Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year

Contrast and Non-Contrast Magnetic Resonance Imaging (MRI) and Risk for Same Day Seizure

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Contrast MRI

• Gadolinium is a rare earth metal with paramagnetic properties which is widely used to enhance magnetic resonance imaging (MRI) for visualization of internal body structures and blood vessels.

• The gadolinium ion is bound to a proprietary ligand to minimize toxicity in gadolinium based contrast agents (GBCA)

• Review of FAERS identified 183 case reports of seizure within one hour of a contrast MRI [Phelan K, 2014].
  – 12 of these reports had no identifiable confounding risk factors
Current Evidence

• Preclinical studies in dogs found a dose-dependent increase in seizure risk with GBCA in the presence of a dysfunctional blood brain barrier [Muldoon, 2015]

• Intraventricular injection of GBCA in rats caused acute neurotoxicity [Ray, 1996]

• Intrathecal injection of GBCA can cause seizures. [Kapoor, 2010; Safriel, 2006].
Study Objective

• Our study aims to quantify the relative risk of same-day seizure requiring transfer to the emergency department (ED) or inpatient admission among patients receiving ambulatory MRI with and without gadolinium contrast.
Cohort of Outpatient MRIs

Inclusion Criteria
• Outpatient Contrast or Non-Contrast MRI
• Extremity or Non-Extremity MRI (i.e. No head MRIs)
• Jan 2008 through Nov 2016
• 2 years of age or older
• 183 days with prescription and medical coverage prior to the index MRI

Exclusion Criteria*
• Recent MRI
• Same day head MRI or head CT
• Seizure or epilepsy
• Antiepileptic drug use
• Myocardial infarction or Stroke
• Syncope
• Brain tumors
• Alzheimer’s disease
• Autism spectrum disorder
• Overdose with illegal or legal drugs
• Head injury
• Kidney Disease
• Drug Dependency
• Brain Compression

*Baseline period for exclusion is 183 days prior to index date
Exposure Definition

- Extremity MRI (e.g., upper or lower extremity joint or non-joint imaging)
- Non-extremity MRI (e.g., cervical, thoracic, and lumbar spine, chest, abdomen, and pelvic imaging).
- MR angiography (MRA; extremity and non-extremity)
Self-Controlled Risk Interval Design

- Relative Risk (RR) for seizure calculated, comparing seizure risk on the day of MRI versus the daily adjusted seizure risk in the following 6 weeks
  - Conducted independently for contrast and non-contrast MRI
  - A relative risk ratio for seizure with gadolinium was produced, comparing the contrast MRI versus non-contrast MRI.
  - Stratifications of extremity and non-extremity MRI locations
  - Subset analysis of Magnetic Resonance Angiography (MRA)
Seizure Outcome Ascertainment

- Emergency Department seizure on day of outpatient MRI
  - Epilepsy: 345, 345.X, 345.XX, A subset of G40 ICD10 codes
  - Convulsions: 780.3, 780.3X, R56.00, R56.01, R56.9
  - PPV: 83.6% to 99.3% [Thyagarajan; Jette; Shui; Klien]

- Hospital Admission on day of outpatient MRI
  - Primary Discharge Diagnosis of Epilepsy or Convulsion
  - PPV: 79.1% to 97.7% [Thyagarajan; Jette; Shui; Klien]

- The sensitivity for seizure coding is unknown.
  - We would expect relatively high rates of presentation to the Emergency Department for a first time convulsive seizure in a non-epileptic
Relative Risk for Seizure with MRI

<table>
<thead>
<tr>
<th>Exposure Cohort</th>
<th>Analysis Cohort</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>No. MRIs</td>
<td>No. Risk Window Seizures</td>
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<td>-----------------</td>
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<tr>
<td>Contrast MRI</td>
<td>1,708,779</td>
<td>1,991,158</td>
</tr>
<tr>
<td>Non-Extremity MRI</td>
<td>1,210,037</td>
<td>1,445,364</td>
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<tr>
<td>Extremity MRI</td>
<td>507,944</td>
<td>535,838</td>
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<tr>
<td>MRA only</td>
<td>57,705</td>
<td>63,919</td>
</tr>
<tr>
<td>Non-Contrast MRI</td>
<td>6,714,901</td>
<td>7,955,932</td>
</tr>
</tbody>
</table>

Relative Risk Ratio attributable to gadolinium contrast was 1.04 (95%CI: 0.62-1.61)
Frequency of Seizure Events by Day

Contrast MRI or MRA - Extremity or Non-Extremity

Non-Contrast MRI or MRA – Extremity or Non-Extremity
Results

- Both contrast and non-contrast MRI were associated with an approximate three-fold increased risk for seizure on the day of MRI procedure compared to the following 6 week control window.

- Absolute risk is very low; 1 seizure per 79,646 MRI procedures, regardless of contrast.

- Gadolinium contrast was not associated with increased seizure risk above that observed with the MRI procedure.

- Our study found a higher frequency of seizure with contrast MRA:
  - It could be a chance finding due to the smaller number of total seizures (n=13) or it could reflect a dose response relationship.
Among 9.9 million MRI procedures, some patients are likely to be more susceptible to adverse effects of magnetic fields.

- Increased susceptibility could occur from factors such as medications, anxiety during the MRI procedure, and acoustic noise from the MRI.

- The absolute risk in our study was one seizure per 79,646 MRI.

- Even if our study outcome has a sensitivity of 70%, the absolute risk is one seizure per 63,300 MRI.
Limitations

• The exposure and outcome were required to occur in different facilities to identify progression of care from outpatient exposure to emergent treatment.
  
  – We felt the reverse was unlikely to occur, where patients presenting to emergent care with a new-onset seizure would later that same day undergo an outpatient extremity or non-extremity MRI for a non-neurological condition.

• Our study also does not assess the long term effect of gadolinium deposition in the brain [McDonald 2015; Kanda 2015].

• The sensitivity of the seizure algorithm in this study is unknown
Conclusions

• We found increased seizure risk on the same day for both contrast and non-contrast MRI with no differential risk associated with administration of GBCA.

• Given the widespread use of MR imaging and the current trend towards introducing MRI scanners with stronger magnetic fields, questions of potential neurologic side effects warrant more attention.
References


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Medicines and Healthcare Products Regulatory Agency.
References

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Acknowledgments

• Many thanks are due to Data Partners who provided data used in the analysis
Questions?