

Peer Review

Review of: "Gadolinium Toxicity: Mechanisms, Clinical Manifestations, and Nanoparticle Role"

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1. Independent researcher

The author has performed a comprehensive review on the subject of Gadolinium Toxicity.

1. As I am the leading author in the peer-reviewed literature on Gadolinium, including both positive effects and safety issues, I take exception to the adding in of the phrase in line 3 of 4.3 "although controversial." I have described the entity Gadolinium Deposition Disease with 8 years of experience. The name is proposed; it is not controversial.
2. The overlap with the symptoms of fibromyalgia and chronic fatigue syndrome is correctly observed. We consider this to represent that Gadolinium Deposition Disease (GDD) is a type of fibromyalgia and similarly a type of chronic fatigue syndrome.
3. Identification of oxalate as a potential cause of dechelation of not only linear agents but also macrocyclic agents is a very novel viewpoint. As such, it is critical that this be verified by other researchers involved in animal research. I would be much more accepting of this theory if it is validated by groups such as those under the direction of Dr. Pietsch with Bayer and the Guerbet group of researchers, who have enormous experience with animal research with GBCAs.
4. The nanoparticles described also need to be verified by the above-mentioned groups. It may be dangerous to make recommendations about diet, for example, if oxalates are incidental rather than causative.
5. Chelation therapy. The author should have better familiarized himself with the concept of chelation therapy, which should be thought of as the mirror reflection of GBCA ligand construction. Reference 124 describes the effect of excess ligand to decrease the incidence of NSF. The inclusion of excess ligand is essentially the inclusion of a concurrent chelating agent. So if we sum the global use of Omniscan with that of Optimark, there have been at least 80 million doses of Omniscan given and at

least 40 million doses of Optimark worldwide. So 120 million doses of concurrent chelation with a GBCA ligand. This is unmatched use of a treatment for 'free' Gd.

6. The author should read ref 75 again. In it, the log stability constants of EDTA and DTPA with Gd are described, approximately 17 and 22. This represents a 300,000-fold greater stability of Gd with DTPA than with EDTA. EDTA was actually looked at as a potential ligand for GBCA contrast, but in early work by Weinmann with Schering in the 1970s, EDTA was found to be far too weak a ligand to be used in a GBCA agent. So it is inappropriate and dangerous and shows, for lack of a better word, ignorance to suggest EDTA as a potential chelator. One has to consider chelation as the mirror image of creating a GBCA with a ligand. With this concept in mind, one can also appreciate that other ligands for GBCAs may be even better than DTPA.
7. HOPO should also be mentioned as a chelating agent.
8. It is dangerous to downplay the role of chelation, as this is the only effective treatment for GDD, as it is for other heavy metal toxicities.
9. Ref 77. I believe Layne is a physicist and has no experience with treating humans, so her impression of chelation is of limited merit.
10. 165 and 167 are papers first authored by Holden Maecker, the director of the Human Immune Monitoring Center at Stanford. A couple of sentences should be devoted to his cytokine work, as Stanford would be as important a center as any mentioned in this article.
11. A full description of nanoparticles. This would be greatly strengthened if validated by other groups, such as Bayer and Guerbet, as I mention above. I caution against the recommendation to avoid oxalate-containing foods until this novel data is validated by independent groups.
12. It may have been worth mentioning the recent paper in Investigative Radiology that reported Parkinson's Disease in patients who received GBCAs but not shown in those who did not receive GBCA, based on a large nationwide database in South Korea.

Declarations

Potential competing interests: board member GadTTRAC.