RAP

Original article

Low-dosage Metadoxine for the treatment of alcohol craving: an open study

Chiara Montemitro[1]
Gaia Baroni[1]
Marco Di Nicola[2]
Riccardo Guglielmo[2]
Alessandra Frustaci[2]
Giovanni Martinotti[1,3]
Luigi Janiri[2]

[1] Department of Neuroscience Imaging and Clinical Science, "G. d'Annunzio" University of Chieti, Italy
[2] Institute of Psychiatry, Catholic University Medical School, Rome, Italy
[3] Department of of Pharmacy, Pharmacology and Clinical Science, University of Hertfordshire, Herts, UK

Address for correspondence:
E-mail: gaia.baroni89@gmail.com

Abstract

***Introduction*: Alcohol is a highly addictive psychoactive substance. Alcohol craving could be very strong and could lead to relapse in alcohol consumption, especially during the first month of detoxification. Several treatments have been approved for alcohol dependence. Among them, Metadoxine has been considered an effective therapy for the treatment of chronic and acute alcohol intoxication and Alcoholic Liver Disease.**
***Aim*: Our aim was to provide additional data about the role of Metadoxine in craving reduction, relapses prevention and abstinence support.**
***Methods*: We collected data about 26 outpatients affected by Alcohol Dependence and treated with low dosage Metadoxine (500 mg/die). The duration of the treatment was 30 days for every patient. Administered psychometric evaluation consisted in: CGI, GSI, QOL, OCDS, VAS, CIWA-Ar.**
***Results*: Under Metadoxine treatment, 3 subjects maintained abstinence, 9 relapsed and 13 dropped out for lack of efficacy. We observed a general trend in reduction of symptoms intensity. No side effects have been reported during the observation interval (T0-T1). CGI and QOL showed a statistically significant improvement in clinical conditions of patients between T0 and T1.**
***Conclusions*: Despite many important limitations, our study suggests that 500 mg of Metadoxine might represent a promising therapeutic strategy to manage AD and to promote the maintenance of abstinence. Additional randomized studies with larger populations and longer follow-up are needed to confirm this finding.**

KEY WORDS: alcohol craving, alcohol abuse, alcohol withdrawal, alcohol dependence, alcohol use disorder treatment, metadoxine.

Introduction

Alcohol is a highly addictive psychoactive substance and alcohol consumption is associated with significant disability and mortality. Europe's alcohol consumption is the largest in the world and 23 million people develop an alcohol-related disorder every year (1). In Italy, despite an overall decrease in alcohol use among Italian population (2), the Italian Society of Alcohology estimates that about 1 million individuals is dependent on alcohol (3). A survey conducted in 2003 reported that alcohol-attributable mortality among Italian population was 2.6% for male and 2% for female (4).
Alcoholism may be considered as a chronic illness. One of the main criteria of the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to diagnose alcohol use disorders is craving (5), defined as strong desire to consume alcohol (5, 6). Especially during the first month of detoxification, craving could be very strong (6) and could lead to loss of control, compulsive use and relapses to alcohol over time (7). As known (8), relapses have been proven to be a primary independent mortality factor.
Several treatments have been approved for alcohol addiction and alcohol-related medical disorder; some of them have been investigated to target craving and different craving mechanisms (6). Among all these new agents, several recent studies have focused on Metadoxine, an ionic complex of pyridoxine-pyrrolidone molecule. It acts as an antioxidant, participates in the synthesis of glutathione (GSH), reduces free fatty acid accumulation and inhibits TNF, preventing the liver damage caused by ethanol (9). Metadoxine is currently indicated for the treatment of chronic and acute alcohol intoxication and Alcoholic Liver Disease (ALD): Higuera de la Tijera et al. demonstrated that Metadoxine in combination with glucocorticoids improves the survival rates and the response to steroid therapy in ALD (9).

Moreover, Metadoxine has been proven to be an effective therapy for alcohol abstinence (8,10) and, in preference to Disulfiram, Naltrexone and Acamprosate, has been approved also in patients with severe liver disease (9).
The most common prescriptions dosage of Metadoxine in previous study are 500 mg three times a day (t.i.d.), also when administered as add-on therapy in ALD (8-10); Guerrini et al. (11) proposed 1000 mg tid. Contrariwise, no studies have yet been conducted on lower doses of Metadoxine in AD patients.
We collected data about 26 outpatients affected by Alcohol Dependence and treated with low dosage Metadoxine. Our aim was to provide additional data about the role of Metadoxine in craving reduction, relapses prevention and abstinence support.

Subjects and methods

Setting

This study was conducted at the *Day Hospital of Psychiatry and Drug Dependence* of the 'Agostino Gemelli' Hospital, Catholic University, Rome, Italy. The study has been approved by the local Ethics Committee and conducted according to the national and local regulatory requirements, Good Clinical Practice guidelines and the Declaration of Helsinki of 1975, as revised in 1983. All participants signed an informed consent before starting any research procedure. As part of the informed consent process, all participants received information on the study procedures and on the possibility to withdraw from the study at any time.

Screening and enrolment

We enrolled 26 patients [age 45.54 ± 11.02; 18 males (69.2%), 8 females (30.8%)]. They presented different education levels, marital status and employment situations (Table 1). Psychiatric comorbidities have been assessed by DSM-IV clinical interview: axis I comorbidities have been found in 42.3% of patients, while axis II comorbidities have been found in 30.8% of subjects (Table 2).
All subjects fulfilled the DSM-IV criteria for Alcohol Dependence. In addition to alcohol, 11 patients (42.3%) also abused other substances. Alcohol addiction has been described by the Cloninger classification (12): 14 subjects (53.8%) have been classified as Type II; 12 subjects (46.2%) have been classified as Type I.
Patients underwent a combination of psychometric tests in order to evaluate the entire course of the treatment: Clinical Global Impression rating scale (CGI) (13), assessing patients' global functioning prior to and after treatment; Global Severity Index (GSI), providing a single composite score for measuring symptom improvement (14); Quality of Life Scale (QOL) (15). Alcohol craving was measured by the Obsessive-Compulsive Drinking Scale (OCDS) (6), evaluating total craving and its obsessive and compulsive components, and by the Visual Analogue Scale (VAS) (16). Severity of alcohol withdrawal was clinically quantised by the Revised Clinical Institute Withdrawal Assessment For Alcohol Scale (CIWA-Ar) (17).

Table 1. Demographic characteristic of the sample.

	N	%
Level of education		
Junior High school	3	11.5
High school	20	76.9
Degree	3	11.5
Marital status		
Single	9	34.6
Married	9	34.6
Divorced	7	26.9
Widowed	1	3.8
Employment Status		
Employed – Regular Job	13	50
Employed – Occasional Job	2	7.7
Unemployed	11	42.3

Table 2. Psychiatric comorbidity.

	N	%
AXIS I COMORBIDITY	**11**	**42.3**
Bipolar I Disorder	1	6.3
Bipolar II Disorder	1	6.3
Generalized Anxiety Disorder	2	12.5
Major Depressive Disorder	7	43.8
Impulse Control Disorder	3	18.8
Obsessive-Compulsive Disorder	1	6.3
AXIS II COMORBIDITY	**8**	**30.8**
Dependent Personality Disorder	2	22.2
Histrionic Personality Disorder	1	11.1
Borderline Personality Disorder	6	66.7

Statistical Analysis

All data have been entered into an SPSS database. The level of significance used to justify a claim of a statistically significant effect was 0.05 for all statistical analyses. Whereas the data were not normally distributed, only nonparametric tests have been used. Frequencies have been calculated for baseline demographic and clinical features. Differences between baseline and follow up have been detected with Wilcoxon signed rank test.

Table 3. Results (T0=baseline; T1=after 30 days of treatment with metadoxine - 500 mg/die).

	T0	T1	p
CGI	26 subjects	5 subjects	**0.025**
	4.92 ± 0.48	4 ± 0	
QoL	26 subjects	8 subjects	**0.034**
	6.96 ± 0.72	8 ± 1.19	
OCDS_Total score	26 subjects	15 subjects	0.07
	12.73 ± 6.15	9.73 ± 4.28	
OCDS_oss	26 subjects	15 subjects	0.27
	6.38 ± 2.98	4.73±1.53	
OCDS_comp	26 subjects	15 subjects	0.06
	6.38 ± 3.9	5±3.55	
GSI	26 subjects	15 subjects	0.08
	0.91 ± 0.63	0.58 ± 0.34	
VAS	26 subjects	14 subjects	0.16
	3.91±2.3	2.96±1.89	
CIWA-Ar	26 subjects	15 subjects	0.48
	5.73±3.9	4.80±3.6	

Intervention and results

Patients have been treated with a dose of 500 mg/die of Metadoxine. The duration of the treatment for every patient was 30 days. Two clinical and psychometric evaluation have been performed: at baseline (T0) and after 30 days (T1). Under Metadoxine treatment, 3 subjects (11.5%) maintained abstinence, 9 (34.6%) relapsed and 13 (53.9%) dropped out for lack of efficacy. A non-significant trend in reduction of symptoms intensity was observed (Table 3). CGI and QOL showed a statistically significant improvement of the clinical conditions of patients between T0 and T1 (Table 3). No side effects have been reported during the observation interval (T0-T1).

Discussion and conclusions

In our small sample, short-term treatment with Metadoxine resulted in an improvement of the clinical conditions of patients assessed by CGI. Furthermore, it was detected an improvement in the quality of life assessed by the QOL. None of our patients reported side effects and 3 of them succeeded in maintaining abstinence. The high percent of missing data at follow-up represents a shortcoming of our study, and results should be interpreted with particular caution for this reason. Anyway this open study confirms a positive role of Metadoxine in AD, according with previous studies (8,10,11,18).

We used a dose of 500 mg/die of Metadoxine. According to literature, the optimal dose to treat AD is 500 mg t.i.d. (10,11,18). This could be the reason why part of our sample dropped-out for lack of efficacy. At the same time, using a lower dosage, we did not observe some side effects such as nausea, headache, tremors, vertigo, sweating and blurred vision, reported by other studies (8,10).

An explanation of how Metadoxine reduces alcohol consumption and promotes alcohol abstinence might be related to the ability of this drug to modify alcohol metabolism, by increasing the activity of acetaldehyde dehydrogenase (10). Moreover, Metadoxine accelerates plasma and urinary clearance of ethanol and acetaldehyde, two components that are able to stimulate the activity of dopamine neurons in reward areas of the central nervous system (CNS). An additional hypothesis of how Metadoxine reduces alcohol consumption might be linked to its direct action on gamma-aminobutyric acid (GABA), acetylcholine and dopamine, which are also involved in the neurobiology of alcohol craving and drinking (19). Despite many important limitations, our study suggests that 500 mg of Metadoxine might represent a promising therapeutic strategy to manage AD and to promote the maintenance of abstinence. Additional randomized studies with larger populations and longer follow-up are needed to confirm this finding.

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