Assessment of pharmacokinetic parameters by different models in dynamic contrast-enhanced MRI of prostate

G. Jia¹, J. T. Heverhagen¹, J. Liang¹, K. T. Baudendistel¹, A. L. Levine², T. J. Rosol², M. V. Knopp¹

¹Department of Radiology, The Ohio State University, Columbus, OH, United States, ²Department of Veterinary Biosciences, The Ohio State University, Columbus, OH, United States

Introduction

Benign prostatic hyperplasia (BPH) is a highly prevalent disease in older men resulting in prostate enlargement with bladder outflow obstruction. Dynamic contrast-enhanced MRI (DCE-MRI) is highly efficient to monitor changes induced with medical treatments like finasteride and minimally invasive therapies like laser ablation of the prostate (1). DCE-MRI can detect prostate cancer early, accurately, and non-invasively by providing vascular density information, and can discriminate prostate cancer from normal tissue as well as from abnormal prostate tissue like BPH. DCE-MRI was also used to monitor the changes induced by chemotherapies like the VEGF-signaling inhibitor and the alkylating drug (2). The heterogeneity in prostate cancer and in the response to treatment was also investigated by DCE-MRI (3).

Quantitative analysis of DCE-MRI data needs pharmacokinetic models with well mixture compartments. Different pharmacokinetic models were used for analyzing DCE-MRI data and the generated pharmacokinetic parameters were used to characterize the microcirculation in the prostate (4). In order to select the most appropriate pharmacokinetic model to characterize the time-signal intensity curves in prostate, this study systematically compared four available pharmacokinetic models on fitting different regions in beagle prostate by investigating the goodness-of-fit and reproducibility of the models.

Material and methods

The study was designed within an interdisciplinary team and approved by the local animal care committee. The subjects consisted of eleven male beagles (mean age ± SD: 4.4 ± 1.0 years, range 3 to 6 years, mean weight ± SD: 11.2 ± 2.6 kg, range 7 to 17 kg) with an initial palpated prostate diameter larger than 2 cm. The subjects were imaged twice with 3 weeks interval as MR1 and MR2. MRI examinations were performed on a 1.5 T clinical MRI system (Twinspeed, GE, Milwaukee, WI) using the standard head coil with the subjects imaged in the prone position. DCE-MRI was performed using a 3D spoiled gradient echo (3D-SPGR) imaging sequence (TR/TE/TI = 7.5 ms/2.6 ms/25°, field of view = 140 x 140 mm², matrix size = 256 x 256, in-plane resolution = 0.55 x 0.55 mm², NEX = 0.5; 2.0-mm slice thickness, contiguous slices; 26 slices, Acquisition time per volume: 24 s, 32 time points). The extracellular contrast agent Gadoteridol (Prohance®, Bracco Diagnostic Inc, Princeton, NJ, 0.2 mmol/kg bodyweight) was intravenously injected at a rate of 0.2 ml/s after 3 time points by a power injector (Spectris®, MedRad, Indiana, PA) followed by a 15 ml flush of saline solution injected at the same rate. These most commonly used pharmacokinetic models are based on the exchange of contrast agent between two compartments: one compartment is blood plasma space; the other compartment is extravascular extracellular space (EES). The volume transfer rate from the blood plasma to the EES is defined as transfer constant (Ktrans), and the volume transfer rate from the EES to the blood plasma is defined as rate constant (kep). The general equation describing the changes of the tracer concentration in tissue is obtained as

\[ \frac{dC_t}{dt} = K_{\text{trans}} C_p - k_{ep} C_t, \]  

where \( C_t \) is the tracer concentration in tissue and \( C_p \) tracer concentration in blood plasma.

Four models were used to fit the DCE-MRI data. The 1st model used three parameters (A, kep, and kel) to directly fit the data by assuming a mono-exponential plasma concentration. The equation used to fit the time signal intensity curves is

\[ \frac{S(t)}{S_0} = 1 + \frac{A}{2(k_{al} - k_{ep})} \left( e^{-k_{al} (t-t_{lag})} - e^{-k_{ep} (t-t_{lag})} \right), \]

\[ 0 \leq t < t_{lag}, \]

where \( S(t) \) is the time-signal intensity data, \( S_0 \) is the baseline signal intensity defined as an average of the signal intensities prior to contrast agent injection, \( t_{lag} \) is the arrival time of the contrast agent to the ROI, and \( t \) is the injection duration of the contrast agent. The 2nd model we proposed here used four parameters (A, kep, kel, and kdl) to directly fit the data by assuming a limited bi-exponential plasma concentration. The equation used to fit the time signal intensity curves is

\[ \frac{S(t)}{S_0} = 1 - \frac{1}{2} \left( \frac{A}{k_{dl} - k_{ep}} \left( e^{-k_{dl} (t-t_{lag})} - e^{-k_{ep} (t-t_{lag})} \right) + \frac{\alpha}{k_{al} - k_{ep}} \left( e^{-k_{al} (t-t_{lag})} - e^{-k_{ep} (t-t_{lag})} \right) \right), \]

\[ 0 \leq t < t_{lag}, \]

The 3rd model used five parameters (A, kep, kdl, kep, and \( \alpha \)) to directly fit the data by assuming a free bi-exponential plasma concentration. The equation used to fit the time signal intensity curves is

\[ \frac{S(t)}{S_0} = 1 + \frac{A}{2(k_{al} - k_{ep})} \left( e^{-k_{al} (t-t_{lag})} - e^{-k_{ep} (t-t_{lag})} \right), \]

\[ 0 \leq t < t_{lag}, \]

The 4th model used the arterial input function (AIF) from external iliac artery to fit the data and generated three parameters (Ktrans, kep, and fpo) by the equation

\[ C_i(t) = K_{\text{trans}} \left( F_p e^{-t/f_p} + f_p C_a(t) \right), \]

where \( f_p \) is the fractional plasma volume of the tissue with the range from 0 to 1.

Three types of region of interest (ROI) were drawn on dynamic images: parenchymal and periurethral regions in the largest cross section of the prostate and suburethral regions in caudal prostate. The model-based parameters for the ROIs were determined by least-squares fitting of the measured data. The goodness-of-fit was defined by R² with 1 as exact fit. The reproducibility of the pharmacokinetic parameters was examined in the two measurements (MR1 and MR2) using ANOVA-based coefficient of variation (CV).

Results

The 2nd and 3rd model gave the best goodness-of-fit: 0.985 for the 1st model, 0.992 for the 2nd model, 0.993 for the 3rd model, 0.935 for the 4th model, as illustrated by Fig. 1. The 2nd and the 4th models gave the smallest CV of A or Ktrans (0.55, 0.43, 0.46, 0.34 for the 1st, 2nd, 3rd, and 4th model respectively), and smallest CV of kep (0.46, 0.37, 0.41, 0.25 for the 1st, 2nd, 3rd, and 4th model respectively).

Discussion and Conclusion

The models (the 1st, 2nd and 3rd model) without using any real input function have higher goodness-of-fit than the 4th model using real AIF from external iliac artery, which has the best reproducibility.

References