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Effects of Disulfiram on Positron Emission Tomography and Neuropsychological Studies in Severe Chronic Alcoholism

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Disulfiram is an aldehyde dehydrogenase inhibitor that is widely used as an adjunctive agent in the treatment of patients with severe chronic alcoholism. Recent positron emission tomography (PET) studies of local cerebral metabolic rates for glucose (lCMRglc) and benzodiazepine receptor binding in alcoholic patients have shown regional cerebral abnormalities; however, some of the patients were studied while receiving disulfiram, which could influence the biochemical processes under investigation. In a retrospective investigation, we examined the influence of disulfiram administration on the results of PET studies of lCMRglc and benzodiazepine receptor binding and neuropsychological tests of cognition and executive function in patients with severe chronic alcoholism. [^{18}F]Fluorodeoxyglucose was used to measure lCMRglc in 48 male patients, including 11 receiving and 37 not receiving disulfiram in therapeutic doses. [^{11}C]Flumazenil was used to measure benzodiazepine receptor binding in 17 male patients, including 3 receiving and 14 not receiving disulfiram. All patients studied with FMZ were also examined with fluorodeoxyglucose. PET studies of lCMRglc revealed significantly decreased global values in the patients receiving disulfiram compared with those not receiving disulfiram. PET studies of benzodiazepine receptor binding revealed decreased flumazenil influx and distribution volume in patients receiving disulfiram. The neuropsychological tests demonstrated no differences between the two groups of subjects. The findings suggest that disulfiram may influence the results of PET studies of glucose metabolism and benzodiazepine receptor binding.

Key Words: Positron Emission Tomography, Disulfiram, Alcoholism, Fluorodeoxyglucose, Flumazenil.

POSTMORTEM STUDIES have demonstrated that excessive and prolonged alcohol intake can lead to extensive neuronal cell loss in the cerebral cortex and cerebellum.[1–9] In living patients with severe chronic alcoholism, these changes are manifested by cerebral atrophy, including focal atrophy in the frontal regions on anatomical imaging studies,[10–15] decreased local cerebral metabolic rates for glucose (lCMRglc) in the medial aspects of the frontal lobes in positron emission tomography (PET) studies with [^{18}F]fluorodeoxyglucose (FDG),[16,17] generalized cerebral changes of lCMRglc, including alterations over time,[18–21] altered cerebral metabolic responses to a benzodiazepine challenge,[22] decreased density of GABA-A/benzodiazepine (GABA-A/BDZ) receptors in the medial portions of the frontal lobes in PET studies with [^{11}C]flumazenil (FMZ),[23] and decreased performance on neuropsychological tests, particularly those reflecting frontal lobe function.[24–27]

Disulfiram (tetraethylthiuram disulfide) is an aldehyde dehydrogenase inhibitor that interferes with the metabolic degradation of acetaldehyde, which is produced in the first step of the oxidation of ethanol.[28–32] The resulting increase in the plasma level of acetaldehyde after ethanol ingestion causes highly unpleasant symptoms, including flushing of the skin with a sensation of warmth, hypotension, tachycardia, tachypnea, palpitations, anxiety, headache, nausea, and vomiting.[32,33] Disulfiram has been used extensively in the treatment of alcoholic subjects since its introduction.[28,29] The metabolic products of disulfiram include a bis(diethyldithiocarbamate) copper complex, which is formed in the gastrointestinal tract and absorbed into the blood along with the parent drug; diethyldithiocarbamic acid (DDC), which is degraded to form diethylamine and carbon disulfide; diethyldithiomethylcarbamate (Me-DDC) and the glucuronic acid of DDC; diethylthiomethylcarbamate (Me-DTC); and the sulfoxide and sulfone metabolites of Me-DTC.[32,34–46] The active agents responsible for aldehyde dehydrogenase inhibition after ingestion of disulfiram appear to be Me-DTC and its sulfoxide and sulfone metabolites.[45–49] Disulfiram and its metabolites are distributed throughout the body in multiple tissues, including small amounts in the brain.[34,50–52] Disulfiram and its metabolites are excreted through the gastrointestinal tract, kidney, and lungs.[29,50,53,54] Many pharmaceutical agents, particularly

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those with known oxidative metabolism, interact with disulfiram,[55,56] and this finding leads to the concern that disulfiram may influence the results of PET studies of lCMRglc. Disulfiram also interacts with benzodiazepines,[57] raising the possibility that the drug may also affect PET studies of GABA-A/BDZ receptors.

Recently, we have utilized PET and neuropsychological evaluation to study patients with severe chronic alcoholism, including a large group examined with FDG and a smaller group with FMZ.[17,23–25] These studies included a small cohort of patients taking disulfiram, providing an opportunity to determine retrospectively whether this medication alters brain function as reflected in PET measurements of lCMRglc and GABA-A/BDZ receptor density and in neuropsychological investigations.

METHODS

Patient Groups and Normal Subjects

The studies were approved by the Institutional Review Boards of the University of Michigan Hospitals and the Ann Arbor Veterans Affairs Medical Center (AAVAMC), and informed consent was obtained from all patients. We studied 48 male chronically alcohol-dependent patients recruited predominantly from the Alcohol Treatment Program of the AAVAMC, including 11 receiving disulfiram in a dose of 250 mg/day and 37 not receiving disulfiram at the time of study (Table 1). Lifetime alcohol use was assessed with the Lifetime Drinking Patterns History, adapted from Skinner and Sheu.[58] This instrument utilizes gender, age, and alcohol consumption, permitting evaluation of patterns of alcohol consumption across multiple time lines across the life span. Data on quantity and frequency of alcohol use and on withdrawal from alcohol were recorded during interviews, and changes in patterns were analyzed. This method has been shown to produce reliable estimates of lifetime drinking. We also applied the criterion of sustained alcohol consumption exceeding 560 g of ethanol weekly as a second major means of benchmarking the length of the patients' histories of "heavy drinking." Comparisons of our data against other studies of alcoholic subjects confirm the status of this group as severe and chronic alcoholic patients.[59] All patients met the DSM-IV[60] diagnostic criteria for alcohol dependence, and all except one exceeded a weekly intake of 560 g of ethanol over 2 of the 3 preceding years. The one patient who was an exception had been abstinent for 5 years. All patients had been hospitalized at least once for alcoholism, and most patients previously achieved sobriety for no more than a few months before beginning the chronic use of alcohol until the current period of abstinence. These patients are characterized as "heavy" drinkers by existing epidemiological data, both in duration and intensity of alcohol intake.[59] Patients were excluded if they had any history of polydrug abuse as defined by the quantitative criteria of the National Institute on Drug Abuse in its National Collaborative Study of Polydrug Abuse.[61] Other exclusion criteria were severe liver disease, severe concurrent psychopathology, and neurological disorders apart from those due to alcohol, including stroke, birth complications, learning disorders, or other acquired or developmental disorders carrying neurological or neuropsychological risk. Patients with closed head injury with loss of consciousness exceeding 30 minutes were also excluded. We recorded the types and doses of all medications administered at the time of study, including disulfiram.

All patients provided a complete medical and neurological history and received a physical and neurological examination. The patients were examined in the absence of medications that could influence cognition, the motor system, or the PET studies. Benzodiazepines that had been administered to reduce withdrawal symptoms were discontinued at least 6 weeks before PET scans in all cases except one, in whom chlordiazepoxide was discontinued 13 days before the study. The patients were studied with PET after they had achieved at least 30 days of sobriety except for one, in whom the PET study was conducted after 17 days of abstinence. At the time of study, the patients were consuming a nutritious diet and had no evidence of ketosis, as determined by urinalysis. We ensured that the patients had achieved sobriety as described by recruiting the patients from an alcohol treatment program involving admission to an inpatient facility that has a 21-day program emphasizing experiential treatment activities. After discharge, the patients were followed in an intensive outpatient program requiring regular appointments for medical follow-up and group therapy. These patients were monitored closely and directly by caregivers experienced in the treatment of alcoholism. The principal focus of the outpatient treatment program in the postacute phase was relapse prevention. In addition, these patients were observed by one of the investigators just before their PET scans, and they were questioned concerning compliance with the prescan requirements concerning food and liquid intake, including alcohol consumption. This observation provided an opportunity to detect signs of drinking.

The patients were divided into two groups based upon use of disulfiram as an adjunct to their treatment program. The patients in both groups had similar clinical and demographic characteristics, because applicants for admission to the Ann Arbor Veterans Affairs Medical Center must qualify for treatment on the basis of both military service history and screens for level of income. These requirements usually limit admissions to patients in the lower middle class or lower class. Almost all of the patients in this study were white, most were in older middle age (Table 1), and all had served in the armed forces in enlisted status. We found no characteristics that differentiated the groups from either a demographic or a clinical perspective. The subjects in both groups had histories of chronic alcoholism that had not been treated successfully. Each of the patients had at least one previous inpatient admission for intensive alcohol treatment. As indicated above, at the time of study the patients had been detoxified, leaving only effects that result from the chronic and not the acute effects of alcohol.

Positron Emission Tomography

These studies were standardized for all subjects. The subjects fasted for 4 hr before the scan and were studied lying supine and awake in a quiet room, alert but not speaking, with eyes open from 5 minutes before injection until completion of the scan. A catheter was placed in a radial artery for blood sampling. PET studies of lCMRglc were performed after intravenous injection of 10 ± 1 mCi of FDG. In the 17 patients also examined with FMZ, 22 ± 2 mCi of this agent were given first for the GABA-A/BDZ studies and followed 90 minutes later by 10 mCi of FDG for the lCMRglc studies.

The subjects were imaged with either a Siemens/CTI 931/08-12 or a Siemens ECAT EXACT-47 scanner. Images from both scanners were reconstructed to a resolution of 8–9 mm full-width at half-maximum (FWHM) in-plane. Because the axial sampling of the EXACT-47 scanner is twice as fine as the 931, two adjacent levels from the EXACT were averaged, providing images with the same axial spacing and nearly the same axial resolution as the 931 scanner. Attenuation correction was calculated by the standard ellipse method.

In the FDG studies, data were acquired from 30 to 90 min after injection and quantified with the static scan method of Hutchins et al.[62] For the FMZ studies, flumazenil was labeled with carbon-11 at high specific radioactivity using a methylation process.[63] A dynamic sequence of 15 scans was acquired for 60 min after tracer administration. Blood samples were taken as rapidly as possible during the first 2 min after tracer injection and then at progressively longer intervals throughout the remainder of the study. We took a total of 25–30 samples per scan. The samples were centrifuged, and the plasma radioisotope concentrations were measured in a NaI well counter. Plasma levels of radiolabeled metabolites of FMZ were determined by a rapid Sep-Pak C_{18} cartridge chromatographic technique[64] in the samples taken at 1 min, 2 min, and every sample from 3 min until the end of the scan. Radioactive fiducials with 1 μCi of [^{18}F]FDG were placed on each subject's scalp. In studies utilizing both

FDG and FMZ in the same subject, radioactive fiducials with 5 μCi of [^{11}C]FMZ were placed initially, then relabeled with 1 μCi of [^{18}F]FDG before the lCMRglc scan without removing them. Computer routines automatically determined the locations of these fiducials and used this information to correct for patient motion. The PET studies were analyzed with a compartmental model and parameter estimation technique that provides pixel-by-pixel determinations of each measurement, thus creating "functional" images.[65] The studies with FMZ provided quantitative measurement of ligand influx (K_1), which is highly correlated with flow because the single-pass extraction fraction for flumazenil is greater than 50%.[66] The studies also provided measurement of FMZ distribution volume (DV), which is linearly related to the density of available receptor sites divided by the ligand dissociation constant (B_{max}'/K_D). The methods for benzodiazepine receptor binding measurement, including the assumptions and limitations and the performance of [^{11}C]flumazenil, are published.[64-66]

PET Data Analysis

PET images were transformed into a standard stereotactic orientation utilizing an automated method for registration into the coordinate system defined by the Talairach atlas[67] followed by linear scaling and nonlinear warping.[68] After anatomic standardization, stereotactically defined volumes-of-interest (VOIs) were placed on all subjects for each group. Comparisons then were made between groups. For studies with [^{18}F]fluorodeoxyglucose, we obtained VOIs bilaterally in regions known from previous studies to show (a) significantly low lCMRglc values in severe chronic alcoholism (medial frontal region);[16,17] (b) correlations between lCMRglc and performance on neuropsychological tests of executive function in severe chronic alcoholism (dorsolateral and orbitomedial frontal cortex);[24,25] and (c) no abnormalities and no correlation with neuropsychological test performance in severe chronic alcoholism (posterior superior temporal region, inferior parietal region, and cerebellar hemispheres). Global measures of lCMRglc were also compared between groups to determine whether disulfiram might affect the entire brain to the same degree as individual regions. The same VOIs were examined in the studies with [^{11}C]flumazenil for comparison with the lCMRglc data and because abnormalities of benzodiazepine receptor binding have been found in the medial portion of the frontal cortex.[23]

Structural Imaging

We obtained magnetic resonance (MR) images utilizing 1.5T scanners. The scans were reviewed with a neuroradiologist.

Neuropsychological Testing

All patients received a neuropsychological evaluation by a clinical neuropsychologist in a well lighted room free of interruptions and distractions. The neuropsychological battery consisted of a modified and expanded Halstead-Reitan Neuropsychological Test Battery (HRNTB), which included several tests of general cognitive function as well as the Category Test, a test of executive cognitive skills the results of which have been found previously to be abnormal in alcoholic subjects. The neuropsychological tests used in this investigation have established reliability and validity and are widely used in neuropsychological laboratories.[69]

Statistical Analyses

Patients in the two groups were compared with univariate tests (t tests with unequal variance). Clinical and demographic characteristics were compared to determine whether groups were comparable on variables that might confound neuropsychological and PET comparisons. Data obtained from PET studies with FDG in the two groups were compared focusing upon regions described above. Data obtained from PET studies with FMZ were compared in the same structures as the FDG studies by examining the percent differences between groups. The data were examined without attempts at statistical comparison because of the small number of cases in the group receiving disulfiram (n = 3) compared with the group not receiving disulfiram (n = 14). Univariate t tests were used to compare neuropsychological test performance in the two groups.

Table 1. Patient Groups

Measure	No disulfiram (n = 37)	Disulfiram (n = 11)
Age (years)	48 ± 9	48 ± 7
Education (years)	13 ± 2	13 ± 2
Lifetime alcohol consumption*	101 ± 65	84 ± 52
Years of heavy drinking†	20 ± 10	21 ± 7

Data are presented as mean ± standard deviation. None of the comparisons are significant.

* Estimated number of lifetime drink equivalents (two ounce 80-proof alcohol units) in thousands.

† Number of years patients consumed an average of 560 grams of ethanol weekly.

Table 2. Local Cerebral Metabolic Rates for Glucose (in mg/100 g/min) Displayed as Mean ± Standard Deviation in Two Groups of Severe Chronic Alcoholic Patients and Percent Decrease in the Group Receiving Disulfiram

Structure	No disulfiram (n = 37)	Disulfiram (n = 11)	Percent decrease
Medial frontal	6.5 ± 1.0	5.7 ± 0.7*	12
Dorsolateral frontal	6.7 ± 0.9	5.9 ± 0.6*	12
Orbitomedial frontal	5.7 ± 0.7	5.0 ± 0.5*	12
Posterior superior temporal	7.0 ± 0.9	6.3 ± 0.7*	10
Inferior parietal	6.7 ± 1.0	6.0 ± 0.7†	10
Cerebellar hemispheres	5.2 ± 0.7	4.7 ± 0.4*	10
Global	5.1 ± 0.7	4.5 ± 0.5*	12

* $p < 0.01$.
† $p < 0.02$.

RESULTS

Patient Groups

Comparison of the 11 patients receiving disulfiram with the 37 patients not receiving disulfiram revealed no significant differences between groups in age, length of education, lifetime alcohol consumption, or years of heavy drinking (Table 1).

PET Studies

Statistical testing revealed significant differences in lCMRglc between groups for global values and for every region examined, with the group receiving disulfiram exhibiting consistently lower values than the group not receiving disulfiram (Table 2). The percent decrease in the disulfiram group was similar for global values and for all regions studied, including the medial frontal region (Table 2). Normalization of these data to the global values eliminated all significant differences between groups (Table 3).

FMZ kinetic data were compared between the two groups using absolute values of K_1 and DV (Table 4). The data revealed lower global and regional values in the group receiving disulfiram than in the group not receiving disulfiram. Larger percentage decreases in the disulfiram group were observed for DV than for K_1 data. After normalization, there were no regional differences in K_1 or DV.

Table 3. Local Cerebral Metabolic Rates for Glucose Normalized to Global Values Displayed as Mean ± Standard Deviation in Two Groups of Severe Chronic Alcoholic Patients

Structure	No disulfiram (n = 37)	Disulfiram (n = 11)
Medial frontal	1.29 ± 0.08	1.27 ± 0.03
Dorsolateral frontal	1.32 ± 0.07	1.32 ± 0.05
Orbitomedial frontal	1.13 ± 0.07	1.12 ± 0.03
Posterior superior temporal	1.38 ± 0.07	1.39 ± 0.04
Inferior parietal	1.32 ± 0.06	1.33 ± 0.06
Cerebellar hemispheres	1.03 ± 0.12	1.06 ± 0.10

None of the above comparisons are significant.

Neuropsychological Tests

The patients receiving disulfiram showed no significant differences from the patients not receiving disulfiram in either measurements of general impairment or of executive function (Table 5).

Structural Imaging

Review of MR images revealed no structural abnormalities apart from atrophy in the patients and no identifiable differences between groups.

DISCUSSION

The results of this investigation utilizing PET with FDG revealed significantly lower absolute lCMRglc values in patients with severe chronic alcoholism receiving disulfiram than in a similar group of patients not receiving the medication. The two groups were comparable in age, education, lifetime alcohol consumption, and years of heavy drinking. Neuropsychological test performance was not different between the two groups. The differences in global values between groups were similar to the differences between groups in each of the regions studied, suggesting that the differences result from a general, probably metabolic, effect of disulfiram. The nature of the effect was not determined in this study; however, it seems likely to result from interactions of one or more of the multiple products of disulfiram metabolism with one or more components of the pathways of oxidative metabolism.[32,55,56] The results give some concern about previous studies that showed abnormalities of lCMRglc in patients with severe chronic alcoholism, most of which did not state whether the patients examined were receiving this medication.[16–22] It was reassuring to find in the present studies that the differences between the patients receiving disulfiram and those not receiving disulfiram disappeared when the data were normalized to global values, because this result indicates that the effects of disulfiram are global, with no regional specificity, and many previous studies have reported normalized rather than absolute data. Moreover, some of the previous studies demonstrated focal abnormalities in the medial frontal region and, in patients with alcoholic cerebellar degeneration, within the midline portions of the cerebellum as well.[17] These focal abnormalities are unlikely to result from a global disturbance of glucose metabolism owing to effects of the medication.

The results of the investigation utilizing PET with FMZ to examine benzodiazepine receptor binding in the two groups of patients must be viewed as preliminary because the size of the group receiving disulfiram was small. Because of the small sample size, statistical testing was not attempted, but the results were generally similar to those obtained with FDG, showing decreased values in the patients receiving disulfiram. Studies of ligand influx (K_1) revealed modest differences between groups, whereas studies of receptor binding (DV) showed much larger differences. This indicates that the differences are not due to changes in cerebral blood flow. Differences between groups in both K_1 and DV were similar in all regions examined, suggesting that the results reflect a global effect of the medication on benzodiazepine receptor binding. Here again the mechanism underlying the results was not addressed, but several metabolic products of disulfiram are capable of influencing benzodiazepine receptor binding.[23]

The results of this investigation raise two issues. First, as noted above, the nature of the changes in lCMRglc and in benzodiazepine receptor binding from administration of disulfiram have not been determined. This agent could affect the results by altering the biochemical processes influencing glucose metabolism and benzodiazepine receptor integrity, by influencing the measurement processes, or by both mechanisms. Although alterations of cerebral glucose metabolism and benzodiazepine receptor function from drug administration are conceivable, disulfiram has been used safely for many years, and the literature does not support the notion of major alterations in cerebral cortical function or of adverse changes in cognition from the medication. Hence, an effect on the measurement process seems more likely than an influence upon cellular metabolism and receptor function. The second issue is that the patients who received disulfiram were treated based upon the clinicians' impression of subjects who would benefit from this substance. Many clinicians prescribe disulfiram for patients at highest risk for relapse, and these are the patients who frequently have the lowest coping skills. It is conceivable that there are clinical differences between the groups studied that in turn influence the use of disulfiram, and these differences might account for the results of the PET studies, irrespective of the effects of disulfiram. This issue deserves consideration in the interpretation of the findings. Future investigations will be needed to explore the issue further.

We should emphasize that this study is retrospective and does not address the neuropsychological effects of disulfiram that might be seen in a randomized and double blind study. Nevertheless, the lack of differences in neuropsychological tests between patients receiving disulfiram and those not receiving disulfiram is consistent with available descriptions of the effects of disulfiram indicating that the medication has no adverse effects on cognition.

Table 4. Benzodiazepine Receptor Binding Studies Showing Absolute Levels of Ligand Influx (K_1) and Receptor Distribution Volume (DV) in Patients with Severe Chronic Alcoholism Receiving Disulfiram (n = 3) and Not Receiving Disulfiram (n = 14) and Percent Decrease (% dec) in the Group Receiving Disulfiram

Structure	K_1 no disulfiram	K_1 disulfiram	% dec	DV no disulfiram	DV disulfiram	% dec
Medial frontal	0.33 ± 0.07	0.30 ± 0.03	9	6.12 ± 1.26	4.78 ± 0.30	22
Dorsolateral frontal	0.33 ± 0.07	0.30 ± 0.02	9	6.00 ± 0.77	4.79 ± 0.22	20
Orbitomedial frontal	0.29 ± 0.05	0.27 ± 0.03	7	5.49 ± 0.78	4.82 ± 0.39	12
Posterior superior temporal	0.37 ± 0.07	0.36 ± 0.03	3	6.72 ± 0.91	5.50 ± 0.51	18
Inferior parietal	0.34 ± 0.07	0.32 ± 0.02	6	6.10 ± 0.87	5.06 ± 0.32	17
Cerebellar hemispheres	0.32 ± 0.05	0.31 ± 0.07	3	4.17 ± 0.76	3.13 ± 0.26	25
Global	0.27 ± 0.05	0.25 ± 0.02	7	4.49 ± 0.66	3.65 ± 0.12	19

Table 5. Comparison of Neuropsychological Test Performance in Two Groups of Severe Chronic Alcoholic Patients

Neuropsychological tests	No disulfiram (n = 37)	Disulfiram (n = 11)
WAIS-R FS	99 ± 9	97 ± 13
TPT Total	17 ± 6	18 ± 9
H-R II	0.5 ± 0.2	0.5 ± 0.3
HCT	60 ± 26	64 ± 30

WAIS-R FS, Wechsler Adult Intelligence Scale-Revised Full Scale IQ; TPT Total, Tactual Performance Test Total Time in minutes; H-R II, Halstead-Reitan Impairment Index; HCT, Total Errors on the Halstead Category Test. None of the above comparisons are significant.

Finally, a clear implication of the findings in this study is the need for caution in interpreting the results of PET studies of glucose metabolism or ligand binding in severe chronic alcoholic patients taking disulfiram. This caution will need to be exercised with other ligands that will be used in the future as probes with PET or single photon emission computed tomographic studies.

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