Time Course and Distribution of Feraheme in the Normal Human Brain at 7T

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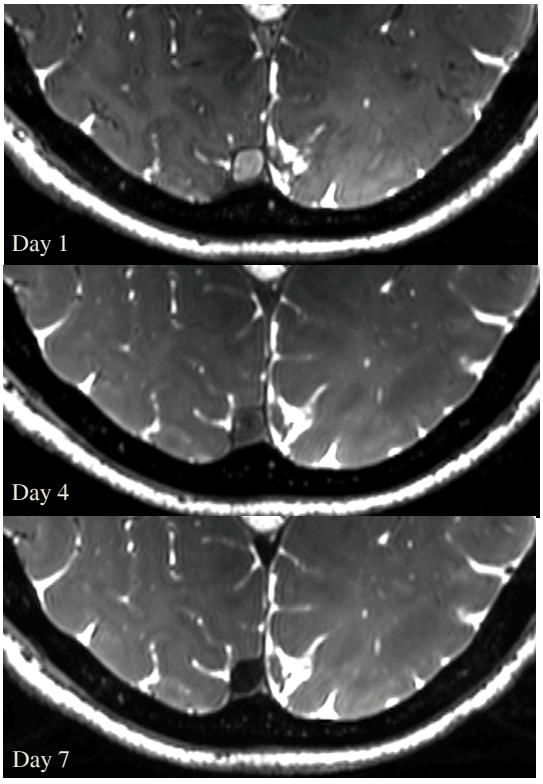
Target Audience: Clinicians/scientists studying iron in the human brain, neurodegenerative disorders, and multiple sclerosis

Introduction: Ferumoxytol (Feraheme, AMAG Pharmaceuticals, Inc., Cambridge, MA) is an intravenous ultra-small iron-oxide particle (USPIO) thought to be useful for visualization of neuroinflammation. Since iron generates robust contrast at ultra-high field, there is potential to characterize with greater sensitivity and specificity microscopic foci of inflammation thought to occur in disorders such as multiple sclerosis. However, in order to detect micropathology in disease, the normal distribution of Feraheme and its time-course over several days (post-contrast Feraheme scans are usually at 1-2 days) needs to be established at high field strength.

Methods: One healthy 63-yo male subject was injected with 510mg of Feraheme in accordance with IRB and HIPAA. The subject underwent MRI scanning at days 1, 4 and 7 post-injection. MRI was performed with a GE Discovery MR 950 7.0T scanner (GE Healthcare, Waukesha, WI) utilizing a Nova 32 channel receive 2-channel transmit head coil (Nova Medical, Wilmington, MA). Sequences included a whole-brain T1-weighted IR-FSPGR (3D coronal, FOV 180, 180x180, 1mm slice thickness, TS 3700, TI 1200, TR 7.22, TE 3.2, FA 6, BW 19, ARC 2x1, 3m53s) and a whole-brain balanced steady-state free precession sequence (bSSFP/FIESTA, 4 phase cycles, 3D coronal, FOV 180, 300x300, 0.6mm slice thickness, TR 8.1, TE 4.05, FA 25, BW 35, ARC 2X2, 2m53s each phase cycle). The phase cycles were averaged together using methods previously reported[1], and all images coregistered with one another to a space intermediate between the scans on Day 1 and Day 4 using FSL's FLIRT using sinc interpolation. Cortical and adjacent subcortical white matter regions of interest were manually drawn on the coregistered bSSFP images in either the coronal or axial plane using ITK-SNAP in the following regions bilaterally: insula, medial frontal lobe, posterolateral superior temporal lobe, hippocampal field CA 1, cingulum, occipital lobe, and intraparietal sulcus. Gray-white contrast was calculated as WM-GM signal difference divided by WM signal using cortical grey matter and subjacent white matter regions, and expessed as a percentage. Day 7 was used as a proxy for baseline imaging assuming complete washout of intravenous Feraheme by this timepoint.



Results: On Day 1, gray-white contrast values in the occipital lobe, parietal lobe, hippocampus, and to a lesser extent posterior temporal lobe were reduced compared to baseline (Day 7). This is explained by cortical hypointensity, likely from cortical vessels (Figure 1). On Day 4, contrast returned close to normal in the occipital and parietal lobes. The insula, frontal lobe, and cingulum did not demonstrate this cortical hypointensity or this change in gray-white contrast. Signal in arteries and large veins on the T1-weighted and bSSFP sequences showed high signal on Day 1 with gradual washout of Feraheme.

Table 1: Gray-white contrast across brain regions

	Day 1	Day 4	Day 7	Day 1/Day 7 (ratio)	Day 4/Day 7 (ratio)
Insula	27.8	25.5	28.9	0.96	0.88
Medial Frontal Cortex	19.6	13.7	19.3	1.02	0.71
Post Temp	42.2	44.9	45.5	0.93	0.99
Cingular Cortex	39.9	34.5	39.8	1.00	0.87
Occipital Cortex	-8.9	1.1	4.2	-2.12	0.27
Parietal Cortex	-8.1	7.1	9.7	-0.83	0.73
Hippocampal CA1	45.0	44.7	63.4	0.71	0.71

Conclusions: There is heterogeneous cortical Feraheme persistent at one day post contrast administration at 7T, likely within cortical vessels, that does not completely washout even at 4 days. In the occipital and parietal lobes, conspicuity of potential inflammatory cortical lesions may be reduced because of this vascular uptake. Variations in the pattern of presumably cortical vascular Feraheme (with the largest effects in the occipital and parietal lobes) may relate to variations in arterial and/or venous density.

References: 1. M.Zeineh *et al.*, *Investigative Radiology* 2014.
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