Gadolinium Deposition in the Brain: Parallels between Patient-, Animal- and In Vitro-Studies

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Conflicts of Interest

Guerbet (consultant, financial study support, advisory boards, lectures); Bayer (consultant, financial study support, advisory boards, lectures); GE (advisory board, expert opinion); Bracco (advisory board); Siemens (lectures); Prime Oncology (lectures); AbbVie (advisory board).
Gadolinium Retention in the Brain

Kanda et al, Radiology 2014

McDonald et al, Radiology 2015
Risk-Benefit Evaluation prior to Injection of a GBCA

1. Side Effects of the GBCA
2. Efficacy of the GBCA
3. „Gadolinium Deposition Risk“

1. What is the Mechanism of Gadolinium-Deposition
2. Are there any clinical correlates?
Question 1: What is the mechanism of Gadolinium Deposition?

1. In vitro studies
2. Animal studies
3. Patient studies

The chemistry must be respected.
In vitro experiments for incubation in serum at 37 C for 2 weeks

**A**

linear, non-ionic

- Gadovist®
- Gadodiamide
- Optimark®
- Omniscan®

**B**

linear, ionic

- MultiHance®
- Magnevist®
- Vasovist®
- Primovist®

Gadolinium release for macrocyclic GBCAs _below the limit of detection_

_Frenzel T. et al_, In vitro release of Gd³⁺ by GBCAs incubated in native Human serum at 37° C, Investigative Radiology 2008
Animal Studies: How does the gadolinium get in the brain?

The same amount of all GBCAs can be found in the brain 24 h after injection.

Jost et al, Penetration and distribution of gadolinium-based contrast agents, European Radiology 2016, Image from Bayer-Brochure „Gadolinium Presence in the Brain“
Long Term Results: How much gadolinium does stay in the Brain?

Presented at the FDA MIDAC meeting by Bayer – material from FDA www.fda.gov

Presented at the FDA MIDAC meeting by Guerbet – material from FDA www.fda.gov
Explanation for Discrepancy: Partly Dechelation of linear GBCAs

Frenzel et al, Investigative Radiology 2016

Presented at the FDA MIDAC meeting by Guerbet – material from FDA www.fda.gov
Pathomechanism Macro cyclic GBCAs

McDonald et al, Radiology 2017

CSF, Choroid Plexus

Cerebellum

Gadolinium
Lin. GBCA
Macr. GBCA
Phosphate
Pathomechanism Macro cyclic GBCAs

Wash out over time

Cerebellum

Gadolinium
Lin. GBCA
Macr. GBCA
Phosphate
Hypothesis 1:
Gad-Deposition depends on specific stability of GBCA

Hypothesis 2:
“Invisible” – precipitated Gad exclusively for linear GBCAs

Hypothesis 3:
SI Increase: Indicator for Gad.-Release in the whole body
Gadolinium Accumulation in the Brain
pre contrast T1 vs Laser ICP-MS: LINEAR GBCAs

Correlation between Gad accumulation displaying on ICP-MS and hyperintensities on MRI

Hyperintense regions following 35 injections of lin. GBCAs: DN, Substantia Nigra.
Gadoliniumaccumulation in the Brain pre contrast T1 vs Laser ICP-MS: MACROCYCLIC

Macrocyclic (Prohance)

Saline (control-group)

Lohrke et al, Invest Radiol 2017

No Signal Intensity increase after more than 20 injections (491 ml GBCA)

Hypothesis: No accumulation on Laser ICP-MS – No Hyperintensities!!!
Patient Studies: Hyperintensities in the Brain

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Macrocyclic GBCAs</th>
<th>Linear GBCAs</th>
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<tr>
<td>Kanda et al.</td>
<td>Gadovist</td>
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Quality of studies varies highly!
4.74 ± 0.72 injections of Gadovist

Significant SI increase DN - Pons (p<0.001)

Example (Radbruch et al, unpublished): Pre and after 29 injections of Gadovist
Bjornerud 2017
Gadovist (macrocyclic)

- 17 Patients
- Abrupt increase after 26 injections (6 patients)
- Only in two patients „visible SI increase“
### Summary Gadolinium Deposition

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<th>Type</th>
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<th>Macrocyclic</th>
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<td>1. In Vitro Experiments</td>
<td>Dechelation</td>
<td>Below the limit of detection</td>
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<td>2. Animal Experiments</td>
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<td>3. Patient Studies</td>
<td>Majority of studies: Hyperintensities</td>
<td>Majority of studies: No Hyperintensities</td>
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**Chelated or dechelated gadolinium deposition**

Although Vikas Gulani and colleagues cite most of the recent literature, Radbruch et al, Lancet Neurology 2017

*The chemistry must be respected.*

„All GBCAs deposit“ Misleading!
What should we do?

- Avoid studies that obviously cannot be finalized in reasonable time!
- Re-evaluate controversial studies!
- End the debate on hyperintensities!
- Comprehensive study in sheep starting in March 2018
- Establishing of a human tissue bank for all tissues

- It is not possible to prove the null hypothesis!