Severe Methanol Poisoning

Application of a Pharmacokinetic Model for Ethanol Therapy and Hemodialysis

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Two patients with extremely high blood methanol concentrations (260 and 282 mg/dl) were successfully treated using pharmacokinetic dosing of ethanol, hemodialysis and supportive measures. Both patients recovered completely without residual ophthalmologic deficits. Early hemodialysis and inhibition of methanol metabolism with effective ethanol concentrations were attributed to the patients' full recovery. Methanol elimination was enhanced by hemodialysis as evidenced by a decrease in half-life from eight to two and a half hours. Methanol dialysance was 98 ml/min. A dosage regimen for ethanol was devised, utilizing dose-dependent pharmacokinetic parameters and the ethanol dialysance (100 to 120 ml/min) from these two patients. An ethanol loading dose of 0.6 g/kg should be administered to an adult with an acute methanol ingestion. This dose will produce a blood ethanol concentration of approximately 100 mg/dl which can be maintained by an ethanol infusion of 66 mg/kg/hour for nondrinkers to 154 mg/kg/hour for chronic ethanol drinkers. Hemodialysis should be initiated if the blood methanol concentration is greater than 50 mg/dl. If hemodialysis is initiated, the ethanol infusion should be increased by 7.2 g/hour.

Methanol poisoning continues to be a serious problem in industrial nations where numerous commercial products contain potentially toxic amounts of methanol. The morbidity and mortality associated with methanol ingestions are due to a combination of systemic acidosis, central nervous system depression and neurotoxicity often resulting in blindness. Neurotoxicity is primarily due to methanol's toxic metabolites [1]. Blood methanol concentrations above 50 mg/dl are commonly associated with death or irreversible blindness [2,3]. Two patients with exceedingly high blood methanol concentrations were successfully treated without sequelae at our institution. In this paper we describe their successful treatment with hemodialysis, ethanol administration and supportive management.

METHODS

Hemodialysis. Patient 1 underwent hemodialysis using a 1.0 m² parallel plate dialyzer with a single pass dialysate delivery. Patient 2 underwent hemodialysis using a 1.0 m² dialyzer with a recirculating 100 liter dialysate reservoir. The dialysis bath was changed hourly. Both patients underwent hemodialysis for 6 hours.

Methanol Kinetics. Blood methanol and ethanol concentrations (Cp) were determined by gas chromatographic assay [4]. First-order methanol elimination was documented by plotting the reciprocal of $\Delta Cp/\Delta t$ versus Cp, where t is time [5]. Methanol elimination rate constants (kd) were determined by linear regression analysis of the concentration-time data. Methanol clearances (CL) were determined prior to and during dialysis by CL = kd × Vd, where Vd is the distribution volume of methanol (0.6 liters/kg) [6]. Methanol dialysance was determined by subtracting the predialysis clearance from the total clearance during dialysis.

Ethanol Clearance and Dosage Calculations. Volumes of ethanol solution were converted to the appropriate weight of ethanol using each solution's specific gravity [7]. Apparent ethanol clearance during dialysis (AEC) was calculated from the ethanol infusion rate during dialysis (Ko$_d$) and the resultant steady-state ethanol concentration: AEC = ko$_d$/Cp. Ethanol metabolic clearance (CL$_M$) was calculated using the Michaelis-Menten relationship: CL$_M$ = Vm/(K$_m$ + Cp), where Vm is the maximal elimination rate and Km is a measure of the enzyme's affinity for ethanol. The apparent ethanol clearance is the total clearance, consisting of metabolic, renal, pulmonary and dialysis clearances. Since pulmonary and renal clearances are negligible compared to the metabolic and dialysis clearances [8], ethanol dialysance (CL$_D$) was estimated by the difference between the apparent ethanol clearance and the endogenous metabolic clearance: CL$_D$ = Ko$_d$/Cp − Vm/(Km + Cp). A previously recommended dosage regimen was utilized in the first patient. In the second patient, the ethanol loading dose was calculated by Dose = Cp × Vd, where Cp is the desired ethanol concentration and Vd is ethanol's distribution volume (0.6 liter/kg) [9]. The infusion rate (Ko) required to maintain a desired steady-state concentration was calculated by Ko = Vm × Cp/(Km + Cp). The ethanol infusion rate during dialysis (Ko$_d$) was calculated by Ko$_d$ = Vm × Cp/(Km + Cp) + (CL$_D$ × Cp). Ethanol clearances and dosage regimens were calculated using a Km of 13.8 mg/dl and a Vm of 175 mg/kg/hour for chronic ethanol drinkers and a Vm of 75 mg/kg/hour for nonchronic drinkers [10,11].

CASE REPORTS

Case 1. A 50 year old, 80 kg man with a history of ethanol abuse was admitted following the ingestion of a gasoline antifreeze (Heet®) containing 94.5 per cent methanol, 4 per cent isopropanol and 1.5 per cent antioxidants. The patient ingested 12 oz of the antifreeze with concomitant ethanol 36 hours prior to admission, and an additional 4 oz of the antifreeze without ethanol 20 hours prior to admission. He complained of severe nausea and blurred vision. Arterial blood gases on admission were oxygen tension (pO$_2$) 125 torr, carbon dioxide tension (pCO$_2$) 14 torr, bicarbonate 4.8 meq/liter and pH 7.16. The blood methanol concentration on admission was 282 mg/dl, without a detectable blood ethanol concentration. Treatment was initiated with intravenous fluids, sodium bicarbonate and hemodialysis. Due to technical difficulties, the initial blood flow rate during dialysis was only 100 ml/min. Ethanol (86 proof whiskey) was administered concurrently as an oral loading dose of 180 ml (60 g ethanol) over 30 minutes. This was followed by an oral maintenance dose of 15 g/hour (45 ml/

hour). After one and a half hours the blood flow rate during dialysis was increased to 180 ml/min. Ethanol etherapy was continued for 36 hours after the termination of dialysis.

Case 2. A 50 year old, 51 kg woman with a history of ethanol abuse was admitted several hours following the ingestion of approximately 12 oz of reagent-grade methanol. Examination revealed a lethargic, oriented woman who was intermittently vomiting. Arterial blood gases were pO$_2$ 92 torr, pCO$_2$ 30 torr, bicarbonate 15.9 meq/liter and pH 7.31. The blood methanol concentration on admission was 260 mg/dl, without a detectable blood ethanol concentration. Treatment was initiated with intravenous fluids, sodium bicarbonate and hemodialysis. The patient was given an oral loading dose of 100 ml of 86 proof whiskey (33.5 g of ethanol), and was maintained on oral ethanol during hemodialysis. Due to hypotensive episodes the initial blood flow rate during dialysis was only 110 ml/min. The oral ethanol maintenance dose at this flow rate was 12 g/hour (35 ml/hour). Subsequently, the dialysis flow rate was increased and maintained at 230 ml/min and the oral ethanol dose was increased to 15 g/hour (45 ml/hour). After dialysis, the ethanol therapy was continued with an intravenous infusion of 10 per cent ethanol at a rate of 5.9 g/hour (75 ml/hour).

RESULTS

Patients. Both patients survived without sequelae. Ophthalmologic examinations over the following year have revealed no abnormalities in either patient. In both patients moderate to severe metabolic acidosis developed, but the acidosis was reversed with sodium bicarbonate administration and hemodialysis.

Methanol. The blood methanol concentration immediately after dialysis in Patient 1 was 90 mg/dl and decreased to less than 5 mg/dl over the next 36 hours. The blood methanol concentration immediately after dialysis in Patient 2 was 40 mg/dl and declined to 10 mg/dl over the next 24 hours (**Figure 1**). Methanol half-lives before dialysis and during dialysis were eight and two and a half hours in the second patient. The slope of the reciprocal of $\Delta Cp/\Delta t$ vs Cp was zero. Therefore, methanol elimination was linear over this concentration range [5]. The total methanol clearance during dialysis was 142 ml/min, whereas the methanol clearance before dialysis was 44 ml/min. Methanol dialysance in the second patient was approximately 98 ml/min. Inadequate data collection precluded calculation of methanol kinetic parameters in Patient 1.

Ethanol. Three blood ethanol concentrations during hemodialysis of Patient 1 were 60 mg/dl. The blood ethanol concentration increased to 240 mg/dl eight hours after dialysis. Four blood ethanol concentrations during hemodialysis of Patient 2 were 80 to 85 mg/dl. The blood ethanol concentration four hours after dialysis was 60 mg/dl (Figure 1). Total apparent ethanol clearances during dialysis for the two patients were 420 and 290 ml/min. Metabolic ethanol clearances were 320 and 170 ml/min. Ethanol dialysances in the two patients were 100 and 120 ml/min.
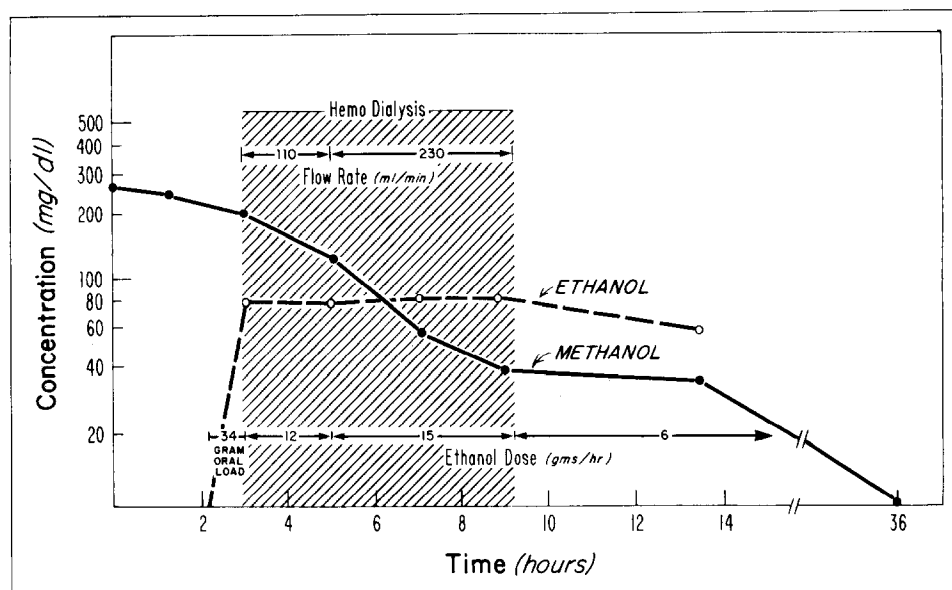
Figure 1. Blood methanol (solid line) and blood ethanol (dotted line) concentrations before, during and after hemodialysis. Methanol elimination was enhanced during hemodialysis (shaded area).

COMMENTS

A review of the literature revealed that the blood methanol concentrations in these two patients were among the highest reported (282 and 260 mg/dl) which were not associated with death or blindness [12]. The therapeutic success in these patients is attributed to the combination of early hemodialysis and adequate ethanol administration. Ethanol competes for the enzyme responsible for the generation of formic acid and formaldehyde. The enzyme system responsible for this major route of elimination is alcohol dehydrogenase. Ethanol has a higher enzyme affinity and is preferentially metabolized, whereas methanol is eliminated by nonmetabolic routes. Blood ethanol concentrations of 100 to 200 mg/dl have been regarded as optimal for inhibition [13], with a variety of ethanol regimens de-

signed to produce these concentrations [3,14-17]. The toxicity from methanol has been attributed to its metabolites for many years [13], although the evidence concerning these metabolites remains uncertain. Formate has been shown to accumulate in methanol poisoning and correlates well with the onset of metabolic acidosis and ocular toxicity [1,18]. Although formaldehyde has not been found in human or other primate methanol poisonings, it may still be responsible for a portion of methanol's toxicity due to formaldehyde's high reactivity [19].

Although zero-order kinetics have been utilized to describe ethanol elimination, several investigators have demonstrated ethanol's dose-dependent characteristics. Vestal et al. [11] determined a Vm of 75 mg/kg/hour in 50 healthy adult men, however, the Vm has been shown to vary significantly with ethanol intake [9,20,21]. A Vm

TABLE I   Ethanol Doses* for a 70 Kg Adult

		Loading Dose	Infusion Rate During Dialysis[†]	Infusion Rate After Dialysis	Total Over 36 Hours[‡]
Amount ethanol	Chronic drinker[§]	42 g	18.0 g/hr	10.8 g/hr	474 g
	Nondrinker[‖]	42 g	11.8 g/hr	4.6 g/hr	251 g
Volume of 10% intravenous	Chronic drinker	530 ml	228 ml/hr	137 ml/hr	6,010 ml
	Nondrinker	530 ml	149 ml/hr	58 ml/hr	3,180 ml
Volume of 43% oral	Chronic drinker	125 ml	54 ml/hr	32 ml/hr	1,410 ml
	Nondrinker	125 ml	35 ml/hr	14 ml/hr	749 ml
Volume of 90% oral	Chronic drinker	60 ml	26 ml/hr	15 ml/hr	666 ml
	Nondrinker	60 ml	17 ml/hr	7 ml/hr	359 ml

* Calculated to achieve and maintain blood ethanol concentration of 100 mg/dl.
[†] Assuming ethanol dialysance of 120 ml/min.
[‡] Assuming a 6 hour dialysis period.
[§] Assuming Vm = 175 mg/kg/hour, Km = 13.8 mg/dl.
[‖] Assuming Vm = 75 mg/kg/hour, Km = 13.8 mg/dl.

of 175 mg/kg/hour may be more appropriate for an alcoholic adult [10]. Wagner characterized a Km of 13.8 mg/dl while studying ethanol elimination in a concentration range which encompassed the Km [10]. This should provide a good estimate for Km.

Enhancement of the extrahepatic clearance of unchanged methanol is essential to prevent the accumulation of toxic metabolites resulting from incomplete inhibition of alcohol dehydrogenase or from a catalase system which is not inhibited by ethanol [22]. Elimination of methanol and its metabolites is greatly enhanced by dialysis [2], with hemodialysis being more effective than peritoneal [23]. Forced diuresis is not an effective method of enhancing removal, since less than 10 per cent of methanol is eliminated unchanged in the urine.

Maintenance of adequate ethanol concentrations during hemodialysis is complicated by the removal of ethanol by the procedure. Variations in flow rate and the ethanol extraction efficiency by various dialysis systems will affect the clearance [24,25]. The specific gravity of the ethanol solution varies with concentration and must be considered in determining the appropriate volume. The oral administration of ethanol is often preferable to the intravenous route because of the large volume of intravenous ethanol which may be required.

Both patients completely recovered without residual neurologic deficits, although previously recommended ethanol concentrations were not achieved. This is not surprising, however, since the affinity between human liver alcohol dehydrogenase and ethanol is 20 times that of methanol [26]. Therefore, substantial inhibition of methanol metabolism can be achieved at ethanol concentrations lower than the simultaneous methanol concentration.

In the treatment of an acute methanol ingestion in adults, an ethanol loading dose of 0.6 g/kg should be administered. An ethanol infusion of 66 mg/kg/hour for nondrinkers to 154 mg/kg/hour for chronic ethanol drinkers should be initiated to maintain the ethanol concentration (**Table I**). Hemodialysis should be considered after instituting supportive care, and ethanol therapy should be considered when the blood methanol level is above 50 mg/dl [2]. If hemodialysis is initiated, the ethanol dose should be increased by an increment of 7.2 g/hour during dialysis. Blood ethanol concentrations are beneficial to monitor and subsequently adjust ethanol therapy. If ethanol dialysance is calculated, the ethanol infusion can be further adjusted for individual dialysances. The ethanol infusion should continue until the blood methanol concentration reaches undetectable levels.

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