanced MRI[9-15]. Therefore, it is better to monitor MS patients regularly under GBCAs administration to prevent complications if GBCAs are deposited in patients' brains[6,16-20].

AUTHORS' CONTRIBUTIONS

EA: Conceptualization, Data curation, Investigation, Formal Analysis, Funding acquisition, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **FG:** Funding acquisition, Methodology, Writing – original draft, Writing – review & editing. **ZE:** Conceptualization, Data curation, Investigation, Formal Analysis, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **ANM:** Conceptualization, Data curation, Investigation, Formal Analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

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