Characterization of Signal Ehnacement following the Intraperitoneal Injection of Gadolinium Based Contrast Agents

S. Portnoy[1], J. Bishop[1], J. Dazai[1], S. Spring[1], and R. Henkelman[1,2]

[1]Mouse Imaging Centre, Toronto Centre for Phenogenomics, Toronto, Ontario, Canada, [2]Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada

Introduction: The intravenous (IV) administration of Gadolinium is routinely used in both human and animal imaging for the diagnosis of lesions that compromise the blood-brain barrier (BBB). Although it is relatively trivial in humans and larger animals, gaining IV access in the mouse turns out to be challenging (1). Mouse IV injections are most commonly administered via one of the two tail veins. Not only is considerable skill required in locating these veins, they cannot be probed multiple times due to sclerosis (1,2). This limits the usefulness of IV Gadolinium administration in longitudinal investigations, and in high-throughput imaging of large numbers of mice, where individual tail vein injections can significantly increase the preparation overhead time.

Intraperitoneal (IP) injection has been proposed as a simpler alternative for Gadolinium administration (1). Since IP administered Gadolinium must gain venous access by absorption through the intraperitoneal cavity, it stands to reason that the dosage requirements in mice and the time-course of signal enhancement would differ from what is currently known for IV injected Gadolinium. The objective of this investigation is therefore to determine the enhancement time-course and dosage requirements for intraperitoneally administered Gadolinium.

Methods: Wild type C57/BL6 mice (16-20 grams) were used in all scans. MRI was performed on a 7 Tesla scanner (Varian Inc., Palo Alto, CA). The imaging consisted of a T1-weighted 3D fast spin echo (FSE) sequence with: TR/TE_{eff}=325/7.3 ms, ETL=6, ESP=7.3ms, and a total scan time of approximately 8 minutes. Images had a 4.0x2.4x2.4 cm^3 FOV (covering the brain), and a voxel size of 156x156x500 μm^3, with the finest resolution in the sagittal plane. Six mice were scanned in parallel (3). During imaging, the mice were anesthetized with 1% isofluorane in pure O_2. Body temperature was maintained at 37°C with flowing warm air. The sequence was applied once before and sequentially over 1.5 hours after IP injection of Gadoteridol (Prohance). Doses ranged from 0.1-4 mmol/kg. The injection volume was maintained constant at 500 μL, while the concentration was varied depending on the dose.

Results: To determine the enhancement following IP Gadolinium injections, the signal was measured in a region-of-interest (ROI) in the pituitary (Figure 1). The pituitary was chosen since it is a structure located outside the blood-brain barrier (2). The BBB is known to limit the uptake and accumulation of contrast agent in the brain. The time-course for enhancement in the pituitary should therefore be similar to what would be observed in instances of BBB disruption due to disease.

Signal intensity in the pituitary over time, normalized to the pre-contrast image, is plotted in Figure 2, for mice that received doses ranging from 1-4 mmol/kg. The solid lines represent a data fit to a bi-exponential function. Error bars refer to the standard error of the mean for the pixels within the ROI. Regardless of dose, more than 90% of the maximum enhancement was obtained at approximately 20 minutes post-injection. Note that the doses shown are more than ten times higher than the 0.1 mmol/kg dose that is typical for intravenous Gadolinium injection (4). In fact, below a dose of approximately 1 mmol/kg, limited (<20%) enhancement was observed. At higher doses, the enhancement was nearly two-fold. Increasing the dose beyond approximately 2.5 mmol/kg did not result in substantial increases in enhancement, as the degree of enhancement began to plateau. This may be attributable to T2 shortening effects, which occur in the presence of high Gadolinium concentrations.

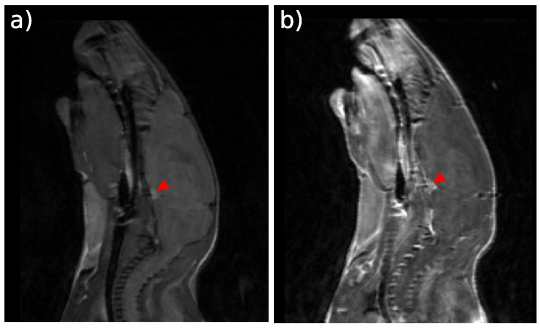

Figure 1: Mid-saggital mouse brain images (with equal window/level) before (a) and 20 minutes after (b) IP Gadolinium injection (dose=2.0 mmol/kg). The pituitary is indicated by a red arrow.

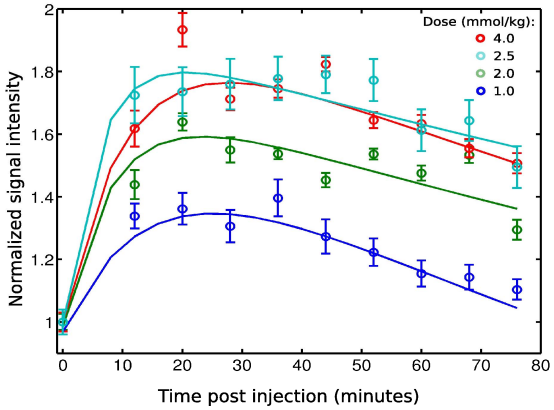

Figure 2: Plot of signal intensity, normalized to the pre-contrast image, in a pituitary ROI over time. Solid lines represent a data fit to a biexponential. Error bars refer to the standard error of the mean for the pixels within the ROI.

Discussion & Conclusion: Due to the indirect nature of the IP injection, enhancement is delayed and higher doses are required. The delay in enhancement may, in fact, be helpful, since injections can be performed prior to loading the mice into the scanner and the need for catheterization and costly injection systems that deliver the contrast within the bore is eliminated. This is particularly important for multiple mouse parallel imaging. Although increased doses of contrast are necessary, 2.5 mmol/kg is still well below the median lethal dose (LD50) in mice for most Gadolinium-based contrast agents (Prohance-LD50=12 mmol/kg, Magnevist-LD50=6-7 mmol/kg, Omniscan-LD50=30 mmol/kg) (4). Although the mice in this study were injected with Prohance, the results obtained should be similarly true for other Gadolinium compounds with similar chelating agents, since their pharmacokinetics are believed to be essentially the same (4).

In conclusion, results suggest that IP injection may be an effective method for Gadolinium administration. The approximately two-fold enhancement obtained with doses greater than 2.5 mmol/kg is comparable to the enhancement seen with IV contrast agent administration (5). The relative simplicity of IP contrast injection makes it a convenient alternative to tail vein injection, particularly in longitudinal studies and high-throughput imaging.

References:

1) Moreno, H., Fan, H., Brown, T. *et al*. Longitudinal mapping of mouse cerebral blood volume with MRI. NMR in Biomedicine 2006; 19: 535.
2) Kuo, Y.T., Herlihy, A., So, P., *et al*. In vivo measurements of T1 relaxation times in mouse brain associated with different modes of systemic administration of manganese chloride. Journal of Magnetic Resonance Imaging 2005; 21: 334.
3) Bock, N.A., Nieman, B.J., Bishop J, Henkelman R.M. In vivo multiple-mouse MRI at 7 Tesla. Magnetic Resonance in Medicine 2005; 54(5): 1311.
4) Oksendal, A., Hals, P.A. Biodistribution and Toxicity of MR Imaging Contrast Media. Radiology 1993; 3: 157.
5) Silver, N.C., Tofts, P.S., Symms, M.R. et al. Quantitative contrast-enhanced MRI to evaluate blood-brain barrier integrity in multiple sclerosis. Multiple Sclerosis 2001; 7: 75.