1H MRS Study of Acute Lorazepam in Healthy Human Brain

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Introduction: Pedatric and adult subjects who are anxious or have difficulty remaining immobile during MR procedures are frequently sedated with benzodiazepines, such as lorazepam, to help complete scans. The effects of these compounds on ^{1}H MRS endpoints is largely unknown. A previous abstract of ours[1], using simple integration of metabolite peak areas, suggested possible reductions in Cr and Cho levels in response to acute oral lorazapam in frontal gray matter and occipito-parietal white matter of normal young adult males. Using STEAM at TE = 20 ms, Brambilla et al.[2], in contrast, found no effects of lorazepam on absolute levels or ratios of ^{1}H MRS metabolites in a left dorsolateral prefrontal voxel containing 60 % white matter. We have since reinvestigated this topic using a greater number of subjects and more rigorous spectral processing and quantitation.

Methods: 12 healthy adult males (21.8 ± 2.3 yr), screened by a board-certified psychiatrist (PD) to exclude medical and psychiatric illness, participated. Subjects agreed to discontinue over-the-counter medication 1 week and to refraim from drinking coffee 1 day prior to scanning. Whole-brain axial MRI (SE: TR/TE = 500/8 ms, NEX = 1, FOV = 28 cm, 256 x 192 matrix, 3-mm slices interleaved) and single-voxel ^{1}H MRS (PRESS: TR/TE = 3000/30 ms; NEX = 64 water-suppressed, 4 non-water-suppressed; 2 x 2 x 2 cc voxels) of frontal midline gray matter (anterior cingulate) and left occipito-parietal white matter were acquired at 1.5 T (GE) with a quadrature head coil. Voxels were placed to maximize gray-, respectively, white-matter content. Initial scans were performed 30 min after 2 mg oral lorazepam ("lorazepam"). One week later, each subject was scanned under identical conditions without lorzepam ("no drug 1"). To ensure constancy of voxel placement across scans, head tilt was minimized with an orthopedic cervical collar and vitamin E capsules (visible on MRI) were inserted bilaterally in the external auditory meatuses and philtra[3]. One week thereafter, 8 of the subjects were again identically scanned without lorzepam ("no drug 2"). Automated post-processing of MR spectra was performed blind to drug condition with LCModel[4], yielding absolute levels for NAA, NAA+NAAG (tNAA), glutamate+glutamine (Glx), Cr, Cho, and mI referenced to water and expressed in Institutional Units (IU). Only metabolite values deemed reliable by LCModel were retained. Ratios to Cr were also analyzed. Repeated-measures ANOVA was performed for each metabolite measure comparing no drug 2 to no drug 1 and comparing the mean of no drug 2 and no drug 1 to lorazepam. We hypothesized no effects of rescanning or of lorazepam on any measure. Criterion for significance was $p < 0.05$ without Bonferroni correction.

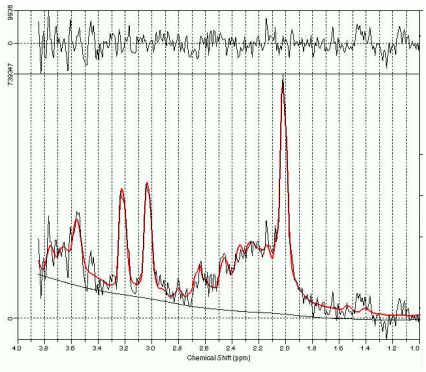
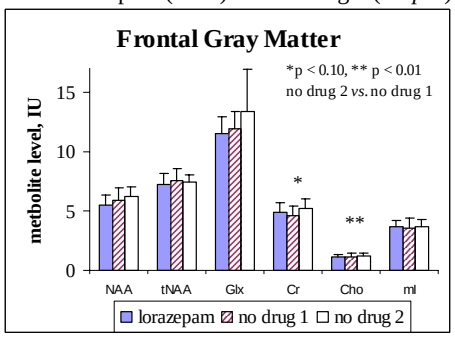


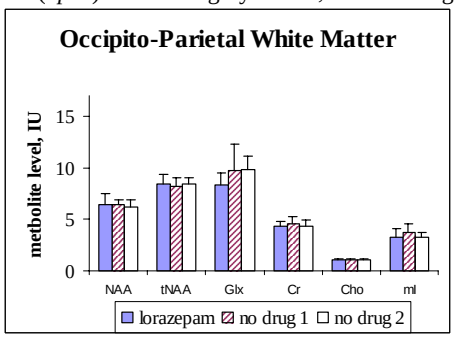
Fig. 1. Sample raw (*thin*) and fitted (*thick*) LCModel output ^{1}H MR spectra from occipito-parietal white matter of a healthy adult male on 2 mg lorazepam.

Results: Spectra were of acceptable to high quality (Fig. 1) and not markedly different between conditions. Across metabolites, variability of of absolute levels from no drug 1 to no drug 2 ranged 1.3-13.0 % in frontal gray matter and 1.0-10.8 % in occipito-parietal white matter. Ratios ranged up to 16.7 % (gray matter), respectively, 14.3 % (white matter). Variabilities of lorazepam values relative to the mean of no drug 1 and no drug 2 were comparable (Fig. 2). Repeated-measures ANOVA found a slight but significant increase in Cho from no drug 1 to no drug 2 (9.1 %; $F(1,7) = 15.3$, $p = 0.006$) and a trend-level increase in Cr (13.0 %; $F(1,7) = 4.6$, $p = 0.07$). No other effects of rescanning and no effects of lorazepam on metabolite levels were signficant. No effects on metabolite ratios were significant.

Discussion: This present, more rigorous investigation does not reproduce the effects of lorazepam on brain Cho and Cr seen in our previous abstract[1]. On the contrary, we found no significant differences between metabolite measures in subjects on and off lorazepam. This implies that rigorous spectral processing and quantitation are critical in ^{1}H MRS studies of effects of benzodiazepines on brain metabolites. Like Brambilla et al.[2], we conclude that acute effects of lorazepam on metabolites do not likely exceed normal scan-rescan variability nor compromise ^{1}H MRS studies. We extend this result to two additional brain regions. *However*, in 6 of 8 subjects we did find a small, but significant, increment in frontal gray matter Cho from week 1 to week 2 post-lorazepam. Systematic instrumental error is an unlikely explanation of this effect, because, across subjects, dates of lorazepam, no drug 1, and no drug 2 acquisitions were highly overlapping. If not spurious, this result may reflect subject habituation to the scanning procedure or sub-acute sequelæ of a single dose of lorazepam. This may be tested in future work by repeat scanning both before and after lorazepam administration. Limitations include low number of subjects and lack of MRS voxel tissue-content determination, although voxels of high gray-, respectively, white-matter density were selected consistently.

Fig. 2. Group-Mean ± SD absolute metabolite levels in frontal gray matter (*left*) and occipito-parietal white matter (*right*) in healthy adult males under lorazepam (*solid*) and no drug 1 (*stripes*) and 2 (*open*). In frontal gray matter, there are slight elevations of Cr and Cho from no drug 1 to 2.





References: 1. Davanzo et al. **ISMRM** (1997). 2. Brambilla et al. **Neuro-psychopharmacol 26**(4),546-551 (2002). 3. Giedd et al. **Psychiatry Res: Neuroimaging 61**,113-119 (1995). 4. Provencher. **NMR Biomed 14**,260-264 (2001).