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^{1}H MRS Brain Measures and Acute Lorazepam Administration in Healthy Human Subjects

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The effects of acute lorazepam administration on ^{1}H magnetic resonance spectroscopy (MRS) in vivo brain spectra were examined in the left dorsolateral prefrontal cortex (L-DLPFC) of healthy human subjects. We wanted to examine whether lorazepam administration would result in significant changes in the levels of ^{1}H-MRS metabolites in this brain region. Ten healthy controls underwent a short echo-time ^{1}H-MRS session immediately before, and a second one 1 h after lorazepam administration (2mg/orally). The measured ^{1}H-metabolites included N-acetyl-aspartate, phosphocreatine+creatine, trimethylamines, myo-inositol, glutamate, and glutamine, which were expressed as absolute values and ratios. No significant differences were found after lorazepam administration for any of the measured metabolite levels or ratios (paired t-tests, $p > .05$). This study demonstrated that lorazepam can potentially be utilized to acutely sedate psychiatric subjects during in vivo ^{1}H-MRS sessions, as it does not appear to produce significant changes in the ^{1}H-MRS spectra in this specific brain region.
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KEY WORDS: *Magnetic resonance spectroscopy; Nuclear magnetic resonance; Dorsolateral prefrontal cortex; Lorazepam; Psychopharmacology; Psychiatry*

^{1}H magnetic resonance spectroscopy (MRS) is a non-invasive method that allows in vivo examination of the human brain biochemistry (Kato et al. 1998; Soares et al. 1996; Stanley et al. 2000; Strakowski et al. 2000). It represents a novel approach to directly assess in vivo brain levels of specific chemicals of interest, such as N-acetyl aspartate (NAA), phosphocreatine+creatine (PCr+Cr), trimethylamines (TMA, or commonly referred to as choline-containing molecules, which mainly includes phosphorylcholine and glycerophospocholine), myo-inositol (INO), glutamate (Glu), and glutamine (Gln), which are involved in key physiological brain processes, and possibly implicated in the pathophysiology of psychiatric disorders (Auer et al. 2000; Deicken et al. 1995; Kato et al. 1996; Keshavan et al. 2000; Stanley et al. 1996; Winsberg et al. 2000).

One important question that often arises in brain MRS studies of psychiatric subjects is whether sedation with benzodiazepines (e.g. lorazepam or diazepam), which is often necessary to successfully complete these studies, could affect the MRS brain measures being performed. It is possible that the MRS spectra could be changed as a result of the administration of a sedative drug. Very few studies to this date examined whether acute sedation with benzodiazepines could cause significant changes in the in vivo brain MRS spectra. Deicken et al.

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(1992) found no significant changes in membrane phospholipids or high-energy phosphate metabolites in white matter and subcortical gray matter regions of 10 healthy human subjects one hour after the oral administration of diazepam up to 20 mg, as detected by in vivo ^{31}P MRS.

We examined whether the in vivo levels of the main peaks in the ^{1}H MRS human brain spectrum would be significantly altered by acute administration of lorazepam, at clinically utilized doses (2 mg orally), in healthy human individuals. Our study focused on the left dorsolateral prefrontal cortex (L-DLPFC), as this brain region is currently being investigated in related studies focusing on the pathophysiology of mood disorders and schizophrenia. Benzodiazepinic agents are commonly and safely used to sedate patients in clinical settings. These medications primarily act as agonists at the $GABA_A$/benzodiazepine receptors (Haefely 1984; Zakusov et al. 1977). Based on the prior study by Deicken et al. (1992), we hypothesized that acute administration of lorazepam would not result in significant changes in the brain levels of the main metabolites that are reliably quantitated with ^{1}H MRS in this brain region.

METHODS

Subjects

Ten healthy controls (mean age ± SD = 30 ± 7 years, range: 21–42 years; 6 males, 4 females) were enrolled, and underwent two MRS sessions (baseline, and post-lorazepam administration). The baseline MRI/MRS session was immediately followed by the administration of lorazepam (2 mg orally), and the second one started 1 h after lorazepam administration. Healthy controls had no DSM-IV axis I disorders, as determined by the SCID-IV non-patient version (SCID-NP). They did not have any current medical problems, nor history of psychiatric disorders among first-degree relatives. This research study was approved by the University of Pittsburgh Biomedical IRB. All subjects provided signed informed consent after having understood all relevant issues involved in participation in this protocol.

^{1}H MRI/MRS Procedures

In vivo ^{1}H MRS was conducted on a GE Signa Imaging System (General Electric Medical Systems, Milwaukee, WI), at a field strength of 1.5T. Subjects were provided with earplugs to reduce noise disturbances, and subject's head was positioned comfortably in the GE quadrature head RF coil with foam cushioning for motion stability. A set of sagittal and coronal scout images was first obtained to verify patient position, image quality, voxel positioning, and locate a midline sagittal image. A 3D spoiled gradient recalled (SPGR) acquisition was performed in the coronal plane (TR = 25 ms, TE = 5 ms, flip angle = 40°, FOV = 24 cm, slice thickness = 1.5 mm, NEX = 1, matrix size = 256 × 192) to obtain 124 images covering the entire brain. A double spin echo sequence was also used to obtain T_2 and proton density images in the axial plane to screen for neuroradiological abnormalities. The single voxel short TE MRS data was collected with a STEAM sequence (TE = 20 ms, TM= 13.6 ms, TR= 1.5 s, bandwidth= 2 kHz, 2,048 complex data points, 300 acquisitions, voxel dimension 2.0 × 2.0 × 2.0 cm^3). This 8 cm^3 voxel was placed in the L-DLPFC, which was identified on the set of sagittal and coronal MR images (Figure 1). A second STEAM spectrum was collected, without water suppression (16 acquisitions).

Based on a semi-automated histogram method (Keshavan et al. 1994, 1995), the percent volume of gray matter, white matter, and cerebrospinal fluid (CSF) within the MRS voxels were estimated from the 3D SPGR data using the NIH Image software package, version 1.62 (National Institutes of Health, Bethesda, MD). The intra-class correlation coefficients (ICCs) for the histogram measurements obtained by two independent raters (P.B. and M.N.), in a group of 10 subjects, were: 0.94 for gray matter, 0.94 for white matter, and 0.91 for CSF.

The short TE STEAM MRS data were quantified using the LC Model software, version 5.2-1 (Provencher 1993). As part of the quantification procedure, eddy current artifacts were corrected using the unsuppressed

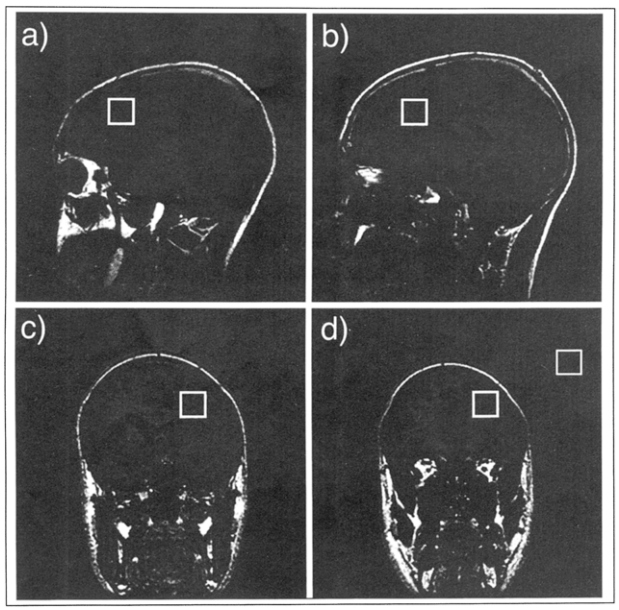

Figure 1. The white box represents the location of the volume of interest (2 × 2 × 2 cc) in the left dorso-lateral prefrontal cortex. Sagittal (a and b) and coronal (c and d) magnetic resonance images are presented.

water MRS data. There was no apodization applied to the MRS data. The list of ^{1}H metabolites utilized in our analyses, based on prior knowledge, included NAA, PCr+Cr, INO, scyllo-Inositol, TMA, Glu, Gln, alanine, aspartate, lactate, taurine, and N-acetyl-aspartate glutamate (NAAG). Only the ^{1}H metabolites with reasonable precision for quantification (Stanley et al. 1995) were reported in the results (i.e., NAA, PCr+Cr, INO, TMA, Glu, Gln), and were expressed as absolute values, as well as ratios. The absolute metabolite levels (institutional units), which included the RF pulse amplitude and receiver gain corrections, and the volume correction for CSF (mean measurement value/1-CSF), excluded any T_1 and T_2 relaxation corrections, and were estimated relative to the phantom signal with a known metabolite concentration.

Statistical Analysis

All analyses were performed using the SPSS for Windows software, version 8.0 (SPSS Inc., Chicago). The statistical significance levels were set at $p < .05$. Paired *t*-tests were performed to determine whether the measured ^{1}H metabolite levels (i.e., NAA, PCr+Cr, TMA, INO, Glu, Gln) and ratios (i.e., NAA/PCr+Cr, TMA/PCr+Cr, and INO/PCr+Cr) differed from baseline after lorazepam administration. The values for percentage change after lorazepam administration for each individual metabolite were also calculated.

RESULTS

A representative illustration of a spectrum obtained with the utilized method for modeling the in vivo short TE MRS data is shown in Figure 2, which illustrates the spectra for a single subject before and after lorazepam administration. The coefficients of variation (defined as the standard deviation of the measurements divided by the mean) of the combined pre- and post-lorazepam measurements for the six main metabolites and three ratios utilized in this study ranged from 12.9% to 31.7%, with values up to 75.6% for Gln (Table 1, Figure 3). The mean percentage change after lorazapam administration for the above metabolite levels and ratios (i.e. post-lorazepam measurement minus pre-lorazepam measurement divided by the pre-lorazepam measurement) ranged from –0.83% to 32.34%, and are all lower than the coefficients of variation for these specific measures (Table 1). There were no significant differences in any of the measured metabolites or ratios when pre- and post-lorazepam measurements were compared (paired *t*-tests, $p > .05$) (Table 1). Additionally, there were no significant differences in gray matter, white matter, and CSF volumes between the pre- and post-lorazepam measurements (Table 2).

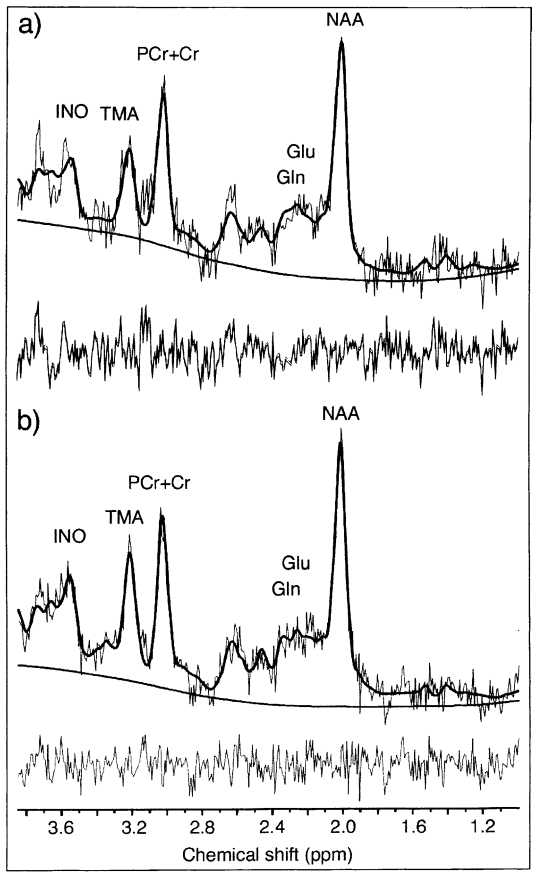

Figure 2. Representative ^{1}H MRS spectra. The baseline (a) and post-lorazepam (b) MRS spectra for a healthy human subject are illustrated.

DISCUSSION

Our present study suggests that the administration of a single oral dose of lorazepam (2 mg) does not alter significantly the values of the main metabolites measured with in vivo ^{1}H MRS in the L-DLPFC of human subjects. These findings demonstrate that lorazepam can possibly be utilized, if needed, to acutely sedate psychiatric patients for completion of MRS sessions, as it does not produce significant changes in the main metabolites that are part of the ^{1}H MRS spectrum in the in vivo human brain. These results have important implications, as they suggest that, for patients suffering from neuropsychiatric disorders, who are often agitated when acutely ill, and therefore not able to remain still in the scanner for participation in MRS studies, acute sedation with lorazepam may be a feasible approach. Bipolar patients in the manic phase, or acutely psychotic schizophrenic patients would be good examples of patient groups that could be very difficult to study in in vivo MRS studies if sedation is not allowed. Also, acute administration of lorazepam may be useful for MRS studies in agitated demented patients, patients suffering from delirium, and claustrophobic individuals who

Table 1. ^{1}H MRS Metabolite Levels and Ratios for Overall Sample (n=10), and Mean Percent Change after Lorazepam Administration

	Overall			% Change		Paired *t*-test	
	Mean	S.D.	CV (%)	Mean	S.D.	t (df= 9)	*p*
NAA	9.91	2.09	21.0	8.25	17.33	-0.34	0.74
PCr+Cr	6.15	1.31	21.3	8.48	17.69	1.26	0.24
TMA	1.55	0.45	29.3	8.20	25.36	-0.84	0.42
INO	4.58	1.14	24.8	8.53	31.62	0.11	0.91
Glu	8.76	2.78	31.7	19.20	33.89	-0.79	0.45
Gln	3.60	2.72	75.6	32.34	115.86	0.31	0.76
NAA/PCr+Cr	1.34	0.17	12.9	1.18	17.07	-0.09	0.93
TMA/PCr+Cr	0.24	0.04	17.9	-0.83	14.45	0.49	0.64
INO/PCr+Cr	0.72	0.11	15.6	0.70	27.82	0.34	0.74

NAA= N-acetyl-aspartate, PCr+Cr= phosphocreatine plus creatine, TMA= trimethylamines, INO= myo-inositol, Gln= glutamine, Glu= glutamate; % change= difference between post-lorazepam and pre-lorazepam conditions, divided by the pre-lorazepam condition; t= paired t-test, df= degrees of freedom, p= significance. CV= coefficients of variation (defined as the standard deviation of the measurements divided by the mean) of the combined pre- and post-lorazepam measurements. Individual metabolite values are expressed as absolute institutional units.

may need to be sedated in order to complete an MRS scan.

Davanzo et al. (1997) compared the brain ^{1}H MRS values obtained with a PRESS sequence (TE = 30 msec, TR = 3 s) in a group of healthy individuals (n = 7) in two distinct situations, *with* or *without* acute administration of lorazepam 2 mg orally. These two situations were separated by a 2-week interval. In the lorazepam condition, the drug was administered half hour prior to the first scan. Higher PCr+Cr (p = .04), TMA (p = .01), and INO (p = .052) in the parietal cortex (8 cc; mainly white matter), and frontal cortex (8 cc; primarily gray matter) were reported in the lorazepam condition. In this report, the authors suggested that the lack of absolute metabolite quantitation and the small sample size were important limitations. Moreover, the fact that a 2-week interval separated the two conditions may have contributed to increased variability in the metabolite measurements. Of importance, in our present study the two scans (before and after lorazepam) were conducted in the same day, and separated by a one-hour period, which may explain the discrepancy between our currently reported findings and the results by Davanzo et al. (1997). In another ^{1}H MRS study involving 23 healthy individuals (Burau et al. 1997), transient but significant increases in lactate and myo-inositol levels were reported in the striatal region (8 cc), but no changes were found for the other metabolites, after intravenous administration of midazolam (0.05 mg/kg), which decreased to initial values by the end of the study (20 min). A ^{31}P MRS study involving oral administration of diazepam 10 mg (n = 8) or 20 mg (n = 9) did

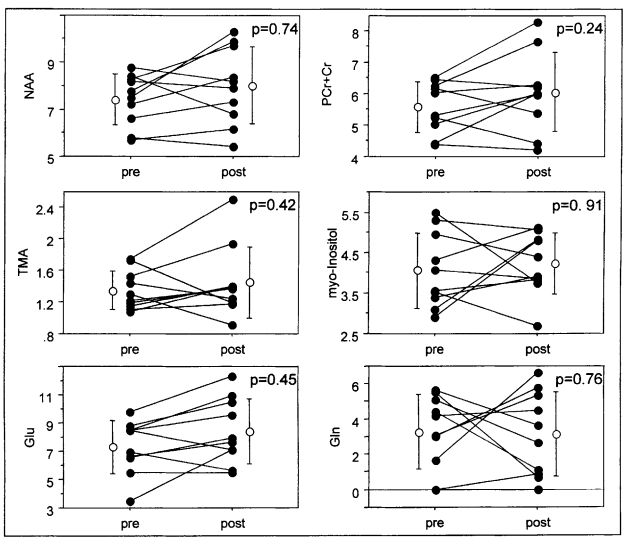

Figure 3. The absolute values for the measured metabolites at baseline and after lorazepam administration are presented. NAA = N-acetyl-aspartate, PCr+Cr = phosphocreatine plus creatine, TMA = trimethylamines, INO = myo-inositol, Gln = glutamine, Glu = glutamate. pre = pre-lorazepam, post = post-lorazepam.

Table 2. Gray Matter, White Matter, and CSF Values in the MRS Acquisition Voxels at Baseline and after Lorazepam Administration

	T1		T2		Paired t-test	
	Mean	S.D.	Mean	S.D.	t (df= 9)	*p*
GM	2.96	0.86	2.99	0.43	-0.13	0.90
WM	4.60	0.91	4.58	0.49	0.06	0.96
CSF	0.14	0.12	0.09	0.07	1.07	0.31

GM= gray matter; WM= white matter; CSF= cerebrospinal fluid content; T1= pre-lorazepam, T2= post-lorazepam; measures are given in cm^3.

not reveal significant changes in brain ^{31}P MRS measures in human subjects at 1 h after drug administration (Deicken et al. 1992). In this study, diazepam administration did not affect the ^{31}P MRS values in either white or gray brain matter. In conclusion, there are some conflicting findings on whether benzodiazepines may significantly change the in vivo brain ^{1}H or ^{31}P MRS measures. However, most studies where the baseline and post benzodiazepine conditions were separated by short time intervals, resembling as best as possible the actual clinical situation of acute lorazepam administration, seem to indicate that the levels of the main metabolites are not significantly affected by single dose administration at clinically useful doses (Deicken et al. 1992; Burau et al. 1997). Furthermore, it is difficult to interpret the discrepant results between our study and some of the previous reports (Davanzo et al. 1997; Burau et al. 1997), since the latter studies have only been presented as congress communications, and have not appeared as published manuscripts, and therefore few methodological details were available. Our present findings indicate that, under the paradigm proposed (in which measures were repeated in the same day, one hour after drug administration, with careful procedures to assure proper placement of MRS acquisition voxels), no evidence of significant changes in the main peaks measured in the ^{1}H MRS human brain spectrum are observed after lorazepam administration.

The mean values for percentage changes in the ^{1}H MRS measures after lorazepam administration were approximately 8.5% for the main metabolites (NAA, PCr+Cr, TMA, INO), and approximately 1% for the ratios (NAA/PCr+Cr, TMA/PCr+Cr, INO/PCr+Cr) (Table 1). The values for Glu and Gln were substantially higher, with mean percentage changes of 19.2% and 32.3%, respectively. The values obtained for the main peaks and metabolite ratios are within the range of previously reported test/retest reproducibility for ^{1}H MRS measures in the in vivo human brain (Bartha et al. 2000; Bertolino et al. 1998; Brooks et al. 1999; Charles et al. 1996; Marshall et al. 1996; Schirmer and Auer 2000), suggesting that the baseline variability of these measures is in the low to moderate range. The variability of NAA, PCr+Cr, TMA, and INO brain concentrations in healthy individuals and schizophrenic patients has been well-documented in several studies (Bartha, et al. 2000; Bertolino et al. 1998; Brooks et al. 1999; Charles et al. 1996; Marshall et al. 1996; Michaelis et al. 1993; Schirmer and Auer 2000; Stanley et al. 1995). Overall, the changes in the various ^{1}H MRS human brain metabolites after lorazepam administration found in our study were similar to previously reported values for test/restest reproducibility of ^{1}H MRS measures, suggesting that acute lorazepam administration does not have specific effects on the main peaks that are part of the in vivo human ^{1}H MRS brain spectra.

A few potential limitations should be considered for interpretation of our findings. Our study involved a sample of 10 subjects, which is a relatively modest sample size. For that reason, small changes in the metabolite concentrations from the baseline to the post lorazepam condition may not have been detected due to limitations in statistical power. Nonetheless, considering the effect sizes normally reported in studies involving similar methods in neuropsychiatric populations, a sample size of 10 subjects studied at baseline and after a certain intervention is a reasonable sample size for comparisons within subjects to detect significant effects. Another potential limitation of our study is the fact that it involved a single brain region (L-DLPFC), and did not examine other cortical brain areas. Even though there is no specific data to suggest that any effects of lorazepam on the ^{1}H MRS metabolites in the brain may be region-specific, we can only comment with certainty on this particular brain region (L-DLPFC), and caution should be utilized when findings are extrapolated for other brain areas. We chose to restrict the study to a single brain region in order to optimize the ^{1}H MRS signal, and be able to resolve well some of the smaller ^{1}H MRS peaks (e.g., INO). Including additional voxels would have brought additional time demands on subjects participating in the study, with long scanning sessions, and would have made the study more difficult to complete. Also, our results showed a large variability in the glutamine measures (see Table 1), suggesting that its reproducibility is poor. In the ^{1}H MRS peak, glutamate, glutamine, and GABA have substantial overlap (Auer et al. 2000; Stanley et al. 2000), and our method was not sensitive to reliably separate these picks. Therefore, we cannot comment on any potential effects of lorazepam on GABA levels, which are likely, and would have been very important to examine, if we were utilizing a ^{1}H MRS method that would allow us to do so.

In conclusion, our findings suggest that the acute administration of lorazepam to manage agitation or anxiety in individuals who require a sedative for successful completion of ^{1}H MRS studies can be performed, as doing so does not change significantly the main chemical measures that are part of the in vivo human ^{1}H MRS brain spectra. These findings have important implications for in vivo MRI/MRS studies in neuropsychiatric populations, and demonstrate the feasibility of approaches that would require sedation of patients with benzodiazepinic agents.

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