Renal safety evaluation after Dotarem®-enhanced-MRI compared with non-enhanced-MRI in patients at high risk of developing contrast medium induced nephropathy

Poster No.: C-0318
Congress: ECR 2012
Type: Scientific Paper
Authors: G. Deray; Paris/FR
Keywords: Contrast agents, MR
DOI: 10.1594/ecr2012/C-0318
With the common use of contrast media (CM) in diagnostic and interventional procedures, **contrast-induced nephropathy** (CIN) has become one of the leading cause of hospital-acquired acute renal injury [1,2].

Although CIN has been well studied for iodinated CM [3], it remains **under-investigated** for gadolinium-based contrast agents (GBCAs).

GBCAs are generally regarded as non-nephrotoxic, but their safety in **high-risk patient populations** still remains controversial [4,5].

As of today, there is a **lack** of **prospective** studies including **control group** (i.e. patients not receiving CM) evaluating the influence of GBCAs on CIN incidence [6].

Moreover, mechanisms involved in adverse drug reactions (ADRs) to contrast agents, their characteristics, frequency and risk factors are still a matter of debate [7].

Nevertheless, it has been observed that GBCAs may be responsible for Nephrogenic Systemic Fibrosis (NSF), especially in severe renal impaired patients [8].

The purpose of the study is to **prospectively** compare the renal safety of meglumine gadoterate (Dotarem®)-enhanced MRI to a **control group** (unenhanced-MRI) in **at-risk** patients (with at least moderate renal insufficiency).
Methods and Materials

Study Design
- Phase IV, open-label, non-randomized study;
- Multinational study: 15 centres (8 in France, 3 in Belgium, 2 in Spain, 2 in Italy);
- 142 patients were enrolled;
- Institutional review board and regulatory approval were granted for each center;
- All patients gave written informed consent.

Main inclusion criteria
- Male or female, aged #18 years,
- Presenting with a known stable stage III/IV renal insufficiency according to the K/DOQI definition (i.e. 15 < estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m²),
- Scheduled to undergo a contrast-enhanced-MRI or unenhanced-MRI examination.

Main non-inclusion criteria
- Patient planned to either undergo surgery or receive chemotherapy within 72 hours post-procedure, or
- Had an imaging procedure (MRI or CT imaging, with or without contrast medium) within 7 days of entering this protocol, or within 72 hours post-procedure, or
- Had a known allergy to contrast medium, or
- Patient with newly discovered unstable diabetes, or needed haemodialysis, or
- Received medication known to be nephrotoxic or to cause increases in serum creatinine level within 2 weeks before first blood sample and for the whole study duration.

**Contrast agent**

- Meglumine gadoterate (Dotarem®, Guerbet, France)
- Administered intravenously by using a power injector at a dose of 0.1 mmol/kg (0.2 mL/kg)

**Primary safety endpoint**

Percentage of patients presenting with a significant creatinine level increase assessed for both MRI procedure groups.

A significant creatinine level increase (nephrotoxicity) was defined as a rise in serum creatinine level at 72±24h of at least 25% or 0.5mg/dl (44.2µmol/l) from baseline*.

* baseline = blood test performed within 24h before MRI procedure

**Secondary safety endpoints**

- Variations (between baseline and 72 ±24 hours after imaging procedure) in serum creatinine level and estimated glomerular filtration rate (eGFR),
- eGFR decrease of more than 25% from baseline,
- Percentage of patients with nephrotoxic variation of serum creatinine returning to baseline level 14 days after the imaging procedure,
- Potential influence of hydration protocol and/or prophylactic treatment on the renal function.

**Adverse events (AEs)**
- All patients were monitored for AEs from the time the signed informed consent was obtained until 72±24h (or 14 days in case of nephrotoxicity) after MRI examination.

- All reported AEs were collected during this study, coded using the MedDRA coding dictionary (version 13.1).

- AEs were classified as serious or non-serious,

- Event severity (mild, moderate, or severe) and its relationship (possible, doubtful, not related) to the study contrast agent or to the unenhanced-MRI procedure were assessed.

- Outcomes of AEs were evaluated: patient recovered with or without sequelae, ongoing, worsened at the time of the report, death.

**Other safety parameters**

- Vital sign (blood pressure, pulse) measurements were monitored just before the MRI procedure, then 15 minutes and one hour after.

- Laboratory parameters (serum creatinine, sodium, potassium, bicarbonate, calcium, uric acid, hematocrit and hemoglobin).

- A 3-month follow-up was performed in order to detect any suspicion and/or occurrence of NSF.

**Statistical analyses**

- All statistical analyses were conducted using the SAS version 9.2 software (SAS Institute Inc, Cary, NC) at the p <0.05 level of significance.

- For the primary endpoint, statistical testing was based on the comparison of the lower bound of the 95% confidence interval (CI) of the difference between groups to the non-inferiority margin. The non-inferiority of gadoterate-MRI over unenhanced-MRI was established if this lower bound was superior to the non-inferiority margin (-15%) (Fig. 1).
Regression models with adjustment on centres were used.

- Student’s t test and Fisher’s exact test were also used.

**Figure 1:** Primary safety endpoint: serum creatinine variation
(≥25% or ≥0.5 mg/dl) from baseline

Hypothesis: non-inferiority clinical margin = -15%

-15%  0

Difference in Scr level
(unenhanced-MRI – gadoterate-MRI)

Lower bound 95CI% ≤ -15% → not significant
→ gadoterate-MRI not « non-inferior » to unenhanced-MRI

Lower bound 95CI% > -15% → significant
→ gadoterate-MRI « non-inferior » to unenhanced-MRI

**References:** nephrology, Pitie Salpetriere Hospital - Paris/FR
Results

Patients eligible for analysis are described in the following Table 1.

Table 1: populations description

<table>
<thead>
<tr>
<th>Eligible populations</th>
<th>No MRI procedure (N=10)</th>
<th>Gadoterate-MRI (N=75)</th>
<th>Unenhanced-MRI (N=57)</th>
<th>Total (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All included population (AIP)</td>
<td>10 (100%)</td>
<td>75 (100.0%)</td>
<td>57 (100.0%)</td>
<td>142 (100.0%)</td>
</tr>
<tr>
<td>Per-protocol population (PP)</td>
<td>0 (0.0%)</td>
<td>37 (49.3%)</td>
<td>30 (52.6%)</td>
<td>67 (47.2%)</td>
</tr>
<tr>
<td>Safety population (full analysis set - FAS)</td>
<td>0 (0.0%)</td>
<td>70 (93.3%)</td>
<td>44 (77.2%)</td>
<td>114 (80.3%)</td>
</tr>
</tbody>
</table>

Table 1

References: nephrology, Pitie Salpetriere Hospital - Paris/FR

As shown in the following Table 2, the two treatment groups were well balanced with regard to demographic and baseline data.
**Table 2: demography and baseline characteristics (safety population)**

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Gadoterate-MRI (N=70)</th>
<th>Unenhanced-MRI (N=44)</th>
<th>Total (N=114)</th>
<th>p-values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean ± SD, (min/max)</td>
<td>69.1±11.5 (34/92)</td>
<td>67.3±12.0 (26/86)</td>
<td>68.4±11.7 (26/92)</td>
<td>p=0.428</td>
</tr>
<tr>
<td>Gender N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>47 (67.1 %)</td>
<td>27 (61.4 %)</td>
<td>74 (64.9 %)</td>
<td>p=0.529</td>
</tr>
<tr>
<td>Female</td>
<td>23 (32.9 %)</td>
<td>17 (38.6 %)</td>
<td>40 (35.1 %)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²), Mean ± SD, (min/max)</td>
<td>27.5±4.9 (16.0/41.2)</td>
<td>27.3±3.9 (18.8/36.4)</td>
<td>27.4±4.6 (16.0/41.2)</td>
<td>p=0.790</td>
</tr>
<tr>
<td>Basal serum creatinine (mg/dl), Mean ± SD, (min/max)</td>
<td>1.99±0.74 (0.9/4.2)</td>
<td>1.97±0.67 (1.0/3.9)</td>
<td>1.94±0.71 (0.9/4.2)</td>
<td>p=0.367</td>
</tr>
<tr>
<td>Basal eGFR (ml/min/1.73m²), Mean ± SD, (min/max)</td>
<td>37.58±13.60 (15.0/82.0)</td>
<td>38.78±12.58 (17.0/65.3)</td>
<td>38.04±13.17 (15.0/82.0)</td>
<td>p=0.641</td>
</tr>
<tr>
<td>Allergy history N (%)</td>
<td>12 (16.0 %)</td>
<td>9 (15.8 %)</td>
<td>21 (14.8 %)</td>
<td>p=1.000</td>
</tr>
<tr>
<td>Premedication and/or prehydration N (%)</td>
<td>2 (2.9 %)</td>
<td>0 (0.0 %)</td>
<td>2 (1.8 %)</td>
<td>p=0.517</td>
</tr>
</tbody>
</table>

*Student t-test, Chi-2, Fisher exact test

Table 2

**References:** nephrology, Pitie Salpetriere Hospital - Paris/FR

All indications for MRI examinations are provided in the following Table 3. There were no between-group statistical differences.
Table 3

References: nephrology, Pitie Salpetriere Hospital - Paris/FR
Primary endpoint: serum creatinine variation from baseline ≥ 25% or ≥ 0.5 mg/dl

As shown in the following Table 4, the non-inferiority of gadoterate-MRI over unenhanced-MRI was demonstrated in both populations (safety and per protocol populations).
Table 4: primary endpoint: serum creatinine variation from baseline (≥25% or ≥0.5 mg/dl)

<table>
<thead>
<tr>
<th>Number of patients with SrC variation from baseline (≥25% or ≥0.5 mg/dl)</th>
<th>Gadoterate-MRI</th>
<th>Unenhanced-MRI</th>
<th>Test (Non-inferiority clinical margin = -15%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety population</td>
<td>(N=70)</td>
<td>(N=44)</td>
<td>Difference (unenhanced-MRI - gadoterate-MRI) = -1.4% 95%CI=[-7.9%; 6.7%] p=0.001 (-7.9%&gt; -15%: non-inferiority demonstrated)</td>
</tr>
<tr>
<td>No</td>
<td>69 (98.6%)</td>
<td>44 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (1.4%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>(N=37)</td>
<td>(N=30)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>36 (97.3%)</td>
<td>30 (100.0%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1 (2.7%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4

References: nephrology, Pitie Salpetriere Hospital - Paris/FR
One male patient (68 years, 33.4 kg/m2) in the gadoterate-MRI group had a serum creatinine variation from baseline of 30%, and returned to baseline level (2mg/dl) within 2 weeks.

Secondary endpoints

No clinically significant differences in serum creatinine and estimated GFR changes from baseline were observed between the two groups (Table 5).

A decrease in estimated GFR of at least 25% was noted in one patient in the gadoterate-MRI group (Table 5).
Table 5: secondary endpoints

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Gadoterate-MRI</th>
<th>Unenhanced-MRI</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety population</td>
<td>(N=70)</td>
<td>(N=44)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine variation from baseline (%) (mean ±SD, min/max)</td>
<td>-1.40 ±0.36 (25.0/30.0)</td>
<td>-3.48 ±9.92 (28.6/18.0)</td>
<td>Difference (gadoterate-MRI - unenhanced-MRI) = 2.08% 95%CI=[-1.80; 5.97] p=0.29</td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>(N=37)</td>
<td>(N=30)</td>
<td></td>
</tr>
<tr>
<td>eGFR variation from baseline (%) (mean ±SD, min/max)</td>
<td>0.05 ±10.84 (21.0/30.0)</td>
<td>-5.17 ±9.16 (28.6/14.5)</td>
<td>Difference (gadoterate-MRI - unenhanced-MRI) = 5.21% 95%CI=[0.24; 10.2] p=0.04</td>
</tr>
</tbody>
</table>

References: nephrology, Pitie Salpetriere Hospital - Paris/FR

Clinical safety

No adverse events occurred in the unenhanced-MRI group. Five adverse events recorded in 5/70 patients (7.1%) (abdominal pain, haematoma, constipation, toothache and increase of blood creatinine) occurred in the gadoterate-MRI group. One case of adverse event (hypotension) occurred before gadoterate injection. No statistical significant difference between groups was observed (p=0.08). All adverse events were non-serious, mild in intensity, resolved within 3 weeks, and not related (except increase of blood creatinine that was possibly related).

No serious adverse event occurred during the study.

No clinically relevant changes in vital signs, hematologic results, or clinical chemistry were detected in the observation period (Table 6).
Among the 70 patients who received Dotarem®, no cases of NSF have been observed during the 3-month follow-up.

### Table 6: vital signs and laboratory data

<table>
<thead>
<tr>
<th>Variation from baseline in vital signs and laboratory data</th>
<th>Gadoterate-MRI (N=70)</th>
<th>Unenhanced-MRI (N=44)</th>
<th>Student's t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diastolic blood pressure (mmHg) (mean ±SD, min/max)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>2.8 ±10.73 (~20/31)</td>
<td>1.1 ±10.48 (~1/35)</td>
<td>p=0.427</td>
</tr>
<tr>
<td>1 hour</td>
<td>0.6 ±11.58 (~30/42)</td>
<td>-2.3 ±7.76 (~19/19)</td>
<td>p=0.173</td>
</tr>
<tr>
<td><strong>Systolic blood pressure (mmHg) (mean ±SD, min/max)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>4.8 ±16.52 (~30/50)</td>
<td>-1.3 ±16.58 (~39/40)</td>
<td>p=0.067</td>
</tr>
<tr>
<td>1 hour</td>
<td>1.5 ±17.86 (~36/90)</td>
<td>-5.7 ±17.14 (~47/35)</td>
<td>p=0.044</td>
</tr>
<tr>
<td><strong>Heart rate (beats/min) (mean ±SD, min/max)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>0.6 ±12.15 (~56/34)</td>
<td>2.0 ±5.49 (~11/12)</td>
<td>p=0.501</td>
</tr>
<tr>
<td>1 hour</td>
<td>0.9 ±9.66 (~22/35)</td>
<td>2.0 ±7.30 (~15/16)</td>
<td>p=0.558</td>
</tr>
<tr>
<td><strong>Laboratory data - variation from baseline (%) (mean ±SD, min/max)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>-0.01 ±0.09 (~0.22)</td>
<td>0.01 ±0.11 (~0.23)</td>
<td>p=0.243</td>
</tr>
<tr>
<td>Calcium</td>
<td>7.27 ±13.48 (~5/13)</td>
<td>2.10 ±8.40 (~0/13)</td>
<td>p=0.017</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>-0.02 ±0.06 (~0.17)</td>
<td>-0.01 ±0.07 (~0.17)</td>
<td>p=0.364</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>1.01 ±13.7 (~16/10)</td>
<td>0.66 ±2.44 (~16/7)</td>
<td>p=0.207</td>
</tr>
<tr>
<td>Potassium</td>
<td>-0.01 ±0.08 (~0.20)</td>
<td>-0.02 ±0.09 (~0.26)</td>
<td>p=0.466</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.00 ±0.07 (~0.04)</td>
<td>0.00 ±0.01 (~0.05)</td>
<td>p=0.646</td>
</tr>
<tr>
<td>Uric acid</td>
<td>-0.36 ±0.46 (~0.95)</td>
<td>-0.35 ±0.35 (~0.95)</td>
<td>p=0.004</td>
</tr>
</tbody>
</table>

**Table 6**

**References:** nephrology, Pitie Salpetriere Hospital - Paris/FR
Conclusion

Dotarem® did not significantly affect renal function and, therefore, proved to be a safe contrast agent in patients with renal insufficiency.
References


Acknowledgement

Guerbet would like to thank all participating centers in the RESCUE study.