Gadolinium Deposition and Washout: Does It Matter?

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Gadolinium Deposition

Objectives

- Review different classes of gadolinium based contrast agents used for MR imaging and their salient biochemical characteristics.
- Review literature discussing gadolinium deposition in brain, differential deposition of various GBCA based on biochemical characteristics, histological, clinical and commercial impact of gadolinium deposition.
- Review literature suggesting the phenomenon of partial gadolinium washout from the brain on follow up.

GBCA Characteristics Associated With Deposition

- Two major classes of GBCA based on ligand structure: Linear and Macrocyclic
- Properties of GBCA ligand structure is associated with brain deposition
- Better kinetic and thermodynamic stability → less demetallation → less deposition
- Macrocyclic GBCA have better kinetic and thermodynamic stability profile.

Most macrocyclic GBCA also have a lower average dose compared to linear GBCA

Functional Effects of Gadolinium Deposition

- Multiple autopsy studies show no evidence of histological damage.
- Welk et al (2016) demonstrated no relationship with parkinsonian symptoms and gadolinium deposition within the globus pallidus.
- Perrotta et al (2017) demonstrated no cerebellar symptoms related to gadolinium deposition.
- Bussi et al (2017) demonstrated no cognitive or behavior changes at highest cumulative doses.

Gadolinium Deposition Outside the Brain

- Multiple autopsy studies involving human and animal subjects have demonstrated deposition of gadolinium in bone, skin, liver, kidney, spleen.
- Concentration of gadolinium in bone is higher than in brain and is thought to serve as a potential reservoir.
- Most studies used ICP-MS used for detection.
- No evidence of histologic damage

Regulatory Changes and Statements

- FDA requires a medication guide to be presented to the patient before first GBCA administration. However, it concluded that gadolinium retention has not been linked to any adverse effects in patients with normal renal function and that the benefit of imaging with all approved GBCA outweighs risks.
- Pharmacovigilance risk assessment committee (PRAC) of the Europeans Medicine Agency (EMA) recommend suspension of linear GBCA for imaging except gadobenic and gadoxetic acid for liver scans and gadopentetate for joint scans.

GBCAs and Their Biochemical Characteristics

Generic Name	Trade Name	Chemical Structure	Ionicity	Thermodynamic Stability Constant (Log KTherm)	Kinetic Stability (T1/2 at pH 1.0)
Gadodiamide	Omniscan	Linear	Nonionic	16.8	<5s at 25°C
Gadoversetamide	Optimark	Linear	Nonionic	16.6	N/A
Gadobenate dimeglumine	Multihance	Linear	Ionic	22.6	<5s at 25°C
Gadopentetate dimeglumine	Magnevist	Linear	Ionic	22.1	<5s at 25°C
Gadofosveset	Ablavir	Linear	Ionic	22	<5s at 25°C
Gadoxetic acid	Primovist	Linear	Ionic	23.5	<5s at 25°C
Gadobutrol	Gadavist	Macrocyclic	Nonionic	21.8	7.9h at 37°C
Gadoteridol	Prohance	Macrocyclic	Nonionic	22.8	2.0h at 37°C
Gadoterate meglumine	Dotarem	Macrocyclic	Ionic	25.4	26.4h at 37°C

Axial T1 weighted non-contrast images after A) 1, B) 3, C) 7 and D) 10 doses of gadodiamide (Omniscan) in a 50 year old female with Multiple Sclerosis show visible increase in dentate nucleus signal intensity.

Axial T1 weighted non-contrast images after A) 1, B) 3, C) 7 and D) 10 doses of gadobutrol (Gadavist) over a period of 2 years in a 23 year old female with a low grade neuroepithelial neoplasm show no visible increase in dentate nucleus signal intensity.

Gadolinium Washout

Adin et al

- 2 patients dentate nucleus (DN) hyperintensity resolved on follow-up, 1 patient had resolution of in one DN.

Radbruch et al

- Increase in dentate nucleus to pons signal intensity ratio (DN/Pons SI) with serial gadopentetate administrations with subsequent decline in DN/Pons SI with macrocyclic injections

Smith et al

- 50% of gadolinium detected one week after low and high dose gadodiamide washed out at 20 weeks.

Behzadi et al

- Patients were followed up for an average of 28 months after switching to gadobutrol from gadavist, all of the patients showed decrease in T1 hyperintensity.

Robert et al

- A total of 139 rats with gadoterate or gadodiamide, 25% of gadodiamide washed out from the cerebellum at 12 months compared to month 0. In gadoterate group, elimination of gadolinium to background was seen within 5 months of follow-up.

Jost et al

- At 52 weeks since last contrast injection, no washout of linear GBCA with 65 - 92% washout of macrocyclic GBCA.

Proposed Hypothesis for Gd Washout

- Potential chelating agents in diet or medication may be involved in removal of gadolinium.
- Precipitation or dechelation of gadolinium in brain to a form with lower T1 relaxivity.

Gadolinium Washout on 6 Year Follow-up

26 year old female with pituitary macroadenoma received 7 doses of gadodiamide during 2002 to 2007 with progressive increase in dentate nucleus to cerebral peduncle signal intensity ratio (DN/CP SI). Follow up after 6 years without any interval GBCA administration showed significant decline in DN/CP SI.

Axial T1 weighted non-contrast images A) after first dose of gadodiamide, images B) and C) after 4 and 6 doses of gadodiamide show progressive increase in dentate nucleus signal intensity. Follow-up after 6 years without any interval administration of gadodiamide shows interval decrease in dentate nucleus signal intensity D).