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Metadoxine in Acute Alcohol Intoxication: A Double-Blind, Randomized, Placebo-Controlled Study

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Background: At present there are only intriguing and preliminary clinical results regarding the efficacy of metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) in acute alcohol intoxication. The present study was planned with the aim of investigating the effectiveness of metadoxine in the management of patients affected by acute ethanol intoxication.

Methods: A double-blind, randomized, multicenter, placebo-controlled trial was carried out on 58 patients of both sexes with acute ethanol intoxication. Patients were treated with a single dose of 900-mg intravenous metadoxine ($n = 29$) or with placebo ($n = 29$). Patients were clinically and biochemically evaluated at 0.5, 1, 2, 3, 6, 9, and 12 hr after treatment.

Results: Treatment with metadoxine significantly decreased the half-life of ethanol in blood (from 6.70 $\pm$ 1.84 to 5.41 $\pm$ 1.99 hr; $p < 0.013$) and showed a faster rate of ethanol elimination. The effects on ethanol half-life in blood were accompanied by a faster onset of recovery from intoxication, defined as the time of the transition of blood ethanol levels to the immediately lower range defined by intoxication categories (in g/liter: 0 to 0.5, absent; 0.51 to 1.0, mild; 1.1 to 2.5, moderate; >2.5, severe). Thus the median time to onset of recovery was 0.95 hr with metadoxine and 2.34 hr with placebo ($p = 0.013$). The effects of treatment on blood alcohol levels were paralleled by a significant decrease in the rating of the toxic clinical symptomatology. At 2 hr the improvement of toxic symptoms (in percent of maximum possible) was 68 $\pm$ 28 vs. 44 $\pm$ 27% in controls ($p < 0.002$).

Conclusions: In patients with acute ethanol intoxication metadoxine accelerated the elimination of ethanol from blood, which led to faster recovery from intoxication, and improved the behavioral toxic symptomatology. Metadoxine could be helpful in the management of acute ethanol intoxication.

Key Words: Metadoxine, Acute Alcohol Intoxication, Treatment, Ethanol Half-Life, Ethanol Elimination.

ACUTE ETHANOL INTOXICATION is a common admission cause in emergency rooms. The treatment is mainly directed toward correcting the possible acid-basic or electrolytic disorders, as well as hypoglycemia and hypovitaminosis, and ensuring adequate respiratory functions. On the other hand, the limiting step that conditions the time required for full recovery of the patient is the elimination of ethanol from blood. Therefore, an increase in the elimination rate of ethanol will conceivably accelerate the recovery of patients from intoxication and reduce the need for nursing. Clinical observations in patients with acute ethanol intoxication suggest that metadoxine may be capable of decreasing ethanol blood levels by accelerating the urinary elimination of ethanol and acetaldehyde (Pellegrini-Giampietro et al., 1989).

Metadoxine (pyridoxol L-2-pyrrolidone-5-carboxylate) is the ion-pair between pyrrolidone carboxylate and pyridoxine. Pyridoxol plays a role in a number of metabolic reactions, including several metabolic transformations of amino acids such as decarboxylation, transamination, and racemization (Oka, 1999).

As regards ethanol metabolism, pyridoxine increases the metabolic degradation rate of ethanol, thereby reducing the damage to cell functions caused by acetaldehyde, the first metabolite in the ethanol elimination process (Wordsworth, 1953).

Pyrrolidone carboxylate is involved in amino acid metabolism through the glutathione pathway, and has been proposed as a primer of protective coenzymes (Meister and Anderson, 1983; van der Werf and Meister, 1975). Pyrrolidone carboxylate also facilitates de novo ATP synthesis (Shull and Kisilevsky, 1971), an effect that may improve cell recovery after ethanol intoxication. Moreover, metadoxine has been shown to prevent a decrease in ATP both in the brain and liver of rats acutely intoxicated with ethanol (Felicioli et al., 1980). The combination of the reported effects of pyridoxol and of L-2-pyrrolidone-5-carboxylate

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has been considered fundamental in explaining the beneficial effects of metadoxine in the recovery from alcoholic liver disease after ethanol withdrawal (Caballería et al., 1998).

On the other hand, metadoxine has been shown to accelerate ethanol metabolism in rats and humans by increasing ethanol and acetaldehyde plasma clearance and the urinary elimination of ketones, which are formed when the oxidation rate of acetaldehyde into acetate is exceeded on massive alcohol intoxication (Calabrese et al., 1986; Inturri et al., 1994; Pellegrini-Giampietro et al., 1989). Indeed, the administration of metadoxine in patients with acute alcohol intoxication significantly shortened the plasma half-life of ethanol (Pellegrini-Giampietro et al., 1989). Similar results were obtained in 11 healthy male volunteers in whom metadoxine administration induced a significant decrease in blood levels of alcohol after an oral loading dose of ethanol (Di Ilio et al., 1982). However, the small number of subjects involved and/or the methodological limitations do not at present make it possible to draw definitive conclusions on the effectiveness of the drug in the management of acute alcohol intoxication.

The aim of the present study was, therefore, to confirm the effect of metadoxine on ethanol elimination rate and evaluate whether it modifies the time course of the intoxication symptoms in a double-blind, placebo-controlled, randomized clinical trial.

Table 1. Characteristics of the Patients on Inclusion in the Study

	Metadoxine (n = 29)	Placebo (n = 29)	p
Age (years)	39.4 ± 11.8[a]	37.9 ± 10.3[a]	NS
Sex (male/female)	25/4	26/3	NS
Systolic ABP (mm Hg)	135.8 ± 12.6	132.4 ± 12.4	NS
Diastolic ABP (mm Hg)	86.9 ± 10.6	83.1 ± 11.7	NS
Heart rate (beats/min)	94.0 ± 12.9	87.8 ± 12.0	NS
Blood alcohol (g/liter)	1.88 ± 0.60	1.74 ± 0.43	NS
Blood acetaldehyde (mMol/liter)	66.2 ± 12.2	62.1 ± 21.1	NS
Blood ketones (mMol/liter)	158.2 ± 61.9	157.1 ± 47.9	NS
Urine alcohol (mMol/liter)	8.3 ± 4.3	8.9 ± 3.9	NS
Urine acetaldehyde (mMol/liter)	14.2 ± 5.1	13.4 ± 5.1	NS
Urine ketones (mMol/liter)	117.6 ± 39.1	137.9 ± 51.0	NS

Values are means ± SD.
[a] Indicates that one value is missing.

Table 2. Intensity of Intoxication Symptoms on Entry

Variable		Metadoxine	Placebo	t (U test)
Agitation	Mean ± SD	1.83 ± 0.80	2.3 ± 0.76	0.022
	Range	0–3	1–3	
Aggressive behavior	Mean ± SD	1.66 ± 0.77	1.7 ± 0.99	0.505
	Range	0–3	0–3	
Mental impairment	Mean ± SD	2.10 ± 0.72	2.62 ± 0.56	0.003
	Range	0–3	1–3	
Jerky movements	Mean ± SD	0.90 ± 0.67	0.90 ± 0.90	0.815
	Range	0–2	0–3	
Toxic symptom score	Mean ± SD	6.48 ± 1.64	7.59 ± 1.55	0.011[a]
	Range	4–10	4–11	
Drowsiness	Mean ± SD	0.38 ± 0.78	0.38 ± 0.62	0.669
	Range	0–3	0–2	
Total symptom score	Mean ± SD	6.86 ± 1.53	7.97 ± 1.30	0.004[a]
	Range	5–10	5–11	

[a] t test (variances homogeneous). Total symptom score results from all variables, including drowsiness.

PATIENTS AND METHODS

The study was carried out in 58 patients of both sexes with clinical signs of acute ethanol intoxication. Two Russian Centers (the Narcological County Dispensary of St. Petersburg and the Scientific Center for Psychiatry and Narcology of Moscow) were involved in this study. A total of 39 patients were enrolled in the St. Petersburg Center and 19 patients were enrolled in the Moscow Center.

Before the study onset, the main investigators and coinvestigators underwent training to assess and standardize the clinical rating of ethanol intoxication. A single coinvestigator for each center performed the clinical rating of ethanol intoxication according to the case report from specific recommendations. Clinical-rate blinding was ensured by the study design.

The inclusion criteria were: age between 18 and 61 years, alcohol blood concentration greater than 1 g/liter, and clinical evidence of acute ethanol intoxication (at least two of the following symptoms: agitation, aggressive behavior, mental impairment, drowsiness, and jerky movements). The exclusion criteria were: confirmed or suspected pregnancy or breast feeding in female subjects; severe liver, kidney, or heart disease; poly-drug addiction; oliguria or anuria; unconsciousness; evidence of gastrointestinal bleeding; or need for supportive treatment beside the standard glucose and bicarbonate solutions.

On entry onto the study, differences in demographic variables, vital signs, and objective alcohol intoxication symptoms were not statistically significant between the metadoxine and placebo groups (Table 1). In addition, the weight and height of the patients, the number of individuals with history of allergic diseases or reaction to drugs, and the number of current smokers and/or coffee or tea consumers, were similar in the two groups. On the other hand, patients assigned to the placebo group by randomization showed a significantly greater intensity of agitation and mental impairment—and consequently of toxic and total symptom score on entry—in comparison with those assigned to metadoxine (Table 2).

The study was approved by the Ethics Committee of each hospital involved and all patients gave written informed consent to the study either personally or, if unable to provide reasonably free and informed consent, through a relative, caregiver, or legal representative.

The study was conducted with a randomized, double-blind, placebo-controlled design. A random code (predetermined randomization design in blocks of four) was distributed to each participating center. Metadoxine was given as a single 900-mg dose (three commercially available ampoules) by bolus intravenous infusion. Placebo was prepared as matching ampoules that contained saline for intravenous use, colored with pyridoxine to match the test medication. Starting from the end of bolus injection, all patients also received a standard basic treatment consisting of an intravenous infusion of 250 ml of 5% glucose solution and 250 ml of 1.7‰ sodium bicarbonate solution, over a period ranging from 30 to 60 min.

Blood and urine samples were collected immediately before injection (baseline) and 0.5, 1, 2, 3, 6, 9, and 12 hr after injection for the determination of ethanol, acetaldehyde, and ketone concentrations. At the same time points, the intensity of toxic symptoms (agitation, aggressive behavior, mental impairment, and jerky movements) and drowsiness were recorded and rated as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe). Vital signs (systolic and diastolic blood pressure and heart rate) were also monitored.

To complement the clinical observation of possible adverse events, laboratory tests were performed before treatment and on discharge of the patient, 12 hr after injection. These included hemoglobin, erythrocyte count, blood urea nitrogen, serum creatinine, blood glucose, erythrocyte sedimentation rate (ESR), and urinalysis.

The rate of alcohol elimination from the blood was the primary endpoint, on which the sample size had been computed. Ethanol elimination under acute intoxication follows a first-order kinetics, yielding a half-life that can immediately be computed from experimental data without any

additional modeling, computed from the $-[\ln(2)/\text{slope}]$, where the slope is obtained by minimization of the ln(concentration) versus time relationship. In sufficiently large samples, the standard deviation of elimination half-life is approximately 30% of the mean; the target difference between control and treated subjects is the one reported in the literature, approximately 20%. However, given the number of measured points, which allows a very accurate calculation of the elimination half-life, it is estimated that in this study differences in half-life of at least 25% should be considered clinically relevant. Thus, the hypothesis to be rejected, with risk of α error ≤ 0.05 and of β error ≤ 0.20 (power $\geq 80\%$), is: H_0: $\mu_{control} = \mu_{treated}$ when $\mu_{treated} \leq 0.75 \cdot \mu_{control}$, using a two-tailed parametric test (t test or analysis of variance ANOVA). The condition $\sigma/\mu = (0.30/0.25) = 0.83$ yields a minimal number of 26 cases per group. The statistical analysis was anticipated in principle to compare the ethanol elimination half-life as indicated, but also to compare the changes in category as indicated below, using the uncorrected χ^2 test, integrated with the relative risk analysis. The time course of concentrations and symptoms was investigated with the repeated-measures ANOVA (using the statistics regardless of the assumption of sphericity if appropriate); summary measures were compared with the t test or ANOVA, using the statistics independent of the equality of variances where appropriate. Additional procedures were used, as available in the program SPSS version 10.0 (SPSS, Inc., Chicago, IL) for Windows, and are discussed where appropriate.

To monitor clinical efficacy, we considered the changes occurring in the first hour after injection, and considered all those patients who showed a decrease in the total intoxication symptom score by 2 points or more (out of a maximum of 12 points, or approximately 20% of the maximum possible) as having initiated clinical recovery ("success"). Unless otherwise stated, all values are means ± standard deviation. The severity of ethanol intoxication was also classified on the basis of ethanol concentrations in the blood, according to the classical categories, defining 0 to 0.5 g/liter as no intoxication; 0.51 to 1.0 g/liter as mild intoxication; 1.1 to 2.5 g/liter as moderate intoxication; and above 2.5 g/liter as severe intoxication (Benowitz, 1992). Moving down by at least one category in the first hour of observation was considered as "initial detoxification" ("success"). These classifications, therefore, made it possible to build a table on which concordance could be properly assessed between ethanol blood concentration decrease and symptom relief, separately for the specific toxic symptoms and the more general symptoms.

RESULTS

Figure 1A illustrates the significant difference in the time course of the ethanol concentration in the blood between the metadoxine and placebo groups at the repeated-measures analysis ($p = 0.030$, repeated-measures ANOVA, homogeneity of variances not assumed). The regression analysis (Fig. 1B) of ethanol blood concentrations versus log of time lapse from treatment administration yielded a significantly different first-order elimination coefficient between groups (0.150 ± 0.069 for metadoxine-treated patients vs. 0.112 ± 0.032 for placebo-treated patients; $p = 0.008$) and a significantly different elimination half-life (5.41 ± 1.99 hr for metadoxine-treated patients vs. 6.70 ± 1.84 hr for placebo-treated patients; $p = 0.013$).

The administration of metadoxine significantly increased the proportion of patients initiating recovery within 1 hr of intoxication. Thus, the faster ethanol elimination also resulted in a reduction, by approximately 60%, of the median time needed to attain a decrease of ethanol blood concentration by at least one intoxication category.

The shorter elimination half-life of ethanol with metadoxine also resulted in a faster onset of recovery from intoxication. Initial recovery, defined as the decrease by at least one category of intoxication according to alcohol levels, occurred within 1 hr in 18 of 29 patients [62.1%; 95% confidence interval (CI): 43 to 79%] treated with metadoxine and in 5 of 29 patients (17.2%; 95% CI: 6 to 37%) given placebo ($p < 0.005$). Recovery from intoxication began after a median time of 0.95 hr with metadoxine, and of 2.34 hr with placebo ($p = 0.013$; Wilcoxon test on life-table analysis data). One hour after treatment, the difference of 44.8 ± 11.4 percentage points (95% CI: 22 to 67%) is statistically significant ($p = 0.0013$), yielding a number needed to treat (NNT) of 2 (95% CI: 1 to 5) (Fig. 2).

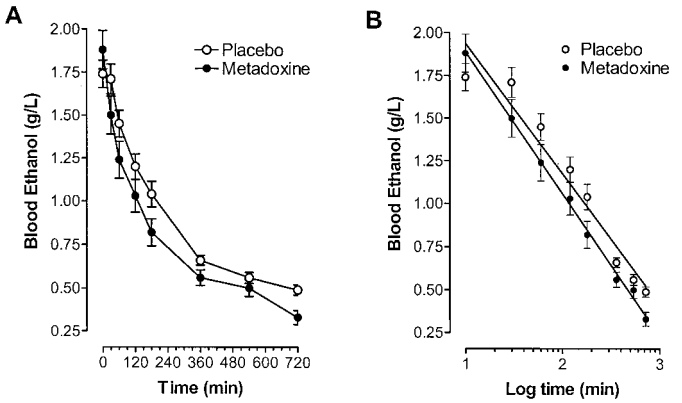

Fig. 1. Time course of ethanol concentration in blood after treatment with metadoxine or placebo during acute alcohol intoxication. (A) Mean alcohol concentrations as a function of time are shown on a linear scale. The time course of alcohol levels in blood is significantly different between groups (ANOVA; $p = 0.03$). (B) Mean concentrations on a logarithm scale of time and the corresponding linear regression lines. The elimination half-life is also significantly shorter with metadoxine ($p = 0.013$). In (A) and (B), data are expressed as mean ± standard error of the mean.

The effects of metadoxine on blood ethanol levels were accompanied by relief of the toxic behavioral symptomatology. Among the recorded parameters, agitation and mental function impairment scores decreased significantly faster in metadoxine-treated patients than in controls. Aggressive behavior also decreased, though not significantly, whereas jerky movements were not affected by the treatment (Table 3).

Overall the time course of toxic symptomatology curves for metadoxine- and placebo-treated patients was similar to those shown in Fig. 1 for alcohol levels. Nevertheless, for a more accurate and conservative analysis of time courses based on intoxication scores, values at all times were normalized to the maximal possible improvement in each patient to account for the differences in alcohol levels on entry. When normalized to the initial score recorded on entry, the time course of toxic behavioral symptoms showed a significantly faster recovery in metadoxine-treated patients than in controls ($p = 0.011$) (Fig. 3). Thus, the improvement of toxic symptoms (expressed as a percentage of the maximal possible improvement) at 2 hr after metadoxine was 68 ± 28 vs. 44 ± 27 in controls ($p < 0.002$).

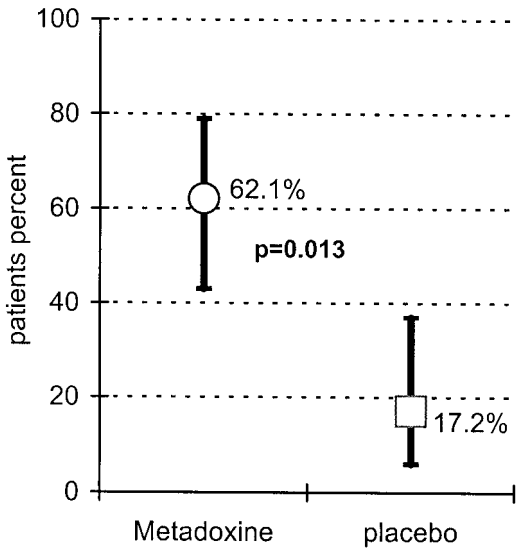

Fig. 2. Proportion of patients who started to recover (decrease of blood alcohol concentration by at least one category) from acute alcohol intoxication within 1 hr after treatment with metadoxine or placebo. With metadoxine the proportion was 62.1% (95% CI: 43 to 79%); with placebo it was 17.2% (95% 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%), yielding a NNT of 2 (95% CI: 1 to 5).

More than 85% of the patients showed a full recovery from behavioral symptomatology within 12 hr, regardless of the treatment. However, the number of symptom-free patients was significantly higher at all intermediate times of observation (Fig. 4). Thus, the proportion of clinically improved patients (total score decreased by ≥25% of the maximal possible improvement) 1 hr after metadoxine was significantly ($p < 0.02$) higher (15 of 29 patients; incidence 51.7%; 95% CI: 33 to 77%) than in control patients (6 of 29 patients; 20.7%; 95% CI: 8 to 40%; $p = 0.014$). In both groups of patients, the scores of drowsiness were significantly higher ($p < 0.001$) at 12 hr of observation compared with those recorded on entry (1.93 ± 1.18 vs. 0.38 ± 0.62 in controls, 1.76 ± 1.12 vs. 0.38 ± 0.78 in the metadoxine group).

The similarity of response on alcohol elimination and symptom relief may raise the question of whether these two effects are correlated, especially whether faster alcohol elimination also results in faster symptom relief. To test whether these effects were correlated, we analyzed the proportion of success as defined from blood alcohol levels, and as defined from toxic symptom relief using the Cohen's concordance analysis. No apparent correlation was detected between the two measures of success among metadoxine-treated patients (Cohen's $\kappa = 0.182 \pm 0.178$; $p = 0.316$). Indeed, the majority of patients (58%) yielded contrasting results when success was measured according to alcohol level or total toxic symptom score.

The secondary endpoints of the present study included the analysis of the time course of acetaldehyde and ketones in the blood, and the time course of ethanol, acetaldehyde, and ketones in the urine. There were no differences between treatment groups in relation to any of these variables, with the exception of a slightly smaller area under the curve (AUC) of alcohol in the urine among metadoxine-treated patients compared to the placebo group (54.6 ± 11.5 vs. 60.4 ± 8.5 $mMol \cdot h \cdot L^{-1}$; $p = 0.047$, two-tailed unpaired t test).

Laboratory data recorded before treatment and at the end of the observation indicated a significant decrease in hemoglobin, blood urea, and blood glucose, and a significant increase in ESR, with metadoxine. Among placebo-treated patients, erythrocytes decreased significantly and ESR increased significantly. Blood urea nitrogen decreased in the metadoxine group only, and the extent of the decrease was borderline to significance in comparison with the placebo group (−2.7 ± 6.3 mg/dL vs. +1.2 ± 6.4 mg/dL; $p = 0.055$). Blood glucose also decreased significantly after metadoxine only, and the extent of the decrease was significantly greater than that observed after placebo (−0.91 ± 1.45 mMol/liter vs. −0.02 ± 1.17 mMol/liter; $p = 0.013$). There were no abnormalities recorded on urinalysis. Small decreases in systolic pressure and heart rate occurred in both groups.

The only possibly drug-related adverse event observed was one case of skin rash appearing 2 hr after metadoxine administration. The event was of moderate intensity, and subsided within 4 days, after treatment with a topical antihistamine and steroids.

DISCUSSION

This double-blind, placebo-controlled study demonstrates that metadoxine accelerates ethanol elimination from the blood of patients with acute alcoholic intoxication. The acceleration of ethanol metabolism was associated with a more rapid regression of the clinical symptoms in the metadoxine group, during the first hr after treatment, compared with the placebo group. As a consequence, the time needed for 50% of the patients to become symptom-free was approximately 5 hr in the metadoxine and 8 hr in the placebo group. Our findings showed that metadoxine exerts favorable effects in acute alcohol intoxication by increasing alcohol clearance and relieving intoxication symptoms. However, these effects were not dependent on each other, but rather were concurrent and coordinate.

The observed half-life values of blood ethanol are fully consistent with those already reported in a pilot study (Pellegrini-Giampietro et al., 1989). At variance with other investigators (Calabrese et al., 1986), however, in the present study we did not find in the metadoxine group a significant modification of plasma AUC of ethanol, of the plasma profile of acetaldehyde and ketones, and of their urinary excretion.

This may be explained by the large variability of our sample with regard to initial intoxication levels, and the time lag between drinking and recovery in the treatment center, as usually occurs in practice. The small difference in

Table 3. Time Course of Individual Symptom Intensity (Mean ± SD) During Observation

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	1.66 ± 0.77	1.76 ± 0.99
	0.5	1.55 ± 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	

urine ethanol AUC, slightly greater among placebo-treated subjects, may be related to the different degrees of intoxication severity, or may be considered an indication of faster alcohol metabolism among metadoxine-treated patients. Nevertheless, this study does not fully support the interpretation advanced by other authors (Calabrese et al., 1986; Pellegrini-Giampietro et al., 1989), i.e., that the faster elimination of alcohol from the blood due to metadoxine treatment can be completely explained by increased alcohol biotransformation, mainly to higher ketones.

The effects of metadoxine on clinical symptoms cannot be explained by the accelerated removal of alcohol from the blood alone. At variance with previous investigations that attributed the effects of metadoxine exclusively to the removal of alcohol from the blood, in our study it is apparent that the effect on alcohol elimination and the effect on clinical symptom relief are concurrent, but at least partially independent.

This suggests that the improvement of behavioral symptomatology may be related to the direct effect of metadoxine on the central nervous system, in addition to its metabolic effects. In agreement with this hypothesis, metadoxine antagonizes the locomotor-stimulatory effect of ethanol in mice by an action that differs from the acceleration of ethanol excretion (Garau et al., 1992).

In conclusion, in agreement with a series of independent studies carried out over a period of more than 10 years (Calabrese et al., 1986; Di Ilio et al., 1982; Pellegrini-Giampietro et al., 1989), the present investigation confirmed that metadoxine significantly accelerates recovery

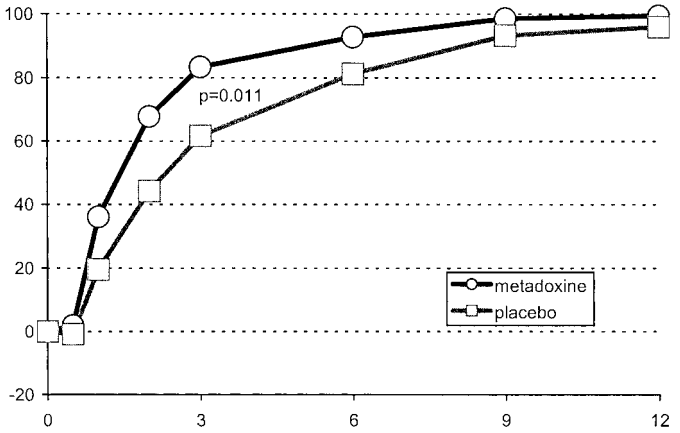

Fig. 3. Time course of improvement expressed as maximal improvement possible in relation to the baseline intensity of the toxic symptoms.

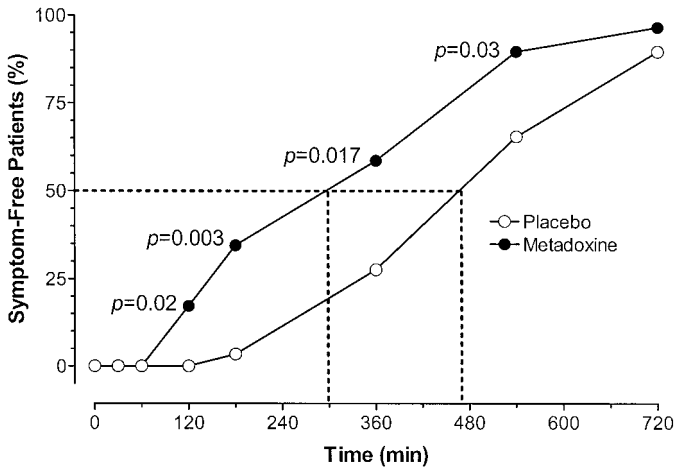

Fig. 4. Time course of the proportion of patients free from toxic symptoms after administration of metadoxine or placebo. Broken lines indicate the time at which 50% of the patients in each group were symptom free; p values (χ^2 comparison) are reported when the difference between groups is statistically significant.

from acute ethanol intoxication. At the same time, as already reported in other studies (Bono et al., 1991; Laprevote-Heully and Larcan, 1981), the clinical symptoms of alcohol intoxication decreased more rapidly with metadoxine, and the proportion of completely symptom-free patients was significantly greater after treatment with metadoxine, compared with standard treatment alone. Finally, as previously reported (Caballeria et al., 1998), treatment with metadoxine was not only effective in determining a recovery of fatty liver, but also did not cause any serious adverse effect. In addition, vital signs and laboratory tests were not negatively affected by metadoxine. The changes in hemoglobin, erythrocytes, and ESR can also be explained by the modifications induced by hydration (the infusion administered to all subjects) and by blood withdrawal (8 samples in 12 hr overall). Of greater relevance, instead, was the decrease of blood urea, nitrogen, and blood glucose.

The blood urea, nitrogen, and glucose decreases are strictly related to the alcohol intoxication; their greater decrease with metadoxine confirms the marked detoxicating effect already detected and reported previously.

The inclusion of a single intravenous injection of metadoxine in the protocol for the management of acute intoxication therefore makes it possible to accelerate clinical and metabolic recovery from intoxication, without any additional workload for the treatment center. Moreover, because no side effects occurred in treated patients, the drug seems to be safe. Taking into account the quick reduction of the alcohol-intoxication–related symptoms together with the need to reduce inpatient time (and also from a cost-effective point of view), the present results suggest the appropriateness of metadoxine administration in clinical practice during acute alcohol intoxication.

However, due to some limits of the study, interpretation of the results requires caution before definitive conclusions can be reached. In particular, the patients assigned to the placebo group showed a significantly higher intensity of some intoxication scores (i.e., agitation and impaired mental function) on study entry. This, however, is related to the randomized, double-blind, placebo-controlled design. Nevertheless, for a more accurate and conservative analysis of the time courses based on intoxication scores, values at all times were normalized to the maximal possible improvement in each patient to account for the differences in alcohol level on entry. Finally, the number of patients enrolled in the study was too small to provide a definitive conclusion on the safety of metadoxine in acute alcohol intoxication.

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