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.

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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 formaldehyde and subsequently to formic acid.[1,2] Ethanol 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.[4] 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 (C_p) of 100 mg per dl[7] and a volume distribution (V_d) of 600 ml per kg of body weight[8] using the formula:

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

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

$$K_o = \frac{(V_{max})\quad(C_p)}{(K_m + C_p)}$$

where V_{max} is the maximum ethanol elimination rate and K_m is the Michaelis-Menten constant for ethanol. A V_{max} of 124 mg per kg per hour (range, 75 mg per kg per hour for nondrinkers 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 (Cl_D) was determined from this patient's plasma ethanol half-life (T½) of 2.75 hours, using the following equation:

$$Cl_D = 0.693 \times V_d / T½$$

The ethanol clearance during dialysis was calculated as 151 mg per kg per hour. The ethanol infusion rate during dialysis (K_{o_D}) was calculated from K_o, Cl_D and C_p by the following equation:

$$K_{o_D} = K_o + (Cl_D \times C_p)$$
$$= 109 \text{ mg/kg/hour} + (151 \text{ ml/kg/hour} \times 100 \text{ mg/dl})$$
$$= 260 \text{ mg/kg/hour}$$

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 dialysate 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 catherization 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

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

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

Patient	Age, Years	Estimated Amount of Methanol Ingested	Time From Ingestion to First Methanol Level	Initial Serum Methanol	Time From Ingestion to Giving Ethanol	Duration of Ethanol Therapy	Range of Ethanol Serum Levels	Initial Arterial Blood Gases			Anion Gap†	Time From Ingestion to Dialysis	Predialysis Methanol Concentration	Postdialysis Methanol Concentration	Clearance of Methanol	Duration of Dialysis	Outcome
								pH	P_{CO_2}	HCO_3							
		ml	hours	mg/dl	hours	hours	mg/dl		mm of mercury	mEq/liter	mEq/liter	hours	mg/dl	mg/dl	ml/min	hours	
1‡	48	373	2	373	4.0	87	55-197	7.41	10.0	6.1	30.9	9	340	45	151	7/5.5	Survived; normal vision
2	39	373	9	220	3.0	24	55-145	7.10	18.0	7.0	31	13	220	14	255	9	Survived; bilateral ocular damage
3	16	unknown	48	49	49.0	16	58-162	7.22	20.0	8.0	26	56	49	10	253	7.5	Survived; normal vision
4§	20	180	4	377	5.5	33	75-194	7.39	37.0	22.0	10	15	340	20	228	11	Survived; normal vision
5	20	300	14	158	15.0	12	70-103	7.35	17.0	9.2	14	17	65	20	286	6	Survived; normal vision
6	20	unknown	67	52	67.0	65	75-208	7.33	25.0	9.0	15	93	42	5	225	4	Survived; normal vision
7	20	240	48	46	48.0	12	80-160	7.16	26.1	7.3	26	56	43	10	260	4	Survived; normal vision

P_{CO_2} = carbon dioxide pressure; HCO_3 = bicarbonate anion

*Access to the circulation was by double-needle except for patient 3 in whom a single needle was used. A Terumo 1.5m² dialyzer was used for each patient except patient 3 in whom a PPD 1.3m² dialyzer was used. The mean blood flow in all cases ranged from 225 to 350 ml/min.

†Anion gap calculated as follows: serum sodium level−(bicarbonate+chloride).

‡Patient was given 40% ethanol intravenously for 10 hours, which was changed to 10% ethanol in a solution of 5% dextrose in water. The patient underwent dialysis twice, the second 21 hours after the first.

§Patient was given ethanol intravenously and orally as a loading dose. Exact oral dose retained was unclear because of vomiting. He was then maintained on 10% ethanol given intravenously.

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-

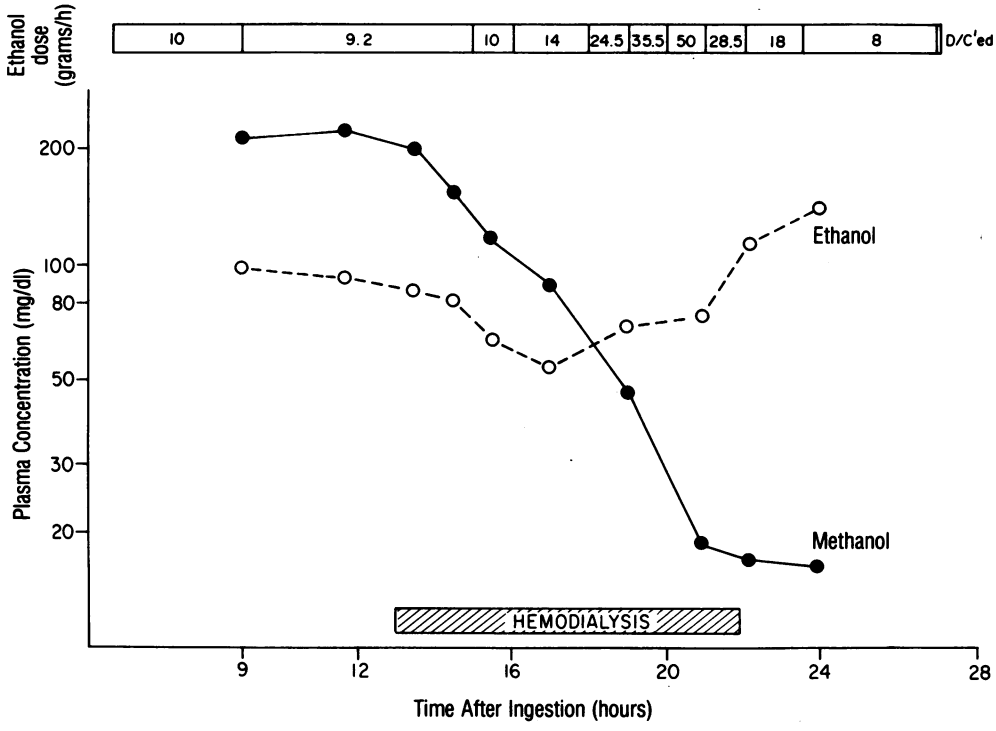

Figure 1.—Ethanol and methanol plasma concentrations from patient 2, plotted as a function of time. The ethanol dose is represented as a composite amount given during the blocks of time represented. It should be noted that the dose of ethanol was not increased until five hours after starting dialysis, resulting in a decrease in plasma ethanol.
D/C'ed = discontinued

TABLE 2.—*Protocol for Ethanol Therapy in Cases of Methanol Overdose*

Type of Dose	*Dose*	*Rate of Infusion of 10% Ethanol*
First hour, ml/kg body weight*	709	8.86
Maintenance dose, ml/kg/h	109	1.36
Maintenance dose during dialysis, ml/kg/h†	260	3.25

*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.[5] 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.[13] The same protocol should be applicable to ethylene glycol poisoning.[5]

REFERENCES

1. Hayreh MS, Hayreh SS, Baumbach GL, et al: Methyl alcohol poisoning—III. Ocular toxicity. Arch Ophthalmol 1977 Oct; 95:1851-1858

2. Martin-Amat G, McMartin KE, Hayreh SS, et al: Methanol poisoning: Ocular toxicity produced by formate. Toxicol Appl Pharmacol 1978 Jul; 45:201-208

3. Blair AH, Vallee BL: Some catalytic properties of human liver alcohol dehydrogenase. Biochemistry 1966 Jun; 5:2026-2034

4. Gonda A, Gault H, Churchill D, et al: Hemodialysis for methanol intoxication. Am J Med 1978 May; 64:749-758

5. Peterson CD, Collins AJ, Himes JM, et al: Ethylene glycol poisoning—Pharmacokinetics during therapy with ethanol and hemodialysis. N Engl J Med 1981 Jan; 304:21-23

6. Swartz RD, Millman RP, Billi JE, et al: Epidemic methanol poisoning: Clinical and biochemical analysis of a recent episode. Medicine (Baltimore) 1981 Sep; 60:373-382

7. Erlanson P, Fritz H, Hagstam KE, et al: Severe methanol intoxication. Acta Med Scand 1965 Apr; 177:393-408

8. Wagner JG, Patel JA: Variations in absorption and elimination rates of ethyl alcohol in a single subject. Res Commun Chem Pathol Pharmacol 1972 Jul; 4:61-76

9. Wagner JG, Wilkinson PK, Sedman AJ, et al: Elimination of alcohol from human blood. J Pharm Sci 1976 Jan; 65:152-154

10. Vestal RE, McGuire EA, Tobin JD, et al: Aging and ethanol metabolism. Clin Pharmacol Ther 1977 Mar; 21:343-354

11. Sargent JA, Gotch FA: Principles and biophysics of dialysis, *In* Drukker W,Parsons FM, Maher JF (Eds): Replacement of Renal Function By Dialysis. Boston, Martinus Nijhoff Medical Division, 1978, pp 38-68

12. Tobin M, Lianos E: Hemodialysis for methanol intoxication. J Dial 1979; 3:97-106

13. Isaac M, Dundee JW: Clinical studies of induction agents—XXX. Venous sequelae following ethanol anaesthesia. Br J Anaesth 1969 Dec; 41:1070-1071