Gadolinium/GBCA Deposition and Retention in the Brain

Discussion

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Conflicts of Interest

Consulting fees or honoraria, directly or indirectly, from: Bayer, Bracco, GE HealthCare, and Guerbet; institutional research support from Bracco, Guerbet, and GE; and joint patent pending with GE.

Is there evidence of CNS toxicity from gadolinium deposits in the brain?

- If there is toxicity, is there a dose dependency and/or toxicity threshold?
- If there is toxicity, is it confounded by underlying (CNS) disease?
- If there is toxicity, are certain populations at increased risk, and should we develop protocols to long term assess their vulnerability?
  - Fetuses
  - Children

CSF deposition

- Gadolinium chelates in the CSF are clearly neurotoxic (animals and human data); macrocyclic GBCA are MORE neurotoxic than are linear ones when introduced directly into the CSF

- What are the relative neurotoxicities, if any, for intact GBCA gadolinium-ligand chelates versus insoluble gadolinium forms (e.g., gadolinium phosphate) versus gadolinium bound to/interacting with macromolecules?

- What is the molecular speciation of the gadolinium found in the CSF (and globe) following intravenous administration for *each* GBCA (as opposed to by “class”)?

CSF deposition

- NOT all patients necessarily show gadolinium in the CSF - or at least not to the same degree - following intravenous administration. Could this play a role in how much is retained and/or, if an association is found with symptomatology claims, who becomes symptomatic?

What mechanisms of CNS injury should be interrogated?

- To date, there is no convincing histopathological or ultrastructural EM data to suggest Gd deposition is associated with cellular injury.
  - Are we not looking in the right place?
  - Should we focus more on gene expression, cellular function assays?