

# Efficacy of Metadoxine in the Management of Acute Alcohol Intoxication

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This randomized, open-label study evaluated the efficacy of 300 mg metadoxine (given intravenously) added to standard treatment compared with standard treatment alone in managing the physical and psychological signs of acute alcohol intoxication. Fifty-two acutely intoxicated patients were randomly assigned to one of two groups and followed during a 2-h period. Changes in clinical symptoms, degree of intoxication, and blood alcohol level were monitored. More patients receiving metadoxine in addition to standard therapy significantly improved by at least one degree of intoxication (one

clinical category) compared with those receiving standard treatment alone (76.9% versus 42.3%, respectively). Metadoxine-treated patients also exhibited a significantly greater decrease in blood alcohol concentration compared with those receiving standard treatment alone ( $-105.4 \pm 61.5$  mg/dl versus  $-60.1 \pm 38.6$  mg/dl, respectively). Metadoxine improved the clinical signs of acute alcohol intoxication and accelerated alcohol clearance from the blood, thus supporting existing data. In contrast to previous data, these effects were concurrent but independent. No adverse effects were observed with metadoxine therapy.

**KEY WORDS: METADOXINE; ALCOHOL INTOXICATION; ACUTE TREATMENT; RANDOMIZED, CONTROLLED TRIAL**

## Introduction

The World Health Organization (WHO) estimates that 140 million people worldwide suffer from alcohol dependency, causing damage to lives and economies.<sup>1</sup> In Europe, approximately one in four deaths among men aged 15 – 29 is alcohol-related.<sup>1</sup> People with acute alcohol intoxication are often encountered in hospital emergency departments,<sup>2,3</sup> and the burden placed on

emergency and out-patient services by this patient group is enormous.<sup>4,5</sup> Although acute intoxication is not the main cause of alcohol-related deaths, it is the major factor contributing to premature death.<sup>6</sup>

Patients with acute intoxication require an integrated approach to detoxification. On admission to the hospital, clinical symptoms caused by acute intoxication must be controlled immediately. At the Toxicological Unit Xochimilco, parenteral solutions,

multi-vitamin preparations, benzodiazepines or neuroleptics may be used in accordance with the established protocols as the initial standard treatment of these patients.

Metadoxine – a new preparation to facilitate the relief of acute symptoms that is now available in Mexico – is an ion-pair consisting of pyridoxine with pyrrolidone carboxylate.<sup>7–9</sup> Some researchers have suggested that the effect of metadoxine is solely attributed to the accelerated biotransformation of alcohol into less harmful compounds, mainly rapidly eliminated higher ketones, resulting in more rapid lowering of alcohol and acetaldehyde concentration in blood and tissues.<sup>10</sup> These studies, however, did not include simultaneous monitoring of alcohol levels and signs of intoxication in the same patients; instead, alcohol levels were evaluated in volunteers and signs of intoxication were assessed in patients.

In contrast, animal pharmacology data suggest that metadoxine may have direct effects on the central nervous system (CNS) that are independent of any effect on alcohol metabolism.<sup>11–13</sup>

The present study was designed to investigate the acute effects of a single dose of metadoxine in patients presenting with clinical signs of alcohol intoxication. Degree of intoxication and blood alcohol concentration were monitored in each patient. This approach was expected to provide direct evidence on whether the overall clinical outcome with metadoxine is due solely to a metabolic effect, or whether direct effects on the CNS play an independent role.

## Patients and methods

### PATIENTS AND STUDY DESIGN

This open-label, add-on, randomized, controlled trial recruited consecutive patients presenting with clinical signs of alcohol

intoxication diagnosed according to the DSM-IV criteria. The study allowed for immediate intervention in case of emergency. Men and women aged 18 – 65 years were enrolled, provided that a legally acceptable representative was present to issue the written, informed consent. Patients with multiple intoxications, intoxication by drug abuse or alcohol other than ethanol, acute organic disorders, patients under anti-coagulant treatment, and pregnant or lactating women were excluded from the trial.

The study protocol and consent procedure were in compliance with the Declaration of Helsinki (Somerset West revision) and were approved by the hospital ethics committee.

### TREATMENT

Blood alcohol concentrations were measured immediately after classification of the clinical intoxication level, physical examination and assessment of patient history of alcohol use. Patients were then randomized to receive either conventional (standard) treatment with parenteral solutions, multi-vitamin preparations, benzodiazepines or neuroleptics, or one dose of 300 mg metadoxine, intravenously, with or without the standard treatment. This dose could be readministered after 1 h (total 600 mg) if deemed necessary. Additional infusions of saline, isotonic solution, 5% glucose solution, vitamins and non-steroidal anti-inflammatory drugs were permitted for all patients if required. Anti-depressant agents, anti-coagulant agents, or any other medication used to manage acute alcohol intoxication were not permitted during the study.

Blood alcohol concentration was again measured 2 h after treatment initiation, and the degree of intoxication was recorded. Any adverse event occurring during the observation period was noted.

## CLASSIFICATION OF INTOXICATION

The clinical degree of intoxication was classified as: absent (no signs of intoxication); mild (euphoria, loss of motor co-ordination, decreased sensory function, mild confusion); moderate (loss of motor co-ordination, ataxia, behavioural modifications, somnolence, vomiting); and severe (hypothermia, dysarthria, amnesia, alteration of consciousness, coma, respiratory depression). To investigate the correlation between clinical intoxication and blood alcohol level, the following classification was used: no intoxication (0 – 49.9 mg/dl); mild intoxication (50.0 – 100.9 mg/dl); moderate intoxication (101.0 – 250.9 mg/dl); and severe intoxication (251.0 mg/dl and above).

Changes in the clinical category of alcohol intoxication were used to monitor the clinical efficacy of metadoxine, and to investigate any correlation with clinical improvement using the measure of agreement. The absolute change in blood alcohol concentration over the 2-h study period was used to monitor the extent of alcohol clearance from the blood. Decrease in blood alcohol concentration during the 2-h treatment period was assessed by analysis of variance, using gender and previous history of intoxication as factors, and age, body weight, and alcohol concentration at baseline as covariates.

## STATISTICAL ANALYSIS

Changes in the clinical category of intoxication were analysed with the uncorrected  $\chi^2$  test, integrated with the relative risk analysis. Continuous variables were compared between groups using the unpaired *t*-test and the analysis of variance; all tests were two-tailed.

Based on the existing literature, a clinical success rate (defined as a decrease of at least one degree of clinical intoxication – the

primary endpoint) of 40% was anticipated among the control group, rising to 80% among metadoxine-treated subjects, yielding a minimum sample size of 23 patients per group to achieve 80% power at a significance level of 0.05.<sup>14</sup>

The correlation of improvement in alcohol levels with that of clinical signs was analysed using the measure of agreement ( $\kappa$ ) and the non-parametric correlation procedures of Kendall ( $\tau$ -B) and Spearman ( $\rho$ ).

## Results

### PATIENTS AT STUDY ENTRY

Overall, 52 patients were enrolled and treated between May and July 1999. Patients assigned to the two treatment groups (26 patients per group) showed no statistical difference in clinical parameters at study entry (Table 1), except for a significantly higher degree of clinical intoxication among the metadoxine treatment group ( $P = 0.014$ ).

### TREATMENT

A higher proportion of patients randomized to metadoxine improved by at least one clinical category (one degree) during the 2-h period following treatment initiation in comparison with those randomized to standard treatment (Fig. 1): 76.9% (95% confidence interval [CI], 57%, 90%) for the metadoxine group versus 42.3% (95% CI, 24%, 63%) for the control group ( $P = 0.011$ ). These data do not substantially differ from those used to compute sample size. The addition of metadoxine to standard treatment increased the odds ratio of improving clinical intoxication in 2 h by at least one degree to 2.26 (95% CI, 1.09 – 4.66), yielding a difference in proportion of improved patients of  $34.6 \pm 12.7\%$  (95% CI, 10%, 60%). Thus, the number needed to treat to achieve one additional degree of

**TABLE 1:**  
Description of patient parameters at study entry

Variable		Control group	Metadoxine group
Gender (male/female)	<i>n</i> (%)	17/9 (65.4/34.6)	19/7 (79.1/26.9)
Age (years)	Mean ± SD (range)	34.3 ± 8.2 (25 – 56)	33.2 ± 9.2 (20 – 62)
Weight (kg)	Mean ± SD (range)	70.5 ± 14.6 (53 – 124)	71.7 ± 12.6 (48 – 97)
Systolic BP (mmHg)	Mean ± SD	113.8 ± 12.5	117.9 ± 15.9 <sup>a</sup>
Diastolic BP (mmHg)	Mean ± SD	75.4 ± 8.9	78.1 ± 10.9 <sup>a</sup>
Hypotension on entry	<i>n</i> (%)	1 (3.8)	1 (3.8)
Heart rate (beats per min)	Mean ± SD	79.6 ± 6.8	77.4 ± 8.8 <sup>b</sup>
Respiratory rate (per min)	Mean ± SD	20.6 ± 2.3	21.3 ± 2.6 <sup>b</sup>
History of previous intoxication	<i>n</i> (%)	15 (57.7)	21 (80.8)
Conscience, disoriented/stupor	<i>n</i> (%)	1/0 (3.8/0)	3/1 (12.0/4.0) <sup>a</sup>
Clinical intoxication (mild/moderate/severe <sup>c</sup> )	<i>n</i> (%)	14/11/1 (53.8/42.3/3.8)	4/20/2 (15.4/76.9/7.7)
Blood alcohol concentration (mg/dl)	Mean ± SD (range)	154.5 ± 75.2 (8.5 – 260.5)	188.8 ± 72.5 (57.4 – 357.1)
Alcohol intoxication level (absent/mild/moderate/severe)	<i>n</i> (%)	3/4/17/2 (11.5/15.4/65.4/7.7)	0/4/17/5 (0/15.4/65.4/19.2)

<sup>a</sup>One patient missing.

<sup>b</sup>Two patients missing.

<sup>c</sup> $P = 0.014$ ;  $\chi^2$  test.

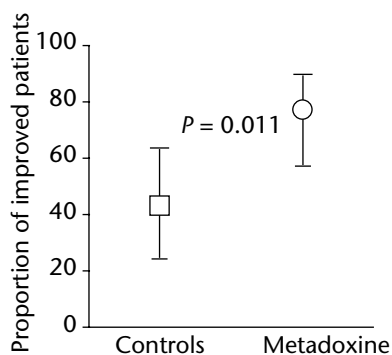
clinical improvement over a 2-h period was just three (95% CI, 2 – 10).

Three subjects from the control group were excluded from alcoholometric analysis since their blood alcohol levels on study entry were below 50 mg/dl, and as a consequence they would not have been able to exhibit a measurable improvement in alcoholometric intoxication following treatment.

Metadoxine-treated patients exhibited significantly greater improvements in degree of intoxication than those randomized to conventional treatment ( $P = 0.044$ , Table 2); the patients receiving metadoxine exhibited a significantly greater decrease in blood alcohol concentration over the 2-h period:

–105.4 ± 61.5 mg/dl with metadoxine versus –60.1 ± 38.6 mg/dl among controls ( $P = 0.003$ ), with a difference of 45.3 ± 14.2 mg/dl (95% CI, 16.7, 74.0 mg/dl) between the treatment groups (Fig. 2). Metadoxine therapy in our sample was effective regardless of previous history of intoxication and regardless of patient gender, age, body weight and blood alcohol concentration at study entry. The only factor significantly affecting the decrease in alcohol concentration was the treatment applied ( $P = 0.011$ ).

From the baseline classification of the clinical degree of intoxication, the maximum possible improvement among control patients was 39 degrees, whereas the



**FIGURE 1:** Proportion ( $\pm$  95% confidence interval) of patients with acute alcohol intoxication showing clinical improvement of at least one intoxication degree during the 2-h observation period under conventional treatment (controls) or after treatment with a single 300 mg metadoxine dose, intravenously

actual monitored improvement was 11, or 28.2% (95% CI, 15%, 45%). Among those treated with metadoxine, the maximum possible improvement was 50 degrees, with the actual monitored improvement being 32, or 64% (95% CI, 49%, 77%) (Fig. 3). The difference between the treatment groups of  $35.8 \pm 9.9\%$  (95% CI, 61%, 55%) is statistically significant ( $P = 0.002$ ).

The analysis of improvement, expressed as

a percentage of the initial clinical severity of the intoxication, demonstrated similar results. Metadoxine-treated patients exhibited an average improvement of  $60.9 \pm 40.0\%$ . This value was significantly higher ( $P = 0.002$ ) than that obtained with conventional treatment alone ( $26.3 \pm 35.0\%$ ), with a mean difference in improvement between the treatment groups of  $34.6 \pm 10.4\%$  (95% CI, 14 – 56%). The correlation between improvement in alcohol levels and clinical classification was analysed in metadoxine-treated patients, but none of the statistical tests used yielded significant results (Table 3).

The administration of 300 mg metadoxine as a single intravenous bolus injection was not associated with detectable adverse events.

## Discussion

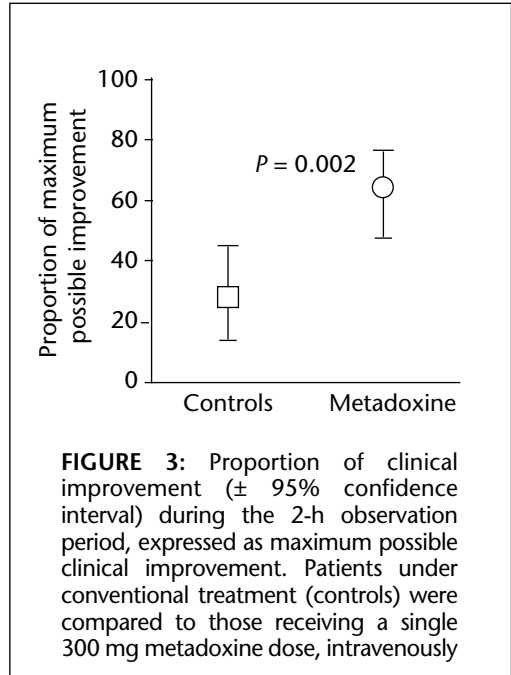
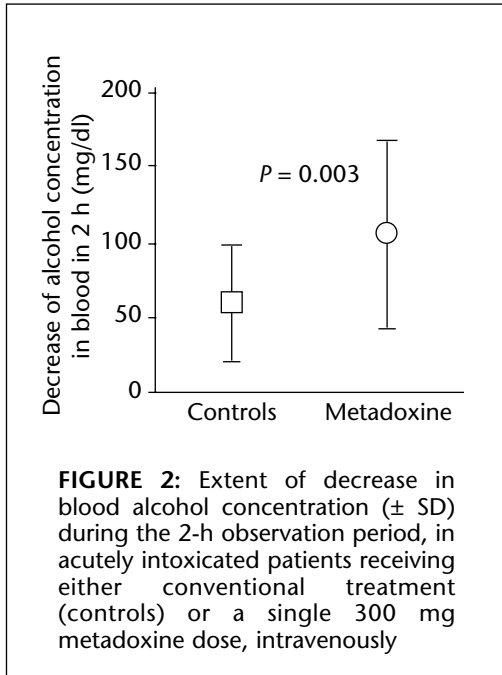
The defined endpoints were reached in this study, confirming the results of existing research of metadoxine in acute alcohol intoxication, although rather old and performed when clinical management techniques were less refined.<sup>7,8</sup> Our data confirm that the intravenous administration of metadoxine to acutely intoxicated patients on hospital admission significantly accelerated clinical recovery and significantly increased alcohol clearance from the blood,

**TABLE 2:** Changes in degree of intoxication as monitored by alcohol levels

Change	Number of patients	
	Controls <sup>a</sup>	Metadoxine
Unchanged	13 (56.5%)	9 (34.6%)
Decreased by one degree	9 (39.1%)	10 (38.5%)
Decreased by two degrees	1 (4.3%)	6 (23.1%)
Decreased by three degrees	0 (0%)	1 (3.8%)
<i>P</i> -value, Mann–Whitney test	0.044	

<sup>a</sup>Three patients were classified as grade 0 at baseline and were, therefore, not considered.

Metadoxine in acute alcohol intoxication



compared with standard treatment. A second vial of medication was not required, although this was made available in accordance with the study protocol.

The addition of metadoxine to standard treatment increased the odds ratio of recovery from clinical intoxication by at least one degree in 2 h and yielded a significant difference in the proportion of improved patients, of benefit to patients and emergency departments. Furthermore, in a crude approach to determine whether the extent of clinical improvement is influenced

by the condition of patients at trial entry, we also observed with metadoxine a greater proportional improvement from baseline. The extent of clinical improvement achieved as a proportion of the total possible improvement takes into account that while a patient with severe intoxication on trial entry might improve by four degrees, another patient entering the trial with mild intoxication can, at most, exhibit an improvement of one degree.

The clearance of alcohol from blood was significantly greater with the use

**TABLE 3:** Classification of decrease in degree of intoxication, as monitored by alcohol blood levels and clinical signs in patients treated with metadoxine

Change in alcohol range	Change in clinical classification		
	Unchanged	One degree	Two degrees
Unchanged	3 (11.5%)	3 (11.5%)	3 (11.5%)
One degree	2 (7.7%)	4 (15.4%)	4 (15.4%)
Two or more degrees	1 (3.8%)	1 (3.8%)	5 (19.2%)

$P = 0.120, 0.255$  and  $0.281$  for  $\kappa$  (measure of agreement), Kendall's ( $\tau$ -B) and Spearman's ( $\rho$ ), respectively.

of metadoxine and although this result may be influenced by several variables, the treatment applied was the only factor that significantly affected the decrease in alcohol concentration. Further investigation with appropriately designed studies and pre-determined stratifications is required to support our findings on the absence of effect of anthropometric and clinical variables.

Metadoxine-treated patients exhibited a significantly greater improvement in alcohol clearance than those randomized to conventional treatment, but when we investigated whether increased alcohol clearance was solely responsible for improving clinical condition, none of the statistical tests used to assess correlation of improvement in alcohol levels with clinical signs yielded significant results. This suggests that there is no evidence to correlate the effects of metadoxine in improving clinical signs of intoxication with its effects on increasing alcohol clearance from the blood. In our sample, the degree of clinical intoxication on trial entry had no effect on clinical outcome.

No adverse events were observed in this study, although it must be emphasized that a low dose of metadoxine was used and the 2-h observation period was relatively short. No conclusion can thus be drawn on the tolerability and safety of metadoxine from this study. Nevertheless, there is no reason to suggest that the safety profile of metadoxine might be different in acutely intoxicated patients from that of patients already monitored in post-marketing surveillance

(an AE prevalence < 0.002%; post-marketing data on file as surveillance reports to the Italian Ministry of Health 1989 – 2000, Laboratori Baldacci SpA, Pisa),<sup>15</sup> or in the most recent clinical study,<sup>15</sup> where no adverse events directly attributable to the medication were reported. In view of the absence of detectable adverse events, future double-blinded studies in acute alcohol intoxication may safely be performed.

In conclusion, metadoxine, when administered as a single intravenous dose, improved the clinical condition of patients with acute alcohol intoxication. This improvement was greater than that observed in patients receiving standard treatment. Alcohol clearance from blood was significantly greater in the metadoxine treatment group. Age, gender, history of previous alcohol abuse, and initial alcohol level did not significantly influence alcohol clearance. The clinical and metabolic effects of metadoxine appear to be independent of each other, although these effects are concurrent and potentially synergistic in allowing a faster and smoother recovery of patients from acute ethanol intoxication.

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