New Perspectives in Contrast Enhanced MRI and MRA of the Brain

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Requirements & Goals of CNS Imaging

Prior Therapy
- lesion extent
- complications
- differential diagnosis
- grading

Therapy
- decision
- approach
- delineation

After Therapy
- monitoring of therapy response
- monitoring of side effects

Therapy
- Prior Therapy
- After Therapy
Problem

- T1 / T2 w SE, Turbo-SE, GRE
- 0.1 mmol/kg BW of Gadolinium
- T1 w post contrast imaging 2/3D

Conventional imaging is not able to fulfill the requirements!
Current and future trends in neuroimaging

Solution I
Current and future trends in neuroimaging

Solution II

Use of functional imaging tools in MRI

- Morphology
- Functional (Neuro) MRI
- Physiology / Pathophysiology
Current and future trends in neuroimaging

Solution III: Optimization of contrast enhanced MRI
What makes the difference in contrast media?

- Stability
- Relaxivity
- Concentration
Gadovist is well tolerated and has a good safety profile comparable to other Gd-based contrast agents

- Experience to date includes clinical studies (> 4,000 patients) and more than 4.5 million (as of Feb 2010) clinical applications
- Adverse event profile does not differ from that of the other extracellular contrast agents
Gd-Retention in the body

Gadolinium deposition in bones known already
Gibby et al Invest Radiol 2004

Gadolinium deposition in the skin!!
a specific trigger for the development of
nephrogenic fibrosing dermopathy and
nephrogenic systemic fibrosis

Grobner et al.: Nephrology Dialysis Transplantation 2006; 21:1104-1108
Nephrogenic Systemic Fibrosee

Gd-Deposition in the skin

Gd-deposit in fibrotic skin tissue

Cowper et al.; Lancet 2000
Gadovist, as macrocyclic agent, belongs to the class of gadolinium chelates with the highest stability, even under conditions mimicking end-stage renal disease.

Native human serum + elevated phosphate levels (10 mM phosphate):

- Macroyclic agents at 15 days: no detectable Gd$^{3+}$ released (<0.1%)
- Linear agents at 15 days: accelerated rate of Gd$^{3+}$ release, non-ionic linear (100-fold) and ionic linear (12- to 30-fold)
Stability of macrocyclic agents

Native human serum, 37°C
Linear non-ionic: out of scale

- Macroyclic agents: no detectable Gd$^{3+}$ released (<0.1%)
- Linear ionic: up to 2%
- Linear non-ionic: up to 22%

Native human serum, % of Gd$^{3+}$ released after 15 days:
Efficacy
What causes the contrast in CE MRI

T1-w MRI: Signal Intensity vs TR

T1-w = T1-weighted.
Courtesy of E. Kanal, MD, FACR.
## Relaxivity of ECCA: 1.5T vs. 3T

Comparison of Magnetic Properties of MRI Contrast Media Solutions at Different Magnetic Field Strengths

<table>
<thead>
<tr>
<th>Agent</th>
<th>R1 – 1.5T</th>
<th>R1 – 3T</th>
<th>R2 – 1.5T</th>
<th>R2 – 3T</th>
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</thead>
<tbody>
<tr>
<td>Magnevist®</td>
<td>4.3</td>
<td>3.7</td>
<td>4.4</td>
<td>5.2</td>
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<tr>
<td>Gadovist®</td>
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<td>5.0</td>
<td>5.4</td>
<td>7.1</td>
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<tr>
<td>ProHance®</td>
<td>4.4</td>
<td>3.7</td>
<td>5.5</td>
<td>5.7</td>
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<tr>
<td>MultiHance®</td>
<td>6.7</td>
<td>5.5</td>
<td>8.9</td>
<td>11</td>
</tr>
<tr>
<td>Dotarem®</td>
<td>4.2</td>
<td>3.5</td>
<td>6.7</td>
<td>4.9</td>
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<tr>
<td>Omniscan®</td>
<td>4.6</td>
<td>4.0</td>
<td>6.9</td>
<td>5.6</td>
</tr>
<tr>
<td>OptiMARK®</td>
<td>5.2</td>
<td>4.5</td>
<td>6.0</td>
<td>5.9</td>
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<tr>
<td>MS-325</td>
<td>19</td>
<td>9.9</td>
<td>37</td>
<td>60</td>
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<tr>
<td>Gadoxetic Acid</td>
<td>7.3</td>
<td>6.2</td>
<td>9.1</td>
<td>11</td>
</tr>
</tbody>
</table>

Martin Rohrer, Ph.D.  Investigative Radiology, Vol. 40, Nov 2005
Gadovist has higher relaxivity at all field strengths (of non-protein binders)

Relaxivities $r_1$ (L mmol$^{-1}$ s$^{-1}$) in plasma at 37°C

- Gadovist has higher relaxivity than Omniscan, ProHance, Dotarem, and Magnevist
- The relaxivity of Gadovist is slightly lower than MultiHance (difference $\approx 20\%$ at 1.5 T, 10% at 3T)

Rohrer et al, Invest Radiol 2005
Advantages of Double Concentrated CM

- 30% higher arterial concentration after intravenous injection of 1.0 M vs. 0.5 M Gadovist® at same dosage*

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* Modified as by Mühler A, Weinmann H-J, “Arterial concentrations following intravenous bolus injection of Gadobutrol. Comparison of 0.5 and 1.0 molar stock solutions.” in “Proceedings of the ISMRM”, Nice, France, 1995
What about conventional imaging - Contrast Media Comparison

How can you prove which is better?

Is this better ...
Contrast Media Comparison

How can you prove which is better?

Or is this better?
Contrast Media Comparison

Intraindividual Crossover Comparative Studies

- Study same patient with 2 contrast media

- Close together in time and standardized imaging parameters

- Independent Blinded read analysis
  - Quantitative (eg, # lesions, accuracy, stenosis, SNR, CNR, etc.)
  - Qualitative (eg, quality score, relative visualization, artifacts, etc.)
Contrast Media Comparison

Intraindividual Crossover Study
Same patient / same parameters / same dose
Effectiveness of Gadobutrol 1M

Rat brain tumor model

Effectivness of Gadobutrol 1M

Rat brain tumor model

Performance in cross over studies

Glioblastoma multiforme
Performance in cross over studies

Glioblastoma multiforme
Performance in cross over studies

Glioblastoma multiforme

16 ml of MultiHance®

8 ml of Gadovist® 1M
Performance in cross over studies

Gadovist® vs Magnevist® in patients with metastases

- 27 patients, 67 lesions

- Qualitative assessment
  - GV = MV, n = 17
  - GV > MV, n = 10
  - GV < MV, n = 0

- In 2 patients, a lesion was seen only after Gadobutrol

Significant difference (P = 0.002)

0.1 mmol/kg BW Gadobutrol

0.1 mmol/kg BW Gd-DTPA

Anzalone et al. Acta Radiologica 2009
Performance in cross over studies
Enhanced Sensitivity in Metastases Detection

7.5 ml Gadobutrol 1M

15 ml of Gd-DTPA

Anzalone et al, Acta Radiologica 2009
Performance in cross over studies

Multicenter Comparative Study

- Cerebral neoplastic enhancing lesions:
  Gadoterate (Dotarem® 0.5 M) vs gadobutrol (Gadovist® 1.0 M)
  randomized at 0.1 mmol Gd/kg BW

- Intraindividual comparative study on 135 patients
  - Quantitative and qualitative assessment of contrast
  - Overall preference

- In both assessments gadobutrol proved to be superior –
  providing a significantly stronger contrast enhancement and
  a superior diagnostic information about enhancing lesions
  at a dose of 0.1 mmol Gd/kg bw
Performance in cross over studies

Dotarem®

Gadovist®

Title: Cerebral neoplastic enhancing lesions: Intra-individual comparison of gadoterate (Dotarem 0.5 M) and gadobutrol (Gadovist 1.0 M) at 0.1 mmol Gd/kg body weight and 1.5 T

Topic: Contrast Media
Performance in cross over studies

Dotarem®

Gadovist®

Courtesy Nicoletta Anzalone
Performance in cross over studies

Multicenter Comparative Study

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Number of patients with rating examination x better</th>
<th>p-value</th>
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<tbody>
<tr>
<td></td>
<td>gadoterate</td>
<td>none</td>
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<tr>
<td>median</td>
<td>16</td>
<td>73</td>
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</table>

Primary efficacy analysis  Overall preference

<table>
<thead>
<tr>
<th>%enh</th>
<th>n=</th>
<th>Mean</th>
<th>Std Dev</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%enh</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>gadobutrol</td>
<td>121</td>
<td>99.196</td>
<td>55.206</td>
<td></td>
</tr>
<tr>
<td>gadoterate</td>
<td>120</td>
<td>90.637</td>
<td>52.565</td>
<td></td>
</tr>
<tr>
<td>difference</td>
<td>119</td>
<td>8.711</td>
<td>26.204</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

SI measurements  %enh - per-protocol population

Courtesy Nicoletta Anzalone
Double Dose Study @ 1.5 T

- 27 patients with cerebral metastases
  - Intraindividual comparison of Gadopentetate dimeglumine and Gadobutrol @ 0.2 mmol/kg of BW (non randomised)
  - Quantative and qualitative (2 reader) analysis of contrast enhancement and lesion count

- Gadobutrol enhanced MRI detected an additional 25 lesions

- Gadobutrol allowed a significant better contrast enhancement (p = 0.0011)
Performance in cross over studies

Double Dose Study @ 1.5 T

* p=0.0011

Kim et al. AJNR 2010
Performance in Multiple Sclerosis

increases specificity in making the diagnosis "MS"
- T2/PD o. FLAIR axial, max. 5mm
- T1 axial
- CA administration
  0.1 mmol Gadovist /kg b.w.
- T2 or FLAIR sagittal, 3mm
- T1 axial + CA (Delay)
Perfusion MRI - Gliomas

Differential Diagnosis and Grading
Perfusion MRI - Gliomas

Differential Diagnosis and Grading
Quality of perfusion MRI depends on the SI time curve.
Gadobutrol 1M: Perfusion study

- Intraindividual, crossover, volunteer study, 480 subjects
- Compare potential advantages of 1.0 M vs 0.5 M gadobutrol for MR brain perfusion imaging
- Results: Brain perfusion images superior with 1.0 M gadobutrol

Do Highly Concentrated Gadolinium Chelates Improve MR Brain Perfusion Imaging? Intraindividually Controlled Randomized Crossover Concentration Comparison Study of 0.5 versus 1.0 mol/L Gadobutrol¹

Bernd Tombach, MD
Thomas Benner, PhD
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Gerhard Schuierer, MD
Eva-Maria Falletberg, MD
Viviane Geens, MD
Thomas Wels, MD
A. Gregory Sorensen, MD

Index terms:
Brain, MR, 10.121411, 10.121412, 10.12142, 10.12143, 10.12144
Contrast media, comparative studies
Gadolinium
Magnetic resonance (MR), contrast media, 13.12143, 14.12143, 15.12143
1.0 M vs. 0.5 M Gadobutrol

Gradient-echo MR images of middle cerebral artery, putamen, cortex, and white matter

Signal intensity-time curves for 28 mL 1.0 M gadobutrol (D) and 56 mL 0.5 M gadobutrol (E) in putamen
Conclusion – Enhanced Contrast in MRI

High molar/relaxivity contrast media in CNS

- High T1 shortening leads to a higher contrast in CNS lesions
- Thus enabling a better detection, delineation and characterization
- This allows a higher diagnostic confidence and is therefore helpful in the patient management process – both at 1.5T and 3T
MRA – new concepts
MRA – Indication for 1.0 molar CM

- New MRA concepts with faster k-space acquisition, e.g. parallel imaging
- Dynamic fast MRI, e.g. TRICKS
- Higher anatomic coverage with new coil concepts, e.g. multistation imaging or whole body MRA
- Combination with other functional techniques, e.g. perfusion MRI

⇒ Special need for high quality contrast media
Why high contrast for MRA

SNR with parallel imaging

\[ \text{SNR}_{\text{PAT}} = \frac{\text{SNR}_0}{g\sqrt{f}} \]

- \( f \): speed factor
- \( g \)-factor: possibility of coil design for parallel imaging in dependence of the phase encoding direction and the speed factor

→ Speed factor of 2 leaves only 70% of the SNR, higher even less
→ High dosage compensates for the SNR loss
High resolution MRA @ 3T

<table>
<thead>
<tr>
<th></th>
<th>SNR @ 3.0 T</th>
<th>SNR @ 1.5 T</th>
</tr>
</thead>
<tbody>
<tr>
<td>no PAT</td>
<td>19.3</td>
<td>10.1</td>
</tr>
<tr>
<td>PAT 2</td>
<td>15.0</td>
<td>7.5</td>
</tr>
<tr>
<td>PAT 3</td>
<td>12.8</td>
<td>5.5</td>
</tr>
</tbody>
</table>

0.9×0.8×0.9 mm³
12 s acquisition time

Supraaortic MRA at 1.5T
*Gadobutrol 1M*

High-res MRA
0.9x0.7x0.9 mm³; $R=2$
24s

Dynamic MRA
2.1x1.3x3.0 mm³; $R=2$
2.4 sec/frame
High-Resolution and Dynamic MRA

Gadobutrol

MRA (30ml diluted; 5.625ml Gadovist)
0.8x0.7x0.8 mm³; R=4
22s

Gadobutrol TWIST (3ml diluted; 0.563ml Gadovist)
1.2x1.0x3.0 mm³; R=3
1.8 sec/frame
Indication in AVMs
Diagnostic Imaging
The need for speed

Introduction
Time-resolved 4D CE MRA with view sharing: Ultrafast imaging with 1.0M Gadobutrol

608 msec. per frame; 140 slices; 1 mm³ resolution
Enhance Speed – dynamic CE MRA

*syngo* TWIST, a new application for 4D MRA
(Time-resolved imaging With Interleaved Stochastic Trajectories)
Need for speed

The ultimate increase in speed: 220 ms
4D-MRA
CTA for radiosurgery planing

25 year old patient after bleeding
4D-TWIST – MRA
Rule out of residual vessels
Investigating MR angiography: contrast meets speed

**Summary**

⇒ Highly concentrated agents improve the performance of accelerated MRA

⇒ 1.0M Gadobutrol vs 0.5M Gd-DTPA:
  - significant better depiction of small vessels
  - significant higher vessel-to-tissue contrast

⇒ „Contrast meets speed“
  - time-resolved 4D MRA with low dose of 1.0M macrocyclic Gadobutrol

⇒ Compact, concentrated bolus

⇒ Results of MRA correspond with DSA
Acknowledgements