Comparison of Signal Intensity and Selection Techniques for Estimation of Pharmacokinetic Parameters in DCE-T1 Studies of Glioblastoma: Using Model Selection

Hassan Bagher-Ebadian, Siamak P Necjad-Davarani, Rajan Jain, Douglas Noll, Quan Jiang, Ali Syed Abarb, Tom Mikkelson, and James R Ewing
1 Neurology, Henry Ford Hospital, Detroit, Michigan, United States, 2 Physics, Oakland University, Rochester, Michigan, United States, 3 Biomedical Engineering, University of Michigan, Ann Arbor, Michigan, United States, 4 Radiology, Henry Ford Hospital, Detroit, Michigan, United States, 5 Neurosurgery, Henry Ford Hospital, Detroit, Michigan, United States

Introduction: In Dynamic Contrast-Enhanced magnetic resonance imaging (DCE-MRI), the time trace of Contrast Agent (CA) concentration can be analyzed with an appropriate pharmacokinetic model to characterize tissue pathology [1]. By fitting the DCE-MRI data to pharmacokinetic model, physiological parameters can be estimated to relate to permeability or hemodynamic properties such as microvascular permeability, plasma volume, extravascular volume, or tissue perfusion [2,3,4]. DCE pharmacokinetic models rely on the construction of an observation equation which demands conversion of the measured signal intensity time course data (S(t)) into an indicator concentration time course. The standard approach utilizes the longitudinal relaxation rate change (ΔR₁) to construct the concentration-time curve of the CA [1,4,5]. This process depends on the accurate estimation of pre injection longitudinal relaxation times (T₁) and signal intensity (S₀) prior to administration of CA. Recent studies have proposed that the normalized signal intensity SI [(S(t)/S₀) / S₀] be used instead of ΔR₁ in DCE-MRI permeability analyses [1,2,5]. However, we know of no assessment of the agreement in the estimated parameters using different measures of CA concentration (SI, ΔR₁). The goal of this study is to evaluate the use of SI, as opposed to ΔR₁, in the estimation of permeability parameters in DCE-T1 3D-Spoiled-Gradient-Echo (SPGRE) studies in the brains of ten treatment-naive patients with glioblastoma (GBM).

Theory: In this study a model selection technique [6, 7] is used to compare the two measures of CA concentration-time curves in estimating permeability parameters. As shown in figure 1, four different nested models with as many as three parameters (plasma volume: v_p, forward vascular transfer constant: Ktrans, and the reverse vascular transfer constant: kep) are used to compare the techniques. Model 0, 1, 2 and 3 describe regions presenting with no evidence of vascular filling with CA, no leakage of CA, with reduced rates of CA leakage (generally enclosed Model 3 regions), and presenting high rates of CA leakage respectively.

MR Imaging and Data Processing: All studies were performed in a 3T GE Excite HD MR system using a standard eight-channel phased-array RF coil and receiver. DCE-T1studies were conducted in 10 treatment-naive patients with GBM. Before CA administration, T₁ mapping was performed using a 3D SPGRE sequence with Variable Flip Angle (VFA). Sequence parameters were as follows: TE/TR = 0.84/5.8 ms, flip angles, θ, of 2, 5, 10, 15, 20, and 25º, matrix of 256 X128, FOV of 240 mm, 16 slices, 5 mm slices, no gap. The maps of T₁ were used to establish baseline precontrast values for the dynamic SPGRE procedure that followed. The 3D SPGRE DCE-T1 sequence was then begun (70 image sets ~5.9s per image set, θ=20º and other parameters as above). About 20s after starting, a dose of Magnevist (0.1 mmol/kg) was injected (IV) at a rate of 4 mL/s. ΔR₁ was calculated analytically for each voxel using the assumed value of the tip-angle, θ, the estimated pre-contrast value of T₁, and the ratio of the post-contrast to baseline pre-contrast MRI signal. An analytical expression was used to estimate the time trace of ΔR₁, and that in turn was used as a measure of the CA concentration-time curve. A nonlinear least squares optimization using the Levenberg-Marquardt (LM) Algorithm [8] was used to fit model 3 to the experimental data, while the linear least-squares method was used for the linear models (models 0–2). Using a manually chosen Arterial Input Function (normalized to white matter), the SI and ΔR₁ data in all voxels were fitted with the linear models 0, 1, 2 and non-linear model 3. Sum Squared Error (SSE) maps for the fitted parameters in all three models were calculated and used for statistical model comparison. Three F-test maps were constructed using the SEE maps that served for model comparison. Model 0 vs. 1, Model 1 vs. 2 and Model 2 vs. 3 were tested with the F-test criteria and a final regional map, and three maps of permeability parameters were constructed accordingly. Figure 2 illustrates an exemplary regional map for a typical patient.

Results and Conclusion: In the patient population, compared to the ΔR₁ technique, the SI technique underestimated the plasma volumes (v_p) for different regions (32% in normal but enhancing core, 26% in white matter, 17% in gray matter, and 32% in Model 2 and 24% Model 3 regions). In contrast with the ΔR₁ technique, the SI technique also underestimated Ktrans around 22% and 28% in regions associated with Model 2 and 3 respectively. The SI technique also overestimated kep around 23% in the model 3 region compared to ΔR₁. The mean calculated interstitial space v_i = Ktrans / kep (only in Model 3) was underestimated about 38% in the SI technique compared to the ΔR₁ technique. In Model 3 regions, excellent curve fits were obtained in both of the techniques to explain the variation of the ΔR₁ and SI data (mean R² = 0.99 and 0.97 for ΔR₁ and SI techniques respectively). Results imply that the SI technique is biased with respect to the ΔR₁ technique in estimation of the pharmacokinetic parameters. This study confirms that using the SI profile instead of ΔR₁ in analysis of DCE-MR data can result in significant bias in estimation of permeability parameters.

Table-1: Summary of Estimates of Vascular Parameters in 10 Patients

<table>
<thead>
<tr>
<th>Model</th>
<th>Permeability Parameters</th>
<th>Mean ± S.D (ΔR₁-Technique)</th>
<th>Mean ± S.D (SI-Technique)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (core)</td>
<td>v_p = S.D</td>
<td>0.0221 ± 0.0195</td>
<td>0.0194 ± 0.0163</td>
</tr>
<tr>
<td>Model 2</td>
<td>v_p = S.D, Ktrans = S.D (min⁻¹)</td>
<td>0.028 ± 0.025, 0.0019 ± 0.0019</td>
<td>0.019 ± 0.021, 0.0014 ± 0.0027</td>
</tr>
<tr>
<td>Model 3</td>
<td>v_p = S.D, Ktrans = S.D (min⁻¹)</td>
<td>0.0037 ± 0.019, 0.019 ± 0.010</td>
<td>0.028 ± 0.024, 0.013 ± 0.016</td>
</tr>
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References: