Comparison of BOLD Response Modulation During Pain Stimulation and Resting-State Conditions Under Intravenous (0.2 mg/70kg) or Sublingual (2 mg) Buprenorphine Treatment

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Introduction: Buprenorphine (BUP) is a mixed opioid partial agonist and antagonist known to have both analgesic and antihyperalgesic effects in patients and healthy subjects [1]. Previously, blood oxygenation level-dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) has been implemented to define the acute central nervous system (CNS) effects of intravenous (IV) administration of 0.2 mg/70kg BUP on pain processing in healthy subjects [2]. Mainly, a potentiation (BUP > Placebo) of the BOLD response was observed within the striatum (bilateral putamen and caudate), while the BOLD response was attenuated (Placebo > BUP) within the thalamus and somatosensory cortices. The present study extends earlier observations by comparing the possible CNS mechanism of action of 0.1 and 0.2 mg/70kg Buprenorphine (IV) as well as sublingual BUP (2 mg) administration during pain processing in healthy human subjects. Furthermore, a characterization of the modulatory effects of IV and sublingual BUP administration on CNS networks in the absence of pain or somatosensory stimulation has also been given.

Methods: 36 right-handed, healthy male subjects (18-50 yrs old) participated in this study where 12 subjects were included in each of the three study cohorts; (i) 2 mg BUP (Sublingual), (ii) 0.1 mg/70kg BUP (IV) and (iii) 0.2 mg/70kg BUP (IV). Each subject underwent both BUP and placebo (physiological saline solution (IV) or sublingual vitamin-K (Sublingual)) scanning sessions separated by ~14 days. In each cohort, 6 subjects received placebo first and 6 received BUP first. **BUP (Sublingual):** 2-15-minute phMRI scans (no pain or somatosensory stimulation) were performed 30 minutes and 60 minutes after BUP administration. **BUP (IV):** BUP was infused intravenously during a 25 minute phMRI scan were no pain or somatosensory stimulation was administered to the subject. This phMRI scan was used to characterize modulation of CNS networks solely due to BUP treatment. For the two IV cohorts, the heat fMRI scan was performed ~30 minutes after BUP administration. The heat fMRI scan for the sublingual BUP group was performed ~75 minutes after BUP administration. Heat stimuli (7 repetitions in block design) used in the heat fMRI scan corresponded to a subject-specific threshold temperature yielding a 7/10 pain rating. The average threshold temperature for 0.1 mg/70kg, 0.2 mg/70kg and 2mg dose cohorts are 46.9 ± 0.7°C, 46.4 ± 0.7°C and 46.9 ± 0.7°C, respectively. Self-reported pain ratings for heat stimulation were recorded simultaneously during fMRI data acquisition. Plasma samples were collected throughout the scanning sessions. fMRI data were collected on a 3T Siemens Trio Scanner using a gradient echo-EPI (GE-EPI) pulse sequence (TR = 2500 msecs (IV phMRI)/ 3000 msecs (Sublingual phMRI), TE = 30 msecs, Resolution = 3.5 x 3.5 x 3.5 mm^3. All image preprocessing (coregistration, spatial smoothing, etc) and GLM analysis was performed using FSL. Group-level results shown below were achieved using a mixed-effects paired comparison. A GLM-based seed region functional connectivity analysis was performed by using subject-specific putamen timecourses. Statistical maps were thresholded and corrected for multiple comparisons using Gaussian mixture modeling (GMM) approach [3].

Results and Discussion: **Figure 1** shows the average BUP concentration curve in plasma for all three cohorts. While the 0.2 mg/70kg (IV) dose of BUP yielded the highest concentration of BUP, the 2mg sublingual dose yielded a comparatively sustained and high BUP concentration in plasma. The mixed-effects, paired comparison analysis showed that both 2.0 mg Sublingual and 0.2 mg/70kg (IV) BUP elicited a significant (z>2.3, corrected) potentiation (blue regions) of the BOLD response to noxious heat stimuli in putamen and caudate, while producing a significant (z>2.3, corrected) attenuation in somatosensory cortex. It is noted that some differences did exist regarding potentiation and attenuation patterns between the two doses (**Figure 2**). For example, only a significant and bilateral attenuation of the BOLD response in the thalamus was detected in the 0.2 mg/70kg (IV) BUP dose, while attenuation in the insula was only observed in the 2mg Sublingual dose. No significant potentiation or attenuation in the BOLD response to noxious heat was observed for the 0.1 mg/70kg (IV) BUP dose. Similar to BOLD fMRI findings, a significant decrease in pain ratings was only observed for 2mg BUP Sublingual and 0.2 mg/70kg (IV) doses (**Figure 2**). Due to the robust and consistent potentiation observed in the putamen and known effects of BUP on this structure, the putamen was used for seed region functional connectivity analysis. In **Figure 3**, a robust decrease in functional connectivity was observed for both the 0.2 mg/70kg and 2.0 mg Sublingual doses, but not for the 0.1 mg/70kg BUP dose (Data not shown). In both BUP cohorts, decreases in functional connectivity between the putamen and regions such as the insula, cingulate, and somatosensory cortex. However, the decreased functional connectivity was more robust in the 2.0 mg BUP (Sublingual) group. This difference is likely related to the sustained BUP concentration resulting from sublingual administration. The current findings may be helpful in defining future phMRI investigations where the mechanism of action for existing and novel pharmacological compounds is sought, and also, in defining similarities and differences in CNS activity during IV and sublingual administration of a drug.

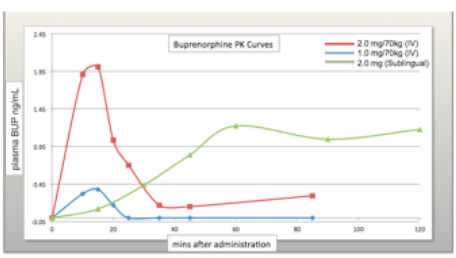


Figure 1.

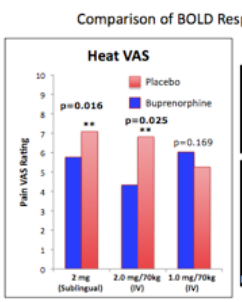
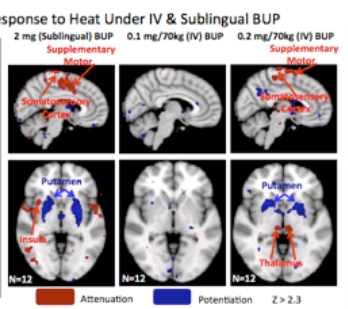


Figure 2.



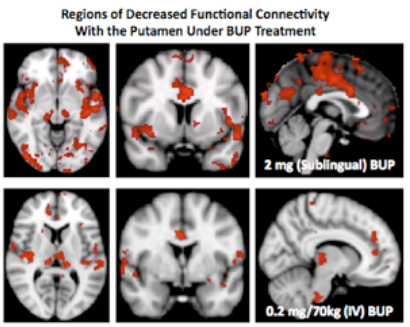


Figure 3.