Determining MRI Signal Intensity Threshold of Gadoteridol using the Nephrectomized Mouse

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INTRODUCTION

One goal of research for new MRI contrast agents is the targeting of specific tissues and pathologies [1]. Specifying the concentration of a contrast agent in a target tissue necessary to produce a discernable change in MRI signal intensity (SI) (i.e., threshold concentration) is a primary requirement, as is knowing the concentration thresholds that will produce a discernable change in SI for the contrast agents designated as reference standards. Approved contrast agents presently available to be used as references 1) distribute extravascularly, 2) do not target specific tissues, 3) are not metabolized or degraded *in vivo*, and 4) are excreted almost exclusively via the renal route. Nephrectomization, therefore, prevents the excretion of a contrast agent and allows correlating changes in SI with the concentration of the agent in a designated tissue. The goal of this study was to determine the tissue concentration of gadoteridol (an extravascularly-distributed agent) required to achieve a visible threshold (20 %) change in the MRI SI of leg muscle when administered i.v. to nephrectomized mice.

METHODS

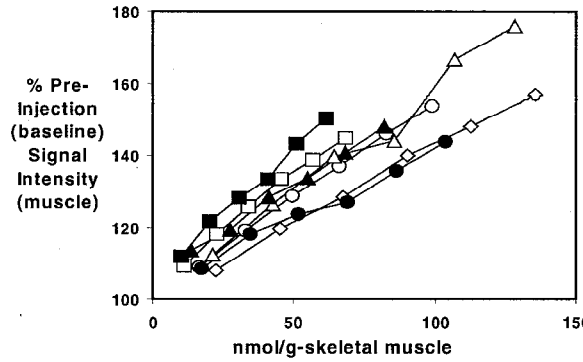
Animal Model: Seven male CD-1 mice (Charles River Laboratories), 20 – 35 g, were used. The mice were anesthetized using ketamine/xylazine [2]. A cannula, filled with and attached to a syringe containing 48 μL of ^{153}Gd-gadoteridol (ProHance™), was placed in a tail vein. (Specifications were: 1 μmol gadoteridol/0.005 μCi ^{153}Gd/10 μL [3].) The mouse was nephrectomized by ligating the renal artery and renal vein of each kidney.

MR Imaging / SI Threshold Determination Protocol: A Varian/Sisco 2.0 T, 31-cm MRI spectrometer with Bruker Accustar™ S180 gradients operating at 85 MHz for protons and a 4-cm bore diameter x 12.5-cm long quadrature imaging coil (Morris Instruments) were used to acquire a pre-injection single-slice coronal (control) MR image (T_1-weighted, spin-echo pulse sequence: TR=0.2 s, TE=0.015 s) of the hind legs. After acquiring the control image, 0.8 μmol (8 μL) of ^{153}Gd-gadoteridol was injected i.v., and 6 min later, a post-injection MR image was acquired. (Six min allowed gadoteridol to reach steady-state in skeletal muscle, d[Gd]/dt = 0, in the nephrectomized mouse.) Another 0.8 μmol of ^{153}Gd-gadoteridol was then injected and another MR image acquired 6 min later. This procedure was repeated 6 times so that a total of 4.8 μmol of ^{153}Gd-gadoteridol had been administered. SI of a region of interest area in the skeletal muscle of the leg images was obtained using image analysis software (ImageBrowser, Varian NMR Instruments). SI data were normalized by calculating a % of pre-injection control SI ($IIN_{post}/IIN_{control}$ * 100) for each post-injection image.

Tissue Concentration Determination: After acquiring the last image, the mouse was sacrificed and the skeletal muscle excised, assayed for ^{153}Gd, and the % of the injected ^{153}Gd-gadoteridol (IG) residual in the muscle calculated [4]. The % IG data were used to calculate the amount of gadoteridol in the muscle after each of the 6 injections.

RESULTS

The normalized SI data vs. the calculated nmol [Gd]/g-muscle obtained following each injection of gadoteridol in each mouse are shown in the figure. Each data set was evaluated via linear regression analysis. SI increases were found to be highly correlated with concentration ($r>0.98$/mouse). The regression analysis equations were used to calculate the concentration that would be necessary to obtain a 20 % increase in SI. (20 % represents the threshold at which a SI change was visibly discerned in MR muscle images.) The threshold concentration that will produce a visible change in SI was calculated to be 33 ± 10 nmol gadoteridol/g-muscle.



DISCUSSION

Nephrectomization eliminated excretion of gadoteridol, and ^{153}Gd-gadoteridol rapidly reached steady state in muscle (<6 min). The method for assessing gadoteridol concentration in muscle assumed that gadoteridol distribution in muscle is directly dependent on the total cumulative amount of gadoteridol injected [5]. Our data show that this assumption is correct.

The goal of this study was to determine the tissue concentration at which an extravascularly-distributed, renally-excreted MRI contrast agent, having a relaxivity of ~4 $mM^{-1}s^{-1}$, produces a 20 % change in the SI of skeletal muscle [1]. It was determined that in our 2.0 T imaging spectrometer and using a T_1-weighted spin-echo pulse sequence, 33±10 nmol of gadoteridol/g-skeletal muscle is necessary to produce a visibly detectable increase in SI.

Gadoteridol is not selective for a specific tissue or pathology, and relaxivities 10 times greater than that of gadoteridol can be obtained with monomeric Gd-chelates via binding to immobilizing objects. Theoretical calculations estimate that it might be possible to increase relaxivities 25 – 50 times when immobilized (*i.e.*, biological receptor targets) [1]. Therefore, a Gd-chelate bound to a target entity could produce a visible change in SI at a considerably lower tissue concentration than the threshold concentration we report here for gadoteridol.

REFERENCES

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