Evaluation of an fMRI USPIO-Based Assay in Healthy Human Volunteers

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Purpose: To present the testretest and contrast dose effect results of cerebral blood volume (CBV) functional MRI (fMRI) in healthy human volunteers using ferumoxytol (Feraheme), an ultrasmall-superparamagnetic iron oxide (USPIO) nanoparticle.

Materials and Methods: This was an open-label, two-period, fixed-sequence study in healthy young volunteers. In eight subjects, using a 3 Tesla field strength system, blood oxygen level dependent (BOLD) and CBV fMRI were acquired in response to a visual black-and-white checkboard stimulation paradigm using an escalating ferumoxytol dose design (250, 350, and 510 mg iron). Multiple outcome measures were analyzed including absolute percent signal change (PSC, primary endpoint), its contrast-to-noise ratio (CNR) and corresponding z-score, percent CBV change (ΔCBV) and respective CNR, concentration of Fe, and baseline CBV.

Results: The PSC in the visual cortex increased with ferumoxytol dose and was up to 3 times higher than BOLD fMRI. Test-retest reliability was comparable for BOLD and CBV fMRI. Intraclass correlation coefficients (ICCs) for PSC were 0.3 (one-sided 95% lower confidence limit = 0.00), 0.81 (0.47), 0.48 (0.00), and 0.3 (0.00) for BOLD and the 250-, 350-, and 510-mg doses of ferumoxytol, respectively. For ΔCBV, ICCs were 0.77 (0.37), 0.48 (0.00), and 0.49 (0.00) for 250 mg, 350 mg, and 510 mg, respectively.

Conclusion: This work demonstrates that CBV fMRI techniques and endpoints are dose dependent, robust and have good test-retest repeatability. It also confirms previous findings that USPIO enhances sensitivity of fMRI stimulus-response endpoints.

Level of Evidence: 1

A common clinical development strategy for novel therapeutics is to study biomarkers of efficacy early in drug development to make development decisions on a candidate drug or mechanism before a larger phase II efficacy study. Chemical or physiological change in response to the candidate drug provides evidence of a pharmacodynamic (PD) response that can contribute to understanding the drug mechanism of action, is suggestive of target engagement, and may be indicative of efficacy. When developing drugs for central nervous system disorders, assessments of brain physiology and biochemistry is often not possible in clinical settings, and functional MRI (fMRI) may be a valuable tool for determination of PD responses. fMRI noninvasively assesses regional changes in hemodynamics, reflecting neuronal metabolic activity. In drug development, modulation of the fMRI signal infers...