Impact of contrast agent osmolality and dose on the quantification of blood-brain barrier disruption in a DCE-MRI study

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Introduction: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is an imaging tool that is particularly suitable for characterizing blood-brain barrier (BBB) damage in humans as well as in animal models as it allows in vivo identification of BBB compromise with high spatial resolution; the contrast agents used are typically gadolinium chelates. There are several gadolinium chelates marketed at this moment, all of which have been employed in animal studies; the administration route, dose, and dilution factor used in these studies vary widely; reasons for a particular selection of conditions are usually not given. The dose of contrast agent (CA) for clinical investigations recommended by manufacturers is 0.1 mmol/kg body weight. In animals, however, this dose is usually increased several fold in order to compensate for their small size [1, 2]. Such a dose is considered sufficient for animal models of severe barrier disruption; in experiments where the disruption of BBB is uncertain, much higher doses are used [3, 4]. The purpose of this study was to identify optimal conditions for detecting low/uncertain BBB disruption and to provide an improved protocol therefor. The studied doses for our mouse experiments were chosen as follows: 1 mmol/kg was chosen to mimic the clinical protocol; 4 mmol/kg Dotarem and 8 mmol/kg Prohance are the maximum doses that can be injected i.p. in mice, when diluted to plasma osmolality, 10 mmol/kg Dotarem is the maximum dose that can be injected undiluted without triggering immediate toxicity. In order to provide a more temporally consistent and sustained enhancement than an intravenous bolus, the CA was administered as an i.p. bolus. In the present study two different gadolinium-based contrast agents have been employed – gadolinium-tetraazacyclododecanetetraacetic acid (Dotarem®), and gadoteridol (ProHance®) – in order to demonstrate the impact of the osmolality and dose of the contrast agent on the estimation of the BBB damage.

Methods: Mouse model: An animal model of mild BBB disruption was chosen, using repeated induced cortical spreading depression (CSD) in the brain of healthy wild type mice, which has been reported to induce BBB damage in the mouse brain [6]. In this study, seven consecutive CSDs were induced in the right hemisphere before allowing the animals to recover. The dynamics of BBB permeability were followed by MRI 24 h post-surgery. MRI scans: The mice were divided into four groups and administered a different osmolality and dose of contrast agent (CA) (see table 1). In vivo RARE T1-weighted DCE-MRI measurements were performed with a Bruker 9.4 T system, consisting of a pre-scan followed by 6 consecutive scans immediately after the intraperitoneally (i.p.) injected CA. Parameters were: TE/TR = 11.67/870 ms, resolution = 0.078 mm/pixel, 22 slices of 0.5 mm thickness, acquisition time 11 min. Processing: A voxel-by-voxel analysis was performed by Patlak plots [7] consisting of plotting the ordinate C(t)/C(t) versus abscissa ln(C(t)/C(t)); the slope of the plot is the CA blood-to-brain transfer rate (Ki). The total volume of the affected area was defined as having a threshold Ki > 0.001 ml/g min−1 and an R2 of the Patlak plot > 0.7, and was composed of all pixels satisfying these conditions after smoothing the image.

Table 1: Dosage and osmolarity of CA used in different groups of mice.

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose CA (mmol/kg)</th>
<th>Osmolarity (mOsm/L)</th>
<th>Injected volume (μl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D10</td>
<td>1D Dotarem 1150</td>
<td>1150</td>
<td>25 μl</td>
</tr>
<tr>
<td>D4</td>
<td>4D Dotarem 245</td>
<td>245</td>
<td>25 μl</td>
</tr>
<tr>
<td>D2</td>
<td>2D Dotarem 245</td>
<td>245</td>
<td>25 μl</td>
</tr>
<tr>
<td>D8</td>
<td>8D Prohance 245</td>
<td>245</td>
<td>25 μl</td>
</tr>
</tbody>
</table>

Results and discussion: At the dose corresponding to clinical practice (D1), no BBB disruption was detectable, therefore this dose was excluded from further analysis. The D4 and D8 groups showed comparable blood-to-brain transfer rate (Ki) values and affected brain volumes (Fig. 1). Interestingly, 10 mmol/kg Dotarem (D10) yielded Ki values that were twice as high as for group D4 (Fig. 1A), as well as a BBB-compromised brain volume that was about 3 times larger (Fig. 1B). This difference could be explained at first glance as an increased sensitivity achieved by a higher dose, but close inspection of the raw MRI data revealed that 6.3±0.6% shrinkage of the total brain volume occurred after CA administration which can be attributed to the high osmolality of the injected CA [8]. The BBB damage in the D10 group is thus exacerbated by the high osmolality of the injected CA.

Conclusions: A high CA dose is required to ensure the visualization and quantification of areas characterized by mild BBB disruption, but a high osmolality of the contrast agent can aggravate BBB damage. Our optimized protocol represents a combination of maximum dosage and iso-osmolality of CA.


Figure 1: (A) Average Ki and (B) lesion volume expressed as a percentage of the total brain volume, for each group, with standard deviation values.

*p<0.01 ***p<0.0001

Figure 2: Decrease in brain volume after injecting 10mmol/kg (p<0.02). In the upper right corner – an example of the observed brain shrinkage in a mouse from D10 group (~3.0 mm Bregma), shown by overlapping the brain area in the last acquired image post-injection (red) over the brain area of the same slice in the pre-injection scan (blue).