REVIEW ARTICLE

METADOXINE IN THE TREATMENT OF ACUTE AND CHRONIC ALCOHOLISM: A REVIEW

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Alcohol abuse and alcoholism are responsible for a wide variety of medical problems. The pharmaco-therapeutic aspect of alcoholism includes the use of drugs, with different actions and objectives. Among them, metadoxine seems to be of interest. Metadoxine is able to accelerate the elimination of alcohol from the blood and tissues, to help restore the functional structure of the liver and to relieve neuro-psychological disorders associated with alcohol intoxication. Metadoxine also seems to be safe; in more than 15 years of post-marketing surveillance only minor aspecific and reversible events were monitored in patients exposed to the treatment. In this review the preclinical and clinical results obtained using metadoxine in acute and chronic alcohol intoxication are reported.

Alcoholism is a multifactorial disorder in which biologic and genetic factor interact along with cultural and social factors (1,2). Alcohol addiction represents a social problem and a relatively common disease of western countries like Europe and the USA. From 20 to 40% of subjects admitted to hospitals have alcohol-related problems (3) and in elderly people alcohol-related disorders represent as frequent a reason for hospitalization as myocardial infarction (4).

The most lasting damaging actions of ethanol are exerted on the liver function and structure (5). A liver disease is often present in patients affected by alcohol abuse and/or alcoholism; however the mechanisms responsible for the liver toxicity of ethanol are still not completely understood (6).

Ethanol also modifies the GABA-mediated neurotransmission (7). Probably it preferentially stimulates the dopaminergic transmission in the mesolimbic system (8), interferes with serotoninergic transmission (9) and with the release of glutamate in the central synapses (10). The neuropathological manifestations usually appear after many years of excessive drinking. In addition to the effects of alcohol on the nervous system, it may be one of the major contributing factors to road accidents, suicide and violent death in young adults (11).

The pharmaco-therapeutic aspect of alcoholism includes the use of drugs, with different actions and objectives (12). Among them, metadoxine seems to be of interest. The present review evaluates the pharmacology and the therapeutic use of metadoxine (figure 1), a drug promoted for the treatment of acute and chronic alcohol intoxication and alcoholic liver disease.

Enzymatic activity of Metadoxine compounds

Metadoxine is formed by the salification of two components, pyrrolidone carboxylic acid (PCA) and pyridoxol, in a single product. PCA is usually present in the diet and produced endogenously by enzymatic conversion of the gammaglutamyl amino acids to PCA and free amino acids in several mammalian tissues, including the central nervous system, where it has a role in the composition of neuroactive molecules (13). PCA is an intermediate in the gammaglutamyl cycle, it is transformed into glutathione by two subsequent reactions catalyzed by gamma-glutamylcysteine synthetase and glutathion synthetase

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respectively, and its production is linked to the gammaglutamyl transferase activity of the liver cell membrane and to hepatic levels of reduced glutathione (GSH) (14). It has also been shown that PCA facilitates ATP synthesis by stimulating the "de novo" synthesis of the purine nucleotide. (15). Pyridoxol is a precursor of coenzymes such as pyridoxal phosphate which accelerates the metabolic degradation of ethanol and prevents ATP inactivation by acetaldehyde, the main ethanol metabolite (16).

In Metadoxine PCA and Pyridoxol are linked by salification and in this form their pharmacological properties seem to be synergic as shown by their superior activity when given together, with respect to separate administration (17,18).

Pharmacokinetic profile

Metadoxine exerts a metabolic effect, the efficiencies of which depend on the presence of both moieties, pyridoxine (PDX) and pyrrolidone carboxylate (PCA); in the same tissue with the same profile, and both in concentrations able to trigger the metabolic biotransformations in which they are implicated. Pharmacokinetic studies have been performed in rats, dogs, monkey and healthy volunteers (18-20). These studies mainly showed that the oral absorption of the drug is fast, with high and reproductive absolute bioavailability (60 to 80%) and with extensive tissue distribution, as shown by the large apparent distribution volume. The half-life is 40 to 60 minutes without appreciable differences between oral or intravenous administration. The kinetic profile is specific to metadoxine as such. The extemporaneous administration of the two individual components can not compete in terms of the blood concentration, thus of tissue distribution and ultimately of therapeutic effect, with Metadoxine.

This is the consequence of Metadoxine being an ion-pair, and was very easily seen comparing the kinetic profile of pyridoxine administered as a component of Metadoxine, with that of the same pyridoxine administered alone (21), which yields lower concentrations with a very long delay.

The identified metabolites are those expected from the metabolism of glutamate and of pyridoxine. In particular, the radioactivity given with metadoxine was found in glutamate, glutamine, glutamylcysteine, glutathione, a-ketoglutarate, pyridoxal, pyridoxal phosphate and pyridoxamine. Approximately 12% of total radioactivity was found in peptide derivatives, probably synthesised via the g-glutamil cycle. (21). Excretion occurs approximately in the same proportion through the urine and the feces, between 40 and 45% in 24 hours in the urine, and between 35 and 50% in 96 hours in the feces (21). This information justifies the dosage scheme recommended for the therapeutic use in humans.

Preclinical studies

Metadoxine has been shown to induce profound alterations of alcohol metabolism in rats. It increases the activity of acetaldehyde dehydrogenase and prevents the decrease in alcohol dehydrogenase activity shown in chronic ethanol fed rats (22,23). Its administration accelerates plasma and urinary clearance of ethanol and acetaldehyde in a dose-dependent manner (22). The accelerated urinary clearance could be due to the inhibiting effect of metadoxine on the formation of macroaggregates between albumin and acetaldehyde shown in alcohol treated rats. Metadoxine significantly inhibits the increase of fatty acid esters in the liver of ethanol treated rats (24), restoring the correct ratio between hepatic saturated and unsaturated fatty substances (25). At 160 mg/kg, Metadoxine also prevented the formation of fatty liver in 50% of rats exposed to a dose of ethanol able to induce fatty liver in 100% of the rats in the control group (23).

In normal untreated rats, Metadoxine has been shown to increase hepatic ATP content through an activation of the purine "de novo" synthesis (15,17), and in hepatocytes of acutely and chronically alcohol intoxicated rats it is able to restore the activity of the aldehyde dehydrogenase and to increase the reduced glutathione levels (26). Pretreatment of animals with Metadoxine one hour before ethanol administration produced significant protection against glutathione depletion and oxidoreductive stress in hepatic and extrahepatic tissue (27,28), and an increment in alcohol metabolism and turnover (25). Recently Metadoxine has been shown to prevent glutathione depletion, lipid peroxidation damage, collagen deposition and TNF alfa secretions induced by alcohol and acetaldehyde in hepatocytes and hepatic stellate cells (29) These mechanisms could be implicated in the ability of Metadoxine to prevent hepatic necroinflammation, fibrosis and progression to cirrhosis in rats chronically exposed to hepatotoxic agents as shown in rat models of hepatic cirrhosis (14,30) (Fig. 2).

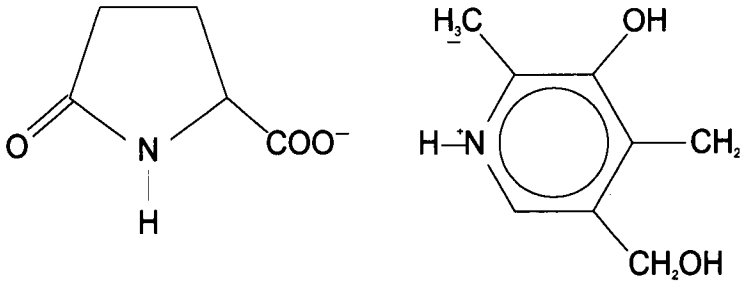


Fig. 1. *Chemical structure of metadoxine (pyridoxine L-2-pyrrolidone-5-carboxyl ate). (Modified from: Metadoxine. Drugs of Today 1988; 24:217-219)*

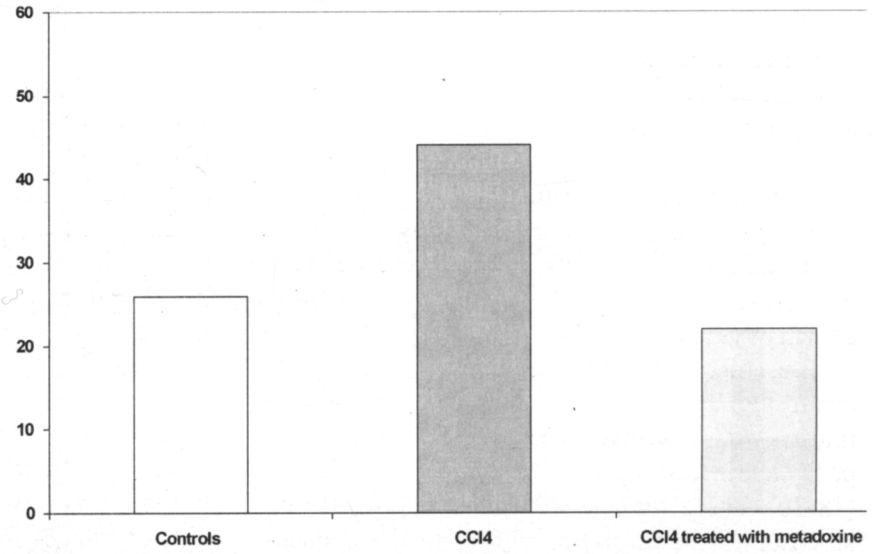
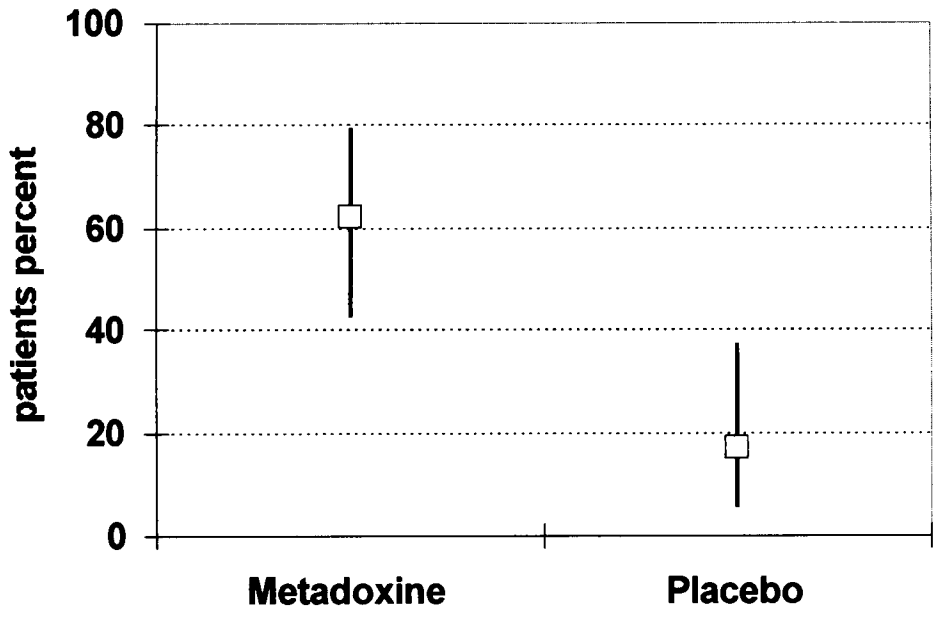


Fig. 2. *Serum levels (Itg/ml: mean±standard deviations) of immunoreactive prolyl hydroxylase (SIRPH). The CCL_4-treated animals have significantly higher SIRPH than controls or rats protected with metadoxine. (Modified from: Annoni G, Contu L, Tronci MA, et al Pyridoxol L, 2-Pyrrolidon-5 Carboxylate prevents active fibroplasia in CC14-treated rats. Pharmacol Res 1992, 25 (1): 87-93)*

Fig. 3. *Proportion of patients who started to recover (decrease of blood alcohol concentration by at least one category) from acute alcohol intoxication within 1 hr after treatment with metadoxine or placebo. With metadoxine the proportion was 62.1% (59% CI: 43 to 79%); with placebo it was 17.2% (95% CI: 6 to 37%). The difference in proportion is statistically significant (0.0013) and corresponds to 44.8 ± 11.4 % (95% CI: 22 to 67%), yelding a NNT of 2 (95% CI: 1 to 5). (Modified from: Shpilenya LS, Muzychenko AP, Gasbarrini G, Addolorato G: Metadoxine in Acute Alcohol Intoxication: A Double-Blind, Randomized, Placebo-Controlled Study. Alcohol Clin Exp Res 2002, 26:340-346)*



Symptom	Time	Metadoxine		Placebo
Agitation	0	1.83 ± 0.80		2.31 ± 0.76
	0.5	1.83 ± 0.85		2.34 ± 0.72
	1	1.03 ± 0.82		1.86 ± 0.92
	2	0.52 ± 0.69		1.28 ± 0.88
	3	0.17 ± 0.38		0.82 ± 0.82
	6	0.00 ± 0.00		0.50 ± 0.64
	9	0.00 ± 0.00		0.11 ± 0.31
	12	0.00 ± 0.00		0.00 ± 0.00
p for difference in time course (repeated-measures ANOVA)			0.001	
Aggressive behavior	0	0.66 ± 0.77		1.76 ± 0.99
	0.5	0.55 ± 0.95		1.83 ± 1.00
	1	1.00 ± 0.71		1.41 ± 0.95
	2	0.41 ± 0.68		0.76 ± 0.79
	3	0.07 ± 0.26		0.50 ± 0.84
	6	0.04 ± 0.19		0.14 ± 0.36
	9	0.00 ± 0.00		0.00 ± 0.00
	12	0.00 ± 0.00		0.00 ± 0.00
p for difference in time course (repeated-measures ANOVA)			0.400	
Impaired mental function	0	2.10 ± 0.72		2.62 ± 0.56
	0.5	2.28 ± 0.75		2.48 ± 0.83
	1	1.62 ± 0.68		2.31 ± 0.97
	2	1.10 ± 0.77		1.83 ± 0.89
	3	0.76 ± 0.83		1.50 ± 0.79
	6	0.36 ± 0.56		0.61 ± 0.63
	9	0.07 ± 0.26		0.29 ± 0.53
	12	0.03 ± 0.19		0.18 ± 0.67
p for difference in time course (repeated-measures ANOVA)			0.016	
Jerky movements	0	0.90 ± 0.67		0.90 ± 0.90
	0.5	0.62 ± 0.73		0.72 ± 0.88
	1	0.54 ± 0.88		0.45 ± 0.74
	2	0.10 ± 0.31		0.21 ± 0.49
	3	0.10 ± 0.41		0.07 ± 0.38
	6	0.04 ± 0.19		0.04 ± 0.19
	9	0.03 ± 0.19		0.00 ± 0.00
	12	0.00 ± 0.00		0.00 ± 0.00
p for difference in time course (repeated-measures ANOVA)			0.873	
Drowsiness	0	0.38 ± 0.78		0.38 ± 0.62
	0.5	0.45 ± 0.83		0.41 ± 0.68
	1	0.93 ± 0.92		0.76 ± 0.79
	2	1.14 ± 0.99		0.79 ± 0.82
	3	1.59 ± 0.87		1.18 ± 0.94
	6	1.54 ± 0.79		1.32 ± 0.82
	9	1.41 ± 1.05		1.82 ± 1.16
	12	1.76 ± 1.12		1.93 ± 1.18
p for difference in time course (repeated-measures ANOVA)			0.199	

Tab. I. *Time course of individual symptom intensity (Mean ± SD) during observation. (Modified from: Shpilenya LS, Muzychenko AP, Gasbarrini G, Addolorato G: Metadoxine in Acute Alcohol Intoxication: A Double-Blind, Randomized, Placebo-Controlled Study. Alcohol Clin Exp Res 2002; 26:340-346)*

	Metadoxine *(n=57)*	Placebo *(n=54)*	*p*
Bilirubin (mg/dl)	- 0.79±1.1	- 0.41±0.7	n.s.
AST (U/l)	- 103.9±60.8	- 33.2±46.7	<0.001
ALT (U/l)	- 85.8±60.5	- 24.9±44.4	<0.001
Gamma GT (U/l)	- 335.4±323.1	- 119.1±220.5	<0.001
Alkaline phosphatase (U/l)	- 139.6±221.1	- 27.8±86.8	<0.001
Prothrombin index (%)	+ 8.82±15.8	+ 4.42±10.6	<0.05

Tab. II. *Mean differences between the initial and final main laboratory data of patients treated with metadoxine and placebo. (Modified from: Caballeria J, Pares A, Bru C, et al: Metadoxine accelerates fatty liver recovery in alcoholic patients: results of a randomized double-blind, placebo-control trial. J Hepatol 1988; 28: 54-60)*

The central nervous system (CNS) activity of metadoxine has been studied in relation to CNS ATP content, neuroactive molecule release and neuropsychologic effects. Ethanol by systemic route causes ATP decrease in brain cells by approximately 50%. Pre-treatment with metadoxine (50 mg/kg) not only completely prevented such a drop in ATP level, but even resulted in an increase lasting more than two hours (17). Metadoxine administration increases the release of GABA and Acetylcholine from the frontoparietal cortex of freely moving guinea-pigs (31) and in mice it has been shown to increase dopamine levels in striatal tissue (32). As a consequence of the interactions with CNS neurotrasmitters Metadoxine has shown neuro-psychological effects on animals. In rats, on the other hand, the administration of Pyrrolidone-carboxylic acid has shown dose-dependent anxiolytic effects (33,34) and an antagonistic effect on ethanol locomotor-stimulant response in mice (35).

CLINICAL STUDIES

Acute Alcohol Syndromes: acute intoxication

In acute alcohol intoxication Metadoxine has been shown to reduce the T/2 of ethanol in healthy volunteers (36) and in acutely intoxicated patients, where it is significantly reduced from 7 hours and 15 min. to 5 hours and 50 min (37). This drug has also been shown to accelerate the biotrasformation of alcohol and acetaldehyde into definitely less toxic higher ketones, to improve the urinary clearance of these compounds (38) and to restore laboratory variables such as alcohol, ammonia, gamma-GT and ALT (39).

As in rats metadoxine has been shown to have an anxiolytic-like effect on man exposed to a conflict situation (40). In alcohol intoxicated patients it induces a significant improvement in symptoms such as psychomotor agitation, depression, aggressiveness, sopor and equilibrium disorders, with respect to a control group treated with supportive measures, multivitamins and electrolyte preparations, Chlordiazepoxide or Valproate (41,42).

In two recent double-blind controlled clinical trials metadoxine was compared to a conventional treatment (parenteral solutions, multi-vitamin preparations, BDZ or neuroleptics as appropriate) for acute alcohol intoxication in the emergency unit; the patients, who received a single dose of metadoxine (300 mg i.v.) and were re-examined at 2 hours experienced a significantly higher improvement on a clinical scale based on somatic and psychological symptoms with respect to the control group; these results seem not to be directly dependent on ethanol blood levels that were lower in the metadoxine group but this parameter reached statistical significance in only one trial. (43,44). In a double-blind controlled clinical trial versus placebo, our group has recently studied the effect of a single intravenous injection of metadoxine (900 mg) on acute alcohol intoxication: clinical symptoms decreased more rapidly in the metadoxine group (table 1) and the recovery from intoxication began after a median time of 0.95 hours with metadoxine and 2.34 hours with placebo (figure 3); the proportion of completely symptom-free patients was significantly higher after treatment with metadoxine in comparison with standard treatment alone; once again, these results seem not only related to ethanol blood level but also may be related to the effects of metadoxine on the CNS (45).

Withdrawal syndrome

In a double blind controlled clinical trial, Bono has demonstrated the efficacy of metadoxine in the treatment of the alcohol withdrawal syndrome. In two groups treated with bromazepam as needed and either metadoxine (900 mg i.v. bid) or pyridoxine in an equivalent dose for ten days, the metadoxine group showed a significantly higher decrease rate of somatic and psychological signs and symptoms and a significantly lower need for benzodiazepine compared to the control group (46).

CHRONIC ALCOHOL ABUSE AND ALCOHOLISM

Maintaining abstinence

In chronic alcohol abuse and alcoholism Metadoxine has been studied with respect to its ability to induce alcohol abstinence through a possible reduction in craving and to ameliorate the clinical features of alcoholism and the laboratory alterations and histopathological signs of chronic alcohol assumption. In two double-blind clinical trial versus placebo metadoxine has been shown to improve the maintenance of abstinence and to reduce alcohol intake and the requirement of benzodiazepine and/or neuroleptics (47,48). In chronic alcoholics metadoxine is thus hypothesized to induce a reduction of the craving for alcohol (47,49). However future studies

are needed to confirm these findings and clarify the possible anti-craving mechanisms.

Symptoms and laboratory parameters

The combination of pyridoxine-pyrrolidon-carboxylate with benzodiazepine in alcohol abusers has been shown to restore the clinical picture with a significant improve of anxiety, mood and thinking disorders, of the sleep/awake rhythm and of the dietary pattern with respect to benzodiazepine treatment alone (50-51). Metadoxine alone has also been shown to reduce the Munich Alcoholism Test 1 and 2 score and to improve insomnia, anxiety and mood disorders versus placebo in double-blind trials (47,48).

In abstinent alcoholics, Sinforiani demonstrated that metadoxine is able to induce a more marked improvement in cognitive functions and tests exploring short-term memory after one month of treatment than a conventional Vit B6 treatment (52).

Several studies have shown the ability of metadoxine to reduce indices of liver cells necrosis (AST and ALT), cholestasis indices (gammaGT and bilirubin) and/or haematologic disorders (MCV) in double-blind trials versus placebo (34,47,53,54) (table 2), versus Vit B6 (56) and versus Tiapride (57). One study reported a non-significant improvement of these indices with respect to placebo (58).

Imaging and histology

Two months of Metadoxine administration seems to be able to reduce sonographic evidence of hepatocyte fat accumulation in alcoholic fatty liver (59). Cacciatore and collegues (60) studied the histological effect of 2 months of metadoxine treatment (600 mg i.m.) in alcoholic fatty liver alone and associated with cirrhosis, showing the disappearance of hepatic abnormal fat content from all patients affected by fatty liver and from the majority of those affected by cirrhosis. These studies have been confirmed in a recent randomized double-blind placebo-control trial on 136 chronic active alcoholic patients affected by fatty liver. After three months of treatment (1500 mg die/os) the percentage of patients with ultrasonographic signs of steatosis was significantly lower in the metadoxine group compared to placebo (55).

Safety

In all the studies examined in this review only three minor adverse drug reactions to metadoxine have been reported: a case of moderate intensity skin rash appearing two hours after metadoxine administration (45), a non-specified gastrointestinal problem that the authors did not relate in a causal manner to the drug (54) and a self-limiting case of diarrhoea (55).

CONCLUSIONS

In the last few years metadoxine has demonstrated a number of effective actions in modifying alcohol metabolism, in reducing toxic effect of acute and chronic abuse of alcohol and in breaking the addiction to ethanol.

Due to its safe and manageable pharmacology profile, Metadoxine could be one of the first drugs for physicians who deal with patients with alcohol problems, especially in the acute setting of the Emergency Unit, where it makes it possible to accelerate clinical and metabolic recovery from intoxication, with a single administration and without any additional workload for the treatment centre.

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