Standardized Treatment of Severe Methanol Poisoning With Ethanol and Hemodialysis

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Seven patients with methanol poisoning were treated with ethanol, hemodialysis and supportive measures. The interval between ingestion and initiation of ethanol therapy varied from 3 to 67 hours and from ingestion to dialysis from 9 to 93 hours. All patients survived, but one had permanent visual impairment. A 10% ethanol solution administered intravenously is a safe and effective antidote for severe methanol poisoning. Ethanol therapy is recommended when plasma methanol concentrations are higher than 20 mg per dl, when ingested doses are greater than 30 ml and when there is evidence of acidosis or visual abnormalities in cases of suspected methanol poisoning.


The ingestion of large amounts of methanol is accompanied by metabolic acidosis, respiratory depression and optic nerve degeneration as a result of its metabolism to formic acid.1,2Ethanol has a greater affinity than methanol for the enzyme alcohol dehydrogenase, which is responsible for the initial step in methanol metabolism.3 A suggested method of treating methanol poisoning is the administration of ethanol, thus reducing the formation of the toxic metabolites of methanol. Excess methanol is then removed from the body by hemodialysis.4

Guidelines for administering ethanol are inconsistent and range from the oral administration of commercially available whiskey to the intravenous administration of large volumes of 5% ethanol. The specific gravity of ethanol solutions varies with their concentration, thus making calculation of the volume of ethanol to be administered difficult.5

The present study was undertaken to determine the feasibility of treating cases of acute methanol poisoning with a commercially available 10% (vol per vol) ethanol solution administered intravenously according to a protocol based on the known pharmacokinetics of ethanol. The protocol is simple, reliable and provides a rational approach for the use of ethanol as an antidote.

Methods

Plasma ethanol and methanol concentrations were analyzed by gas liquid chromatography using a hydrogen flame detector and a 5% Carbowax on a 60/80 column with N-propanol as the internal standard. The sensitivity of the assay for both methanol and ethanol is 5 mg per dl. Linearity for methanol ranged from 5 to 300 mg per dl and for ethanol from 5 to 350 mg per dl.

Patients were initially treated with gastric lavage, activated charcoal, saline cathartic and fluids given intravenously—including sodium bicarbonate solution when appropriate—and then transferred to the University of Utah Medical Center. The criterion for beginning ethanol therapy was a history of ingesting more than 30 ml of methanol or a plasma methanol concentration greater than 20 mg per dl. Plasma methanol concentrations of less than 20 mg per dl have historically not been associated with signs of serious intoxication. In a prospective study of 46 cases based on clinical outcomes, it was concluded that a concentration of methanol in the range of 20 to 30 mg per dl would be a safe level at which ethanol therapy could be stopped.6 The criterion for simultaneous ethanol therapy and hemodialysis was a plasma methanol concentration greater than 50 mg per dl or

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metabolic acidosis unresponsive to sodium bicarbonate given intravenously. The clinical information from seven consecutive patients with severe methanol poisoning is presented in Table 1.

A commercially available 10% (vol per vol) ethanol solution in 5% dextrose in water (McGaw Laboratories, Chicago) was administered to each patient. Calculation of the loading dose (LD) of ethanol was based on a desired plasma concentration (Cp) of 100 mg per dl² and a volume distribution (Vd) of 600 ml per kg of body weight using the formula:

\[ LD = C_p \times V_d = 600 \text{ mg/kg} \]

The intravenous infusion rate (Kp) to maintain an ethanol plasma concentration at 100 mg per dl was based on the following equation:

\[ K_p = \frac{V_{\text{max}}}{K_m + C_p} \]

where \( V_{\text{max}} \) is the maximum ethanol elimination rate and \( K_m \) is the Michaelis-Menten constant for ethanol. A \( V_{\text{max}} \) of 124 mg per kg per hour (range, 75 mg per kg per hour for non-drinkers and 175 mg per kg per hour for long-term drinkers) and a \( K_m \) of 13.8 mg per dl were used to calculate the maintenance infusion.⁹,¹⁰ Using these figures a maintenance infusion rate of 109 mg per kg per hour was obtained. The loading and maintenance doses are given together over the first hour (600 mg per kg plus 109 mg per kg). The maintenance ethanol infusion rate during dialysis was calculated using pharmacokinetic values measured in patient 2. The clearance of ethanol during dialysis (\( C_{\text{lp}} \)) was determined from this patient’s plasma ethanol half-life (\( T_{1/2} \)) of 2.75 hours, using the following equation:

\[ C_{\text{lp}} = 0.693 \times \frac{V_d}{T_{1/2}} \]

The ethanol clearance during dialysis was calculated as 151 mg per kg per hour. The ethanol infusion rate during dialysis (\( K_{\text{dp}} \)) was calculated from \( K_p, C_{\text{lp}}, \) and \( C_p \) by the following equation:

\[ K_{\text{dp}} = K_p + (C_{\text{lp}} \times C_p) = 109 \text{ mg/kg/hour} + (151 \text{ ml/kg/hour} \times 100 \text{ mg/dl}) = 260 \text{ mg/kg/hour} \]

Hemodialysis was carried out with a Travenol RSP delivery system in a standard recirculating single pass configuration for patient 1 and in a single pass configuration with a diastale flow of 400 ml per minute for the other six patients. Large surface area-plate or hollow fiber dialyzers were used for each patient. The Seldinger technique of femoral vein catheterization was used for double catheter access with high flows and minimal recirculation. Methanol clearance during dialysis was calculated using standard equations.¹¹

**Results**

The clinical data from seven consecutive patients with methanol poisoning are given in Table 1. The amount of methanol ingested and the time from ingestion until an initial plasma methanol concentration was obtained varied considerably in our patients. Patient 6 allegedly consumed methanol over a 24-hour period, precluding calculation of the exact time since ingestion. All patients survived and, except for patient 2, had normal vision with no signs of optic neuritis at time of discharge. Patient 2 suffered severe ocular damage characterized by blurring of all images and central scotomata.

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*Gregory H. Done, CHT, provided technical assistance and gathered data.

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**TABLE 1** — Summary of Findings in Seven Men With Methanol Poisoning Treated With Ethanol Therapy and Dialysis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Weight</th>
<th>Hours of Methanol Exposure</th>
<th>Ethanol Infusion Rate</th>
<th>Maintenance Dose</th>
<th>Duration of Dialysis</th>
<th>Initial Arterial Blood Pressure (mm Hg)</th>
<th>Initial Serum Levels (mg/dl)</th>
<th>Post-Dialysis Serum Level (mg/dl)</th>
<th>Post-Dialysis HCO₃⁻ (mEq/l)</th>
<th>Outcome</th>
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<tr>
<td>1</td>
<td>24</td>
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<td>16</td>
<td>48</td>
<td>102</td>
<td>16</td>
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<td>16</td>
<td>48</td>
<td>102</td>
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<td>48</td>
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<td>65</td>
<td>16</td>
<td>48</td>
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<td>48</td>
<td>0.2</td>
<td>15.0</td>
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<td>120/60</td>
<td>48</td>
<td>0.2</td>
<td>15.0</td>
<td>Normal</td>
</tr>
</tbody>
</table>

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*Non-survivors: Patient 2, 3, 4, 5, 6; survivors: Patient 1, 7.*

*Administered during dialysis for all patients.*

*Post-dialysis HCO₃⁻ (mEq/l) was determined using the standard method.*

*Patient 1 was given 2% saline and methanol in water (1:1).*

*Patient 2 was given 8% saline and methanol in water (1:1).*

*Patient 3 was given 10% saline and methanol in water (1:1).*

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with small islands of normal vision around the macula. This patient came into treatment with a prominent acidosis that may have played a larger role in the toxicity. An error in the time element of the ingestion and the initiation of treatment may have also contributed to greater toxicity.

In five of seven patients ethanol therapy was started by the referring physician, with clinical information being supplied by telephone consultation. The loading and maintenance doses of ethanol provided therapeutic plasma concentrations of ethanol. The mean plasma ethanol concentration obtained between one and two hours of beginning the ethanol therapy was 118 ± 43 mg per dl (mean ± standard deviation [SD]) for the seven patients. Infusion in forearm veins was mildly uncomfortable for some patients; postinfusion phlebitis was not observed, however.

Hemodialysis was continued until the plasma methanol concentration was less than 20 mg per dl (except in patient 1). The mean whole blood clearance of methanol was 251 ± 22 ml per minute (mean ± SD) in the six patients in whom a single pass dialysis was used. This was considerably higher than previously reported for a recirculating-single pass system.12

Figure 1 shows the entire course of therapy for patient 2. It is evident that the ethanol therapy delayed the metabolism of methanol in that the methanol concentration did not decrease until hemodialysis was initiated. Hemodialysis resulted in a prompt reduction in the plasma methanol concentration, resolution of acidosis and improvement in the patient's clinical condition. When we used the described ethanol protocol during dialysis, the plasma ethanol concentration never fell below a concentration that would inhibit alcohol dehydrogenase.

Discussion

The initial plasma concentration in cases of acute methanol poisoning usually reflects the amount ingested and the time between ingestion and blood collection. In patient 4 the plasma methanol concentration, measured four hours after ingestion, was 377 mg per dl, yet the patient had only mild metabolic acidosis. On the other hand, in patient 7 the initial plasma methanol concentration, measured 48 hours after ingestion, was 46 mg per dl, and the patient had severe acidosis with a wide anion gap. This discrepancy between plasma concentration of methanol and clinical signs of toxicity is compatible with the concept that methanol needs to be metabolized to formaldehyde and formic acid before the toxicity is fully manifest.3 This provides the rationale for ethanol therapy, which inhibits the metabolism of methanol. The enzyme alcohol dehydrogenase, responsible for the generation of formaldehyde from methanol, has a higher affinity for ethanol than for methanol. Thus, ethanol is preferentially metabolized and methanol can be eliminated by nonmetabolic routes, including hemodialysis.

The data of this study, obtained in a prospective manner from seven consecutive patients, indicate that commercially available 10% (vol per vol) ethanol solution can be safely and easily administered intravenously to treat cases of acute methanol poisoning. The doses of 10% ethanol to be administered as a loading dose, maintenance dose and a maintenance dose during hemodialysis are shown in Table 2. It should be noted that during the first hour of ethanol therapy the loading dose (600 mg per kg) and the maintenance dose (109 mg per kg) must be given. This is to compensate for the metabolism of the loading dose that occurs during the initial hour of therapy. When these doses are used, the plasma ethanol concentration one to two hours later is predictably in the 100 mg per dl range. Plasma ethanol levels should be monitored hourly for the first several hours and continued until good control is obtained. Once the desired plasma level is obtained, sampling can decrease to every two to four hours. Maintenance ethanol infusion rates may differ from those in Table 2 due to variations in the rate of ethanol metabolism. When the recom-
TABLE 2.—Protocol for Ethanol Therapy in Cases of Methanol Overdose

<table>
<thead>
<tr>
<th>Type of Dose</th>
<th>Dose</th>
<th>Rate of Infusion of 10% Ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>First hour, ml/kg body weight*</td>
<td>709</td>
<td>8.86</td>
</tr>
<tr>
<td>Maintenance dose, ml/kg/h</td>
<td>109</td>
<td>1.36</td>
</tr>
<tr>
<td>Maintenance dose during dialysis, ml/kg/h†</td>
<td>260</td>
<td>3.25</td>
</tr>
</tbody>
</table>

*First hour dose includes loading dose and first-hour maintenance dose.
†Maintenance dose during dialysis may have to be adjusted according to efficiency of the dialyzer.

Mended doses of 10% ethanol are administered during dialysis, relatively stable plasma ethanol concentrations are maintained. Maintenance of adequate ethanol concentrations during dialysis is essential but is complicated by the increased clearance of ethanol during the procedure. Variations in blood flow rate and dialyzer efficiency will dramatically influence the amount of ethanol removed during dialysis. During dialysis sampling should be done at least hourly. The figures for maintenance ethanol infusion in Table 2 may have to be adjusted according to variations in these factors. It is practical to measure the plasma ethanol concentrations during dialysis and to make the appropriate adjustments in the infusion rate.

The oral route of administration of ethanol has been advocated in cases of acute methanol poisoning. There are several circumstances that limit the use of oral ethanol as an antidote in methanol poisonings. These include erratic absorption of ethanol, severe nausea and vomiting, the concurrent use of activated charcoal and delay in initiating treatment while the stomach is being emptied. In the seven patients reported here, there were no complications as a result of the intravenous administration of ethanol in a 10% solution. There was minimal discomfort associated with the procedure and neither thrombosis nor phlebitis developed, a finding consistent with other investigations. The same protocol should be applicable to ethylene glycol poisoning.

REFERENCES