Clinical Manifestations of Gadolinium Retention: Summary of Animal Data

Paul Evans – GE Healthcare
February 16th, 2018
NIH/RSNA/ACR Workshop on Gd Retention
Conflicts of Interest

Employee of GE Healthcare.
<table>
<thead>
<tr>
<th>In scope</th>
<th>Out of scope</th>
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</thead>
<tbody>
<tr>
<td>GBCA Administration</td>
<td>Gd Salts e.g. GdCl$_3$</td>
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<tr>
<td>Retained Gd</td>
<td>Acute toxicity/effects</td>
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<tr>
<td>Macroscopic changes</td>
<td>Microscopic changes</td>
</tr>
<tr>
<td>Behavioural effects</td>
<td>Sub-clinical effects</td>
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</tbody>
</table>
Overview

• **Macroscopic Effects**
  – Skin lesions

• **Behavioural Effects**
  – Adult animals
  – Juvenile animals
  – In utero exposure
Macroscopic Effects – Skin Lesions in Rats

• First reported by Harpur et al. 1993\(^1\)
• Further studies conducted in post-NSF era
• Skin reddening, fur loss, scab formation and ulceration
• Seen with high (4xHED) repeated doses of Omniscan/gadodiamide in naïve and nephrectomised male rats\(^2,3,4\)

Skin Lesions not observed in Females or Primates

“At necropsy, treatment-related findings in males in the 5.0-mmol/kg group included skin desquamation (90%) and sores (60%)”\(^1\) This effect was not seen in female animals.

Skin lesions were not observed in male or female monkeys 28 repeated high doses, 4xHED daily, 112xHED total cumulative dose\(^1\)

Available data indicate this effect is specific to male rats

Skin lesions resolve with no or less frequent dosing

Skin lesions dependent on the injection interval and not on the amount of Gd in tissue.

“the skin lesions resolved during the experimental phase, although the Gd concentration in the skin further increased due the continued Gd-DTPA-BMA injections.”

Skin lesions: Acute response unrelated to Gd retention

Behavioural Effects

- Adult animals
- Juvenile animals
- In utero exposure
Behavioural Effects – Adult Animals

• During drug registration the potential for neurological effects of GBCAs were investigated in acute studies (e.g. single dose, Irwin test observations up to 24 hours).

• Mid- to long-term Gd retention and the potential for associated neurological effects were not investigated.

• Since the more recent observations of Gd retention in the brain, long-term studies in adult animals have been initiated.
Mayo Clinic long-term study of rat behaviour

McDonald et al. Adapted from presentation at CMR2017, Durango, CO.
Mayo Clinic Rat Study: Preliminary data @6 weeks

No effect on tests of memory, locomotor activity or anxiety

McDonald et al. Adapted from presentation at CMR2017, Durango, CO.
Behavioural Effects – Juvenile Animals

In the last 5 years some companies have performed juvenile animal studies as a requirement to expand US indications to paediatric patients younger than 2 years of age.

<table>
<thead>
<tr>
<th>PND</th>
<th>10</th>
<th>11</th>
<th>14</th>
<th>18</th>
<th>22</th>
<th>26</th>
<th>30</th>
<th>31</th>
<th>71 - 72</th>
<th>91 - 92</th>
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<tbody>
<tr>
<td>C</td>
<td>0 mmol/kg/adm</td>
<td>cumulative dose: 3.6 mmol/kg</td>
<td>60-day recovery</td>
<td>sacrifice</td>
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<td>1.25 mmol/kg/adm</td>
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<td>cumulative dose: 15 mmol/kg</td>
<td>60-day recovery</td>
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Gadobenate dimeglumine (Multihance)

Adult rat behaviour after juvenile exposure

Gd was detected in the brain 60 days post-dosing with gadobenate dimeglumine (Multihance)
No effect on water maze, open-field test, & functional observation battery (with grip strength measurement, gait, pupillary & auditory reflex)

Behaviour after juvenile exposure

- A similar study on gadoterate meglumine (Dotarem) was published in 2015
- Brain Gd not measured, Gd detected in the liver & bone of a few high dose rats and in the kidneys at 60 days recovery
- No effect on behaviour:
  - Gripping reflex PND17
  - Papillary/Auditory PND21
  - Watermaze PND 38 & 45
  - Open Field PND 52
In utero exposure – Drug registration studies

Teratogenicity

• Potential teratogenic effects assessed by dosing pregnant animals (usually rats & rabbits) during organogenesis

• In general no specific teratogenic effects attributed to GBCA exposure

Developmental

• Peri- & post-natal studies in rats performed to examine potential effects on F1 generation

• Daily dosing from GD 6 or 16 to PND 21. At PND 30 to 60 selected behavioural tests such as open field test and water maze. No specific effects attributed to GBCA exposure.
The Effect of Perinatal Gadolinium-Based Contrast Agents on Adult Mice Behavior

Miski Aghnia Khairinisa, MBiomedSc,*† Yusuke Takatsuru, MD,* Izuki Amano, MD,* Khongorzul Erdene, MD,‡ Takahito Nakajima, MD,‡ Satomi Kameo, PhD,§ Hiroshi Koyama, MD,§ Yoshito Tsushima, MD,‡‖ and Noriyuki Koibuchi, MD, PhD*
Brain Gd detected in pup brain on PND 28

Gd detected with both gadodiamide & gadoterate
Gadodiamide > gadoterate
Females > Males

Various effects reported in 6 behavioural tests

- Rotarod Test
  - Male
  - Control (n=13)
  - Gadoterate (n=12)
  - Gadodiamide (n=10)

- Object Recognition Test
  - Female
  - Control (n=12)
  - Gadoterate (n=11)
  - Gadodiamide (n=14)

- Open Field Test
  - Male
  - Control (n=13)
  - Gadoterate (n=12)
  - Gadodiamide (n=10)

- Object-in-Location Test
  - Female
  - Control (n=12)
  - Gadoterate (n=11)
  - Gadodiamide (n=14)

Perinatal exposure to gadodiamide or gadoterate induced behavioural changes in adult mice. Gadodiamide> Gadoterate

<table>
<thead>
<tr>
<th></th>
<th>Open Field Travel Distance</th>
<th>Open Field Time in Centre</th>
<th>Rotarod</th>
<th>Object recognition</th>
<th>Object in location</th>
<th>Von Frey hair</th>
<th>Grip strength</th>
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<tbody>
<tr>
<td><strong>Gadodiamide</strong></td>
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<td><strong>Gadoterate</strong></td>
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Statistically significant effect: Y  
No effect: N

Summary

- Skin lesions in male rats are an acute response & unrelated to Gd retention
- Behavioural studies following long-term Gd retention in adult rats are ongoing & will fill a knowledge gap
- Juvenile rat studies with some GBCAs have shown no behavioural effects
- Recent study of perinatal exposure reported behavioural effects in adult mice
## Animal Clinical/Behavioural – Knowledge Gaps

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Adult animals:</td>
<td>Data on potential long-term effects</td>
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<tr>
<td>Juvenile animals:</td>
<td>Not all GBCAs have been studied <em>Additional adult testing e.g. rotarod</em></td>
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<tr>
<td>Peri-/Post-natal:</td>
<td><em>Historical data in rats - selected tests</em></td>
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<td></td>
<td><em>Single mouse study - not all GBCAs</em></td>
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<td>Studies in rodents:</td>
<td>Relevance to human</td>
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