Evaluation of a Cerebral-Blood-Volume (CBV) pharmaco-MRI (phMRI) Assay Utilizing Low (0.1mg/70kg) and High (0.2mg/70kg) Dose Buprenorphine Infusion and a Novel USPIO Contrast Agent (Ferumoxytol) in Healthy Human Subjects.

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Introduction: Recently, it has been shown in human fMRI studies using simple sensory stimulation (which included motor and visual stimulation paradigms) that the Ultra-small Superparamagnetic Iron Oxide (USPIO) nanoparticle ferumoxytol (Trade name Rienso/Feraheme, AMAG Pharmaceuticals (7)) greatly enhances stimulus induced signal changes relative to BOLD (1,2). Here, we report a clinical study that explored the potential use of ferumoxytol as a blood pool contrast agent for interrogation of hemodynamic changes in the brain as a pharmacodynamic (PD) biomarker of drug effects. This test case employed buprenorphine (a partial mu-opioid agonist and k-opioid antagonist) as a pharmacological challenge. The study was motivated by and built on a previously reported investigation of buprenorphine effect using BOLD phMRI (3).

Methods: This was a two-part study. Each part was designed as a placebo controlled, randomized, balanced two period crossover with healthy male subjects. Each subject completed both Parts 1 and 2. Part 1 was a BOLD phMRI assessment of responses to infusion of buprenorphine or placebo. Part 2 was a CBV phMRI assessment to the same challenge using 510 mg doses of ferumoxytol.

24 healthy males were randomized into two separate dose panels (12 subjects each panel). The buprenorphine doses administered were 0.1 mg/70 kg (low dose) and 0.2 mg/70kg (high dose) for Panels 1 and Panel 2, respectively.

Images were acquired during double-blinded administration of either buprenorphine or placebo in a 20 minute infusion protocol similar to (3). Specifically, 6 minutes pre-infusion baseline was followed by an ~8 minutes continuous infusion of buprenorphine followed by a ~ 6 minute post-infusion period.

Prior to and following infusion and phMRI image acquisition, fMRI during a simple visual stimulation paradigm with 6 cycles (each 25s on/25s off) was performed as a control.

Whole brain images were acquired using an EPI sequence (TR/TE=2500/30ms). A GLM analysis as in (3) was implemented using FSL software. The model consisted of a 6 minute baseline, ~8 minutes linear rise and 6 minute plateau above baseline. Following the GLM analysis, average absolute percent-signal-change (|PSC|), (the signal increases for BOLD and decreases for CBV) was calculated from thalamus as primary phMRI response endpoint as stipulated by the study protocol. Statistical analysis was carried out for each dose panel separately using a mixed effects linear model with fixed factors for fixed factors for treatment and period and a random factor for subject. In addition, whole brain group activation maps were also obtained using the FSL mixed effect linear model to explore possible response of other brain structures for BOLD and CBV-phMRI.

Results: Single doses of both buprenorphine and ferumoxytol were well tolerated. No serious adverse effects were reported in this study.

Group activation maps of CBV and BOLD phMRI are shown in Figure 1. Administration of both low and high doses of buprenorphine decreased CBV-phMRI percent signal change (PSC) in the thalamus (the primary region of interest) compared to placebo (p=0.038 and p=0.014, respectively). In contrast, administration of neither low nor high doses of buprenorphine significantly increased BOLD-phMRI PSC in the thalamus compared to placebo. In addition to thalamus, both CBV and BOLD phMRI reported hemodynamic effects in the anterior cingulate cortex (ACC), putamen and primary and supplementary motor cortices by high dose. CBV phMRI also reported hemodynamic effects in putamen after low buprenorphine doses.

Visual stimulation elicited robust activation responses in both BOLD and CBV modalities. GLM analysis of pre- vs post- infusion comparison of mean PSC in primary visual cortex as well as the group activation maps did not reveal any significant difference between placebo and buprenorphine, except for high dose of buprenorphine for BOLD phMRI (p=0.002).

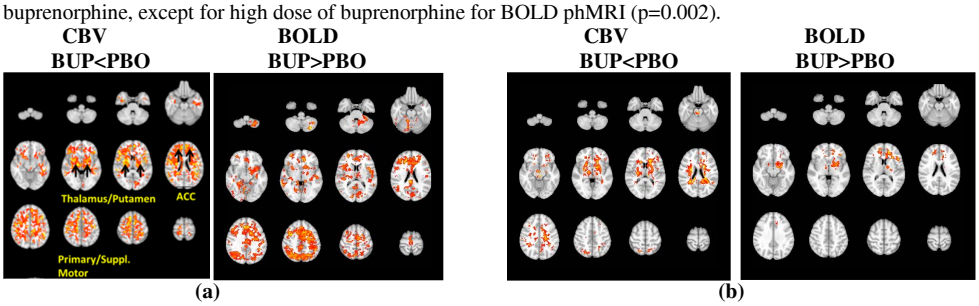

Figure 1.

Group activation maps derived for CBV and BOLD phMRI for buprenorphine doses of 0.2 mg/70kg (a) and 0.1mg/70kg (b). Hemodynamic effects were observed afteror high (0.2 mg/70kg) dose buprenorphine in thalamus, putamen, anterior cingulate cortex (ACC) as well as primary and supplementary motor cortices using both CBV and BOLD phMRI. For low (0.1mg/70kg) dose of buprenorphineCBV-phMRI reported hemodynamic effects in thalamus and putamen (paired t-test, $p<0.05$, $Zt=1.6$, multiplicity corrected).

Discussion and Conclusions: This study represents the first known clinical study with USPIO-based CBV phMRI. BOLD phMRI results were similar to outcomes of an earlier buprenorphine BOLD phMRI study in healthy subjects (3). Overall, we found that ferumoxytol-based CBV phMRI was more sensitive than BOLD in detecting pharmacodynamic effects of high and low dose buprenorphine infusion. In particular, at low dose of buprenorphine, CBV phMRI detected more robust responses in thalamus and putamen than BOLD.

As successful applications of CBV phMRI and fMRI are being reported in preclinical trials (4,5,6), additional clinical studies with brain-penetrant molecules need to be carried out in order to qualify CBV phMRI and fMRI as a clinical PD biomarker.

References: 1) Qiu et al, NeuroImage, 2012, 2) Baumgartner et al, ISMRM 2012, 3) Upadhyay et al, Neuropsychopharmacology, 2011 4) Sander et al, PNAS 2013 5) Sforazzini et al, 2014, 6) Zhao et al, NeuroImage, 2014.

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