Qeios

Peer Review

Review of: "Chelation Therapy for Rare Earth Element Toxicity: Current Evidence, Challenges, and Future Directions"

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1. Independent researcher

The study is well-researched and overall very well-written. I have the following comments:

1. P7, last line ...to years, likely lifelong
2. Table 1. With Gd. Highlighted organs should be skin, brain and nervous system, bones. Symptoms to describe: fibrosis, central and peripheral nervous system dysfunction, bone retention.
3. p 11. Section 3.23. Second line: add in ..... ,and likely lifelong
4. p 11. Section 3.23. Second line "The most recognized" not the only
5. p 12. On the topic of vulnerable populations and fetuses. I did not check the reference list for the large study from Ontario, Canada, that described fetal loss from GBCAs.
6. Principle of chelation. If I were a co-author on this paper, I would include in this section wording to the fact: "A science-based approach to evaluating the effect of a chelator that two properties are necessary for a chelator to be effective for a particular REE: i. high log stability constant and ii. documentation of removal of the REE. The standard we use is pre- and post-chelation 24-hour measurement of the urine content of the REE.
7. I do not like the description that the metal is central in the chelator; more effective chelators are cation-exchange based, and the locus for exchange may be on a linear arm.
8. p14 EDTA. Line 1: I prefer using the term "effective chelator" and not chelator of choice.
9. p14. I would substitute 'represented' for 'meant'.
10. Section 3.4.2 Limitations. I believe I had a seizure when I read that DTPA was not effective for chelating Gd. It is highly effective. The model for the chelator using a ligand that had been

 doi.org/10.32388/GAMCSU

established for clinical use (> 100 million doses of Magnevist given worldwide) is unique among REEs. In fact, understanding the principles of creating optimal ligands for GBCAs provides unique insight into creating chelators for REEs, highlighting the importance of the log stability constant (AKA thermodynamic stability) and rapid elimination by the kidneys (and some with the addition of hepatobiliary elimination).

11. 3.3.3 Emerging Therapies. HOPO does not appear in this manuscript; it is an important addition on the subject matter and must be added in.
12. It may be of value to mention that for most REEs, the toxicity issue reflects an immunologic/toxic process. Radioactivity is observed in a few of these agents, and this is a separate issue that would prompt a more rapid removal requirement.
13. Sorry, I did not check, but is this paper in the references? It describes what I mention on p 12, especially the combination of chelation and steroids. Autoimmunity Reviews 23 (2024) 103509

Available online 28 December 2023

Metal-induced autoimmunity in neurological disorders: A review of current understanding and future directions

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Declarations

Potential competing interests: No potential competing interests to declare.