ARTICLE

Effectiveness of IV Ethanol Therapy Combined with Hemodialysis in the Treatment of Methanol and Ethylene Glycol Poisoning

Danica Lister, Michael Tierney, and Garth Dickinson

ABSTRACT

Background: The management of methanol and ethylene glycol poisoning includes inhibition of alcohol dehydrogenase by IV ethanol therapy or fomepizole. There is a lack of contemporary information on IV administration of ethanol in this setting.

Objective: To evaluate the effectiveness of IV ethanol therapy in combination with hemodialysis for the treatment of methanol and ethylene glycol poisoning.

Methods: The medical records of patients with methanol or ethylene glycol poisoning who had been treated with at least 6 h of IV ethanol therapy were reviewed. Patients were included in the study if initial serum methanol or ethylene glycol concentration was at least 6.2 or 3.2 mmol/L, respectively, or if the laboratory findings were consistent with poisoning. Outcomes included in-hospital death, incidence of visual disturbances secondary to methanol poisoning, incidence of renal dysfunction secondary to ethylene glycol poisoning, incidence of hypoglycemia secondary to IV ethanol therapy, and success in achieving target ethanol concentration of greater than 22 mmol/L.

Results: Twenty-seven patients met the eligibility criteria, 25 of whom survived. Twenty-six of the 27 patients underwent concurrent hemodialysis. Renal dysfunction occurred in 2 of 11 patients with ethylene glycol poisoning, and 1 of these patients required long-term dialysis. No visual disturbances secondary to methanol poisoning were documented, and there were no episodes of hypoglycemia in any patient during infusion of ethanol. In 56% of all serum samples obtained during ethanol treatment, the ethanol concentrations were above the threshold of 22 mmol/L.

Conclusion: IV administration of ethanol, combined with hemodialysis, appears to be effective and safe for the management of patients with methanol and ethylene glycol poisoning.

Key words: methanol, ethylene glycol, poisoning, ethanol

RÉSUMÉ

Historique : Le traitement de l'intoxication par le méthanol et l'éthylène glycol comprend le blocage de l'alcool déshydrogénase par l'éthanol IV ou le fomépizole. On manque cependant d'information actualisée sur l'administration IV de l'éthanol dans ce contexte.

Objectif : Évaluer l'efficacité de l'administration IV de l'éthanol jumelée à l'hémodialyse dans le traitement de l'intoxication par le méthanol et l'éthylène glycol.

Méthodes : Les dossiers médicaux des patients intoxiqués par le méthanol ou l'éthylène glycol qui ont reçu un traitement IV à l'éthanol pendant au moins six heures ont été examinés. Les patients ont été retenus si leur concentration plasmatique initiale de méthanol ou d'éthylène glycol était d'au moins 6,2 ou 3,2 mmol/L, respectivement, ou si les valeurs de laboratoire indiquaient une intoxication. Les critères d'évaluation étaient les suivants : décès à l'hôpital, trouble visuel secondaire à l'intoxication par le méthanol, dysfonctionnement rénal secondaire à l'intoxication par l'éthylène glycol, hypoglycémie secondaire à l'administration IV d'éthanol et obtention d'une concentration plasmatique d'éthanol supérieure à 22 mmol/L.

Résultats : En tout, 27 patients ont satisfait aux critères d'admissibilité et 25 d'entre eux ont survécu. Des 27 patients, 26 ont été mis sous hémodialyse concomitante. Deux des 11 patients intoxiqués par l'éthylène glycol ont présenté un dysfonctionnement rénal et un de ces patients a nécessité une dialyse prolongée. Aucun trouble visuel secondaire à l'intoxication par le méthanol n'a été rapporté et aucun épisode d'hypoglycémie n'a été observé chez tous les patients pendant la perfusion d'éthanol. Les concentrations d'éthanol de 56 % de tous les échantillons sériques obtenus durant le traitement étaient supérieures au seuil de 22 mmol/L.

Conclusion : L'administration IV d'éthanol jumelée à l'hémodialyse semble être sûre et efficace dans le traitement des patients intoxiqués par le méthanol et l'éthylène glycol.

Mots clés : méthanol, éthylène glycol, intoxication, éthanol

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INTRODUCTION

Poisoning with methanol or ethylene glycol is potentially life-threatening, and prompt treatment is required to reduce the risk of permanent sequelae, such as renal dysfunction, visual disturbances, or death. The toxic effects of methanol and ethylene glycol result from their conversion to toxic metabolites: methanol is converted to formic acid, whereas ethylene glycol undergoes biotransformation to glycolic and oxalic acids. Conventional treatment of these poisonings has consisted primarily of IV administration of ethanol with or without hemodialysis. Ethanol has a higher affinity for alcohol dehydrogenase and inhibits the metabolism of methanol and ethylene glycol.[1] Despite the widespread use of IV ethanol therapy for this indication over the past several decades,[2,3] limited information has been published regarding the effectiveness and safety of this mode of treatment, other than in case reports and small case series.[4-7]

More recently, the alcohol dehydrogenase inhibitor fomepizole has become available for the management of methanol or ethylene glycol poisoning.[8-11] Fomepizole has been recommended as a preferred alternative to ethanol because of its higher affinity for alcohol dehydrogenase, its ease of administration and a lower requirement for monitoring.[8] Recent publications have described the effectiveness of fomepizole for the management of methanol and ethylene glycol poisoning,[9,10,12,13] but the clinical outcomes associated with ethanol administration in this setting have not been as well studied. Therefore, a retrospective study was undertaken to examine the administration and clinical effectiveness of ethanol for treatment of this potentially life-threatening event.

METHODS

Experimental Design

For this retrospective study, patients admitted to The Ottawa Hospital—General Campus, an adult tertiary-care hospital, for methanol or ethylene glycol poisoning between January 1995 and February 2002 were identified by screening the hospital's medical records for specified codes from the International Classification of Diseases, 9th revision, and their medical records were reviewed. The study was approved by the Research Ethics Board of The Ottawa Hospital.

Patients

Patients were defined as having methanol poisoning if they had an initial serum concentration of methanol of at least 6.2 mmol/L or 2 of the following laboratory findings: arterial pH less than 7.3, serum bicarbonate concentration less than 20 mmol/L, or serum osmolal gap greater than 10 mmol/kg.[10]

Patients were defined as having ethylene glycol poisoning if they had an initial serum concentration of ethylene glycol of at least 3.2 mmol/L or 3 of the following laboratory findings: arterial pH less than 7.3, serum bicarbonate concentration less than 20 mmol/L, serum osmolal gap greater than 10 mmol/kg, or oxaluria.[9]

All patients had to have received at least 6 h of IV ethanol therapy. At the Ottawa Hospital, the ethanol infusion is administered intravenously as a 10% volume/volume solution in 5% dextrose in water.

Outcome Measurements

The study had 2 main objectives: to determine the effectiveness of IV ethanol therapy in cases of methanol or ethylene glycol poisoning and to evaluate the safety of IV ethanol therapy. To evaluate effectiveness, survival to hospital discharge was determined. In addition, visual impairment in association with methanol poisoning and changes in renal function in association with ethylene glycol poisoning were assessed. Visual disturbances secondary to methanol poisoning were based on any documentation in the medical record of a change in visual acuity at the time of hospital discharge. Renal dysfunction was defined as elevation in serum creatinine concentration above the upper limit of normal (106 μmol/L) at any time during the hospital stay in patients with no known prior renal dysfunction or an absolute increase in serum creatinine concentration of greater than 100 μmol/L in patients with prior renal dysfunction. Serum creatinine concentration and the requirement for dialysis at discharge were noted. As a secondary outcome measure, the appropriateness of dosing relative to current guidelines[1,8] (Table 1) was assessed. Doses were considered appropriate if within 15% of those recommended by the guidelines. Safety was assessed by determining the occurrence and incidence of hypoglycemia, defined as serum glucose concentration less than 4 mmol/L during infusion of ethanol.

The frequency of rate changes during the ethanol infusion, the total number of determinations of serum ethanol concentration, and the proportion of these that were greater than the target of 22 mmol/L during IV ethanol infusion were assessed. These variables were chosen to evaluate the appropriateness of ethanol dose selection and the intensity of laboratory monitoring.

Table 1. Guidelines for Ethanol Dosing in Methanol or Ethylene Glycol Poisoning[1,8]

	Ethanol Dose	
Type of dose	**Quantity**	**Volume (10% v/v)**
Loading dose	600 mg/kg	7.6 mL/kg
Maintenance dose		
Average alcohol intake	110 mg kg^{-1} h^{-1}	1.4 mL kg^{-1} h^{-1}
Excessive alcohol intake	154 mg kg^{-1} h^{-1}	2.0 mL kg^{-1} h^{-1}
Does not drink alcohol	66 mg kg^{-1} h^{-1}	0.8 mL kg^{-1} h^{-1}
During hemodialysis		
Average alcohol intake	154 mg kg^{-1} h^{-1}	2.0 mL kg^{-1} h^{-1}
Excessive alcohol intake	237 mg kg^{-1} h^{-1}	3.0 mL kg^{-1} h^{-1}
Does not drink alcohol	118 mg kg^{-1} h^{-1}	1.5 mL kg^{-1} h^{-1}

RESULTS

Of 32 cases of potential methanol or ethylene glycol poisoning that were identified, 5 patients were excluded for the following reasons: 2 patients with confirmed ingestion had received ethanol infusions of less than 6 h duration; for 2 patients there was insufficient documentation of the initiation and discontinuation times of the ethanol infusion, which made it impossible to accurately assess treatment duration; and 1 patient did not meet the laboratory-based entry criteria (serum methanol concentration undetectable, arterial pH 7.34, serum bicarbonate concentration 15.8 mmol/L, and osmolal gap 6 mmol/kg). All of the excluded patients survived, and 4 did not experience any visual disturbances or renal dysfunction. One excluded patient (who had ethylene glycol poisoning) experienced an elevation in serum creatinine concentration, from 109 µmol/L on admission to 571 µmol/L on discharge. This patient presented with severe acidosis (pH 7.08) and serum ethylene glycol concentration of 3 mmol/L, which suggested a substantial delay between ingestion and presentation. One patient had ingested methanol and ethylene glycol simultaneously; this patient's baseline characteristics were included in the analyses for both groups, but were counted only once in the analysis of the overall group and the ethanol administration data.

Patient Characteristics

The patients' baseline characteristics are summarized in Table 2. Ten patients had detectable serum ethanol concentrations at the time of initial assessment (mean 25.0 mmol/L). Five of these patients (mean serum ethanol concentration 27.0 mmol/L) had been transferred from other hospitals, and 5 (mean serum ethanol concentration 22.8 mmol/L) presented directly to the authors' institution.

Nine of the 27 patients presented with pH less than 7.3, and 17 had serum bicarbonate concentrations less than 20 mmol/L. At the time of admission, all 17 of the patients who had ingested methanol had serum methanol concentrations above the threshold of 6.2 mmol/L (mean ± standard deviation [SD] 43.2 ± 33.3 mmol/L). On admission, 8 of the 11 patients with ethylene glycol poisoning had concentrations above the threshold of 3.2 mmol/L (mean ± SD 57.1 ± 48.9 mmol/L). For the other 3 patients, serum ethylene glycol was undetectable on admission, but all had significant metabolic acidosis.

Patient Management

The mean duration of IV ethanol infusion was 25.7 h (range 6.0 to 54.5 h) from the time of the ethanol loading dose or initial infusion until discontinuation. Twenty-six of the 27 patients received concurrent hemodialysis in addition to IV ethanol infusion. The mean duration of dialysis was 9.2 h (range 4.0 to 23.3 h). In the single patient who did not undergo hemodialysis, the presenting serum methanol concentration was 11 mmol/L, the initial pH was 7.37, and the serum bicarbonate concentration was 25 mmol/L.

Clinical Outcomes

Two of the 27 patients died; both had ingested methanol. One of these patients had initially presented to another hospital with severe acidosis (pH 7.03, bicarbonate concentration 5.2 mmol/L) and seizures. The seizures had continued and the patient had been transferred to the intensive care unit for intubation. On transfer to the authors' institution, the patient remained intubated and was treated with IV ethanol and hemodialysis. Magnetic resonance imaging showed cerebral edema and infarction, and active treatment was

Table 2. Baseline Characteristics of Patients with Ethylene Glycol (EG) or Methanol (MeOH) Poisoning

Characteristic	Overall (*n* = 27*)	Ethylene Glycol (*n* = 11)	Methanol (*n* = 17)
Median age (and range) (years)	38 (19–59)	38 (19–59)	38 (19–59)
Sex	16 M, 11 F	5 M, 6 F	11 M, 6 F
Mean initial serum concentration of EG or MeOH (and range) (mmol/L)	NA	42.6 (0–137)	43.2 (7–133)
Mean arterial pH on presentation (and range)	7.31 (6.85–7.51)	7.28 (7.00–7.42)	7.33 (6.85–7.51)
Mean serum bicarbonate on presentation (and range) (mmol/L)	16.0 (3.2–26.0)	13.1 (8.7–21.2)	17.9 (3.2–26.0)
Mean osmolal gap on presentation (and range) (mmol/kg)	60.0 (2–180)	62.6 (4 –166)	58.4 (3–180)
Co-ingestion of EtOH and initial serum EtOH concentration	5 patients (mean 22.8 mmol/L)	2 patients (mean 5.4 mmol/L)	3 patients (mean 34.3 mmol/L)
Oxaluria	NA	6 patients	NA

EtOH = ethanol, NA = not applicable
*One patient had ingested both methanol and ethylene glycol simultaneously; this patient's baseline characteristics were included in the analysis for each group but were counted only once in the analysis for the overall group and the ethanol administration data.

withdrawn. The patient did not recover consciousness and died 2 days later. The other patient also initially presented to another institution and experienced respiratory arrest before transfer to the authors' hospital. At the time of transfer, the patient's pupils were fixed and dilated, and intubation and ventilation were performed. Active treatment was withdrawn on day 4 after admission, and the patient subsequently died.

Of the 17 patients who had ingested methanol, only 4 received formal ophthalmologic consults. Three of these patients had no methanol-induced damage. The fourth patient, who subsequently died, had pre-existing progressive blindness that was difficult to distinguish from any damage that might have been caused by methanol. Among the patients who did not receive formal ophthalmologic evaluation, no visual disturbances were documented in the health record.

During the course of the hospital stay, 2 of the 11 patients admitted with ethylene glycol poisoning experienced elevation of serum creatinine concentration. One patient, whose serum creatinine concentration was 476 µmol/L at the time of admission, was discharged with dialysis-dependent renal dysfunction (serum creatinine concentration 983 µmol/L). The other patient was admitted with a serum creatinine concentration of 95 µmol/L, which progressed to a peak of 882 µmol/L on day 5 after admission. This patient was discharged about 1 month after admission with a serum creatinine concentration of 80 µmol/L. Although this case might appear to have been a therapeutic failure, the patient had been admitted to the authors' institution about 18 h after ingestion of ethylene glycol with severe metabolic acidosis (initial serum bicarbonate concentration 8.7 mmol/L), undetectable ethylene glycol in the serum, and oxaluria. It is likely that acute renal toxicity had already occurred by the time of presentation, despite the initially normal serum creatinine concentration.

Adverse Effects

Because this was a retrospective study that depended on information available in the medical record, the incidence of hypoglycemia was the only adverse effect evaluated. Of the 162 serum glucose determinations during the IV ethanol infusions, none had a value below 4 mmol/L.

Outcomes of Ethanol Administration

In addition to the 6 patients who had received loading doses at other institutions before transfer, 18 patients received an IV loading dose of ethanol upon presentation at the authors' institution. For these 18 patients, the dose was appropriate in 6 patients (33%), higher than recommended in 7 (39%), and lower than recommended in 3 (17%). Two (11%) of the 18 loading doses could not be evaluated because the patients' weights were not documented in the medical record.

Ethanol infusion rates were considered appropriate if within 15% of recommended guidelines,[1,8] taking into account both patient weight (if documented in the medical record) and concurrent hemodialysis. The infusion rate after the loading dose (if given) or after transfer from another institution was considered the initial infusion rate. Weights (some approximate) were documented in 25 of the 27 medical records. Initial IV ethanol infusion rates were appropriate in 10 (40%) of the patients, lower than recommended in 6 (24%), and

higher than recommended in 9 (36%). After initiation of the ethanol infusion, the average number of changes in the infusion rate during treatment was 3.8 per patient (range 0 to 11). There was no apparent association between the appropriateness of the initial ethanol infusion rate and the number of subsequent changes in infusion rate: there were 4.8, 4.0, and 3.4 rate changes per patient in patients with appropriate, lower-than-recommended, and higher-than-recommended initial infusion rates, respectively.

Serum ethanol concentration was measured in 194 samples obtained during ethanol infusion (average 7.1 per patient, range 4 to 20). In 108 (55.7%) of these, the concentration was greater than or equal to the target concentration of 22 mmol/L. In 5 of the 27 patients (19%), the target concentration was never achieved during the course of treatment. Only 4 patients had serum ethanol concentration greater than 22 mmol/L throughout the course of ethanol therapy.

DISCUSSION

To the authors' knowledge, this study represents the largest case series on the use of IV ethanol therapy for the management of methanol or ethylene glycol poisoning. Despite difficulty in achieving target serum ethanol concentrations, treatment with IV ethanol therapy and hemodialysis was associated with favourable patient outcomes. Of the 27 patients, 25 (93%) survived, and the 2 deaths occurred in patients with evidence of severe central nervous system damage who presented late after ingestion. Only one patient was discharged with renal dysfunction induced by ethylene glycol, and this patient may have had pre-existing kidney disease. No visual disturbances associated with methanol were reported.

Brent and others recently published 2 case series describing the results of treatment of methanol and ethylene glycol poisoning with fomepizole.[9,10] The patient characteristics in those studies, including demographic characteristics, severity of intoxication, and use of hemodialysis, were similar to those in the study reported here. The outcomes of treatment were also similar. Among patients with ethylene glycol poisoning, 1 (9%) of 11 in the current series and 3 (16%) of 19 patients in one of the fomepizole studies[9] were discharged with elevated serum creatinine concentration. Overall survival was 93% in the current study and 90% (27/30) in the 2 fomepizole studies.[9,10]

Two other case series reporting the use of fomepizole in methanol[12] and ethylene glycol[13] poisoning indicate that this drug can be effective without concomitant hemodialysis. If these results receive further confirmation, fomepizole therapy may have an advantage over ethanol treatment, especially in centres where expedient hemodialysis is not available for patients with poisoning.

Because of the lack of direct comparative trials, there is limited information on potential differences in effectiveness between IV ethanol therapy and fomepizole. Each treatment has advantages and disadvantages. The recommended fomepizole dose regimen is advantageous in situations where frequent laboratory monitoring or continuous IV infusion is not feasible. Fomepizole is the only drug that has received regulatory approval for use in methanol and ethylene glycol poisoning. However, the higher acquisition cost of fomepizole is a significant consideration, especially in view of limited data to suggest its superiority over ethanol. The cost of ethanol for IV administration is lower, but the requirement for continuous IV infusion is inconvenient, achieving recommended serum concentrations can be problematic, and monitoring may be costly. Although hypoglycemia has been cited as a potential consequence of IV ethanol use, no patients in this series exhibited this adverse effect, despite frequent monitoring of blood glucose concentrations. It is possible that hypoglycemia was avoided by use of dextrose solution as the diluent for the ethanol. In summary, the lack of comparative trials and formal pharmacoeconomic analyses makes it difficult to choose between fomepizole and ethanol for the management of methanol or ethylene glycol poisoning.

Concurrent hemodialysis was used for all but one patient in the series reported here. It could be argued that the favourable outcomes observed here, which were evident despite the fact that serum ethanol concentration targets were not consistently achieved, were due in large part to timely and adequate hemodialysis. Ethanol can prevent metabolism of the parent compounds methanol and ethylene glycol to their toxic metabolites, but provides no protection once those metabolites have formed; therefore, hemodialysis appears to be an essential component of appropriate management.

The results of this study raise questions regarding the traditional target serum ethanol concentration of 22 mmol/L in patients undergoing hemodialysis. An animal study has suggested that lower-dose ethanol therapy has results comparable to those achieved with the traditional higher doses.[14] This, together with the current results demonstrating good clinical outcomes in spite of inconsistency in reaching target ethanol

concentrations, suggests that lower, fixed-dose ethanol infusions in combination with hemodialysis may be an effective alternative for the treatment of methanol or ethylene glycol poisoning.

The limitations of this study's design, a retrospective examination of medical records, must be acknowledged. The treatment protocol for IV ethanol administration was not standardized, and the reporting of subjective outcome data such as visual disturbances associated with methanol and adverse effects caused by ethanol were incomplete. Nonetheless, these results do provide insight into the "real world" effectiveness and safety of IV ethanol therapy and hemodialysis in the management of methanol and ethylene glycol poisoning.

In conclusion, IV ethanol administration combined with hemodialysis appears to be effective and safe for the management of patients with methanol or ethylene glycol poisoning. This continues to be the preferred therapeutic approach at the authors' institution.

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Danica Lister, BScPharm, is with the Department of Pharmacy, The Ottawa Hospital, Ottawa, Ontario.

Michael Tierney, BScPhm, MSc, is with the Department of Pharmacy, The Ottawa Hospital, Ottawa, Ontario.

Garth Dickinson, MD, FRCPC, is with the Department of Emergency Medicine, The Ottawa Hospital, Ottawa, Ontario.

Address for correspondence:
Michael Tierney
Department of Pharmacy
The Ottawa Hospital
501 Smyth Road
Ottawa ON
K1H 8L6

e-mail: mtierney@ottawahospital.on.ca