Evaluation of the safety and efficacy of gadobenate dimeglumine (Gd-BOPTA) in MRI of CNS metastatic disease

La Noce A, Cherryman GR, Colosimo C, Ruscallada J, Kirchin M, Salerio I, Pirovano G, Spinazzi A

INTRODUCTION: Contrast-enhanced MRI is commonly used for the diagnosis of brain diseases. The usual dose of contrast employed for brain imaging is 0.1 mmol/kg, although for the imaging of brain metastases and multiple sclerosis higher doses, up to 0.3 mmol/kg, of contrast are often recommended for optimal lesion detection (1-3).

Gadobenate dimeglumine (MultiHance, Gd-BOPTA) is a newly developed contrast agent recently marketed in Europe for liver imaging and currently under evaluation for imaging of the CNS (4). In common with other T1-relaxing MR contrast agents, Gd-BOPTA has been shown in pre-clinical studies to diffuse rapidly into the extracellular space and to cross the blood-brain barrier (BBB) when BBB breakdown occurs (5). Due to a capacity for weak and transient binding to serum proteins such as albumin, Gd-BOPTA possesses a high relaxivity which translates into a T1 relaxation enhancement of blood which approaches twice that of other extracellular fluid contrast agents at the same dose (6). Such results are also to be expected at sites of damaged BBB where a leakage of serum albumin into the extracellular space of lesions has also been shown to occur (7).

Preliminary single center phase II studies have shown that Gd-BOPTA at doses of 0.1 and 0.2 mmol/kg is both safe and efficacious for use in CNS imaging and that the post-dose imaging window is quite wide (4, 8).

The present study was conducted in a selected population of patients suffering from metastases to the CNS. The aim was to select the most appropriate dose regimen of Gd-BOPTA for the detection and evaluation of this kind of brain lesion.

PATIENTS AND METHODS: The study was performed in 150 patients with 1 to 8 proven brain metastases. Gd-BOPTA was administered intravenously at cumulative doses of 0.2 mmol/kg (dosing regimen 1: 0.05 + 0.05 + 0.1 mmol/kg) or 0.3 mmol/kg (dosing regimen 2: 0.1 + 0.1 + 0.1 mmol/kg). Doses were administered to 10 minute intervals. MR images were acquired before (T1- and T2-W SE) and immediately after (T1-W SE) each injection. The primary efficacy end point comprised a quantitative evaluation of the lesion to brain ratio (L/B/B). Secondary end points consisted of a quantitative evaluation of the percent enhancement with respect to pre-contrast of the same lesion chosen for the L/B ratio determination, a qualitative assessment of lesion count, confidence in lesion detection/exclusion, size of the smallest detected lesion, matched pairs confidence in lesion detection/exclusion and matched pairs lesion conspicuity. Pre- and post-contrast images were qualitatively evaluated by two off-site assessors not affiliated with any study center and blinded to the patient's clinical profile. An off-site assessor performed the quantitative image evaluation using standardized methodology. Safety in this study was assessed by means of physical examination, vital signs, ECG, clinical laboratory investigations and adverse events (incidence and severity).

RESULTS: Lesion contrast with respect to surrounding parenchyma increased significantly from pre-contrast with incremental dosing of Gd-BOPTA. No difference between the two dosing regimens was evident (see table).

<table>
<thead>
<tr>
<th></th>
<th>L-B/B - mean (sd)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-W pre-contrast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative dose</td>
<td>Regimen 1</td>
<td>Regimen 2</td>
</tr>
<tr>
<td>0.05 mmol/kg</td>
<td>0.31 (0.26)</td>
<td>0.36 (0.31)</td>
</tr>
<tr>
<td>0.1 mmol/kg</td>
<td>0.53 (0.33)</td>
<td>0.58 (0.40)</td>
</tr>
<tr>
<td>0.2 mmol/kg</td>
<td>0.70 (0.42)</td>
<td>0.73 (0.44)</td>
</tr>
</tbody>
</table>

Additional lesions, compared to T1- and T2-W pre-contrast images, were found in 22-29% of patients after the initial single dose in regimen 1 and in 31-33% of patients after the initial dose in regimen 2. A statistically significant increase in the number of patients with additional lesions after the second dose (0.1 + 0.1 mmol/kg) was observed in regimen 2 only. A non-significant further increase was reported after the 0.3 mmol/kg dose.

The administration of Gd-BOPTA led to improved lesion conspicuity in over 50% of patients as well as to improved confidence in lesion detection. Both these parameters improved with the second dose, and tended to be greater in regimen 2. The two dose regimens showed comparable safety profiles and no safety concerns were apparent up to a dose of 0.3 mmol/kg.

CONCLUSION: Gd-BOPTA is clearly useful for detecting metastatic lesions of the CNS. Though the single 0.05 mmol/kg dose provides an improvement with respect to unenhanced MRI, the initial dose of 0.1 mmol/kg provides better results in terms of lesion detectability and conspicuity. A second 0.1 mmol/kg dose can be administered to obtain a higher lesion to brain contrast as well as improved lesion conspicuity and delineation. The 0.3 mmol/kg cumulative dose does not appear to provide further important diagnostic information.

REFERENCES: