CASE REPORT

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Definitive Identification of an Exceptionally High Methanol Concentration in an Intoxication of a Surviving Infant: Methanol Metabolism by First-Order Elimination Kinetics

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ABSTRACT: Intoxication by methanol was identified in a five-week-old infant suffering from moderate metabolic acidosis. The initial serum methanol at admission was 1148 mg/dL as measured by gas chromatography. The osmolal gap and formic acid concentrations were consistent with methanol intoxication. The child was treated with folic acid and a continuous ethanol infusion and survived without any apparent permanent problems. Because expected toxic symptoms did not develop in this case, and the methanol concentrations were at levels that might be deemed to be incompatible with life, blood and urine samples were assayed by a specific enzymatic assay, and by gas chromatography/mass spectrometry (GC/MS). Positive results definitively confirmed the presence of methanol. In contrast to previous reports, the elimination of methanol in this case appeared to following first-order kinetics. If hepatic ADH activity is low in neonates and young infants, another enzyme system such as catalase may be involved to explain this data. The lack of formic acid accumulation may have been due to folic acid therapy.

KEYWORDS: toxicology, methanol intoxication, formic acid, alcohol dehydrogenase, catalase, first-order kinetics, gas chromatography/mass spectrometry

While there have been numerous reports of intentional consumption of methanol by adults, there are only a few published reports of accidental poisoning in young infants. Brent et al. found a methanol concentration of 27.1 mg/dL at 25 h after admission in an 6-week-old infant given infant formula accidentally diluted with methanol [*1*]. Shahangian et al. reported a concentration of 323 mg/dL at 7 h after the alleged administration in an 8-month child given an antibiotic preparation accidently diluted with methanol [*2*]. Kahn et al. found 40 mg/dL of methanol in an 8-month-old boy who subsequently died [*3*]. The route of administration was thought to be due to passive and continuous percutaneous resorption of a compress soaked with methanol, used to treat the child's cold.

As serum methanol concentrations in this case greatly exceed levels previously reported in either adults or children, questions were raised concerning the validity of the methanol measurement. In a similar highly publicized case, a woman was convicted of poisoning her child with ethylene glycol and was jailed. Reanalysis of the samples from the deceased child revealed that propionic acid from a methylmalonic acidemia was present, and not ethylene glycol [*4*]. The woman was subsequently exonerated and released. Without mass spectrometric detection, gas chromatography with flame ionization detection (FID) alone cannot distinguish ethylene glycol from propionic and glycolic acids in some assays, because the retention times are nearly identical [*5*]. Studies were conducted in this case to determine if an endogenous analyte mimicking methanol might be present in this child's serum and urine.

Because serum samples were collected very early and often during the intoxication, this case provides a unique opportunity to examine the pharmacokinetics of methanol.

Case History

S.P. was 7 pounds, 15 ounces at birth to parents of Indian descent. He has a two-year old sister who is alive with no medical problems. There was no significant family history of recurrent illnesses or early childhood deaths. For the first four weeks, the infant was doing well on infant formula, and was appropriate in weight gain. At five weeks, he became limp, lethargic, and was barely arousable. He was afebrile but was admitted to New Britain General Hospital (New Britain, CT) to rule out sepsis. The results of lumbar puncture were unremarkable. The infant was started on antibiotics pending blood, CSF, and urine cultures. He was acidotic with a serum bicarbonate of 18 meq/L. Cranial ultrasound and EEG were unremarkable. The infant's lethargy and weakness and acidosis gradually resolved and he was discharged to home on no medications after three days.

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He was readmitted to the same hospital two days later for the sudden onset of respiratory distress, irritability, lethargy, and weakness. He was transferred to the John Dempsey Hospital of the University of Connecticut (Farmington, CT) and was noted to have suprasternal retractions and stridor, consistent with an upper airway obstruction. Bronchoscopy demonstrated mild tracheomalacia. Laboratory results (Table 1) indicated a metabolic acidosis. He was treated with sodium citrate and citric acid (Bicitra), resulting in gradual clearing of the acidosis over a four-day period. The respiratory distress associated with the compensatory respiratory alkalosis and tracheomalacia also improved. He was discharged to home after nine days in good health with no medications.

The following day, the infant was again noted to be lethargic, irritable, with labored respirations. Because the previous hospitalizations failed to identify the cause of his recurrent episodes, he was referred to Hartford Hospital. Blood gases and electrolytes indicated a metabolic acidosis, with a bicarbonate of 18 meq/L that dropped to 14 by the following morning. Respiratory compensation was again complicated by tracheomalacia. Liver function and coagulation tests were normal as were lactate and pyruvate. He was treated and discharged to home after five days.

The next day, he was readmitted for decreased feeding, respiratory distress, lethargy, irritability, and poorly reactive pupils. Laboratory results again demonstrated a metabolic acidosis (Table 2). Because of the elusive nature of his recurrent acidosis, other studies were ordered. A very high serum osmolality result prompted analysis for volatile alcohols. A sample from admission was retrieved and tested for alcohols, producing a methanol concentration of 1148 mg/dL. The infant was started on folic acid and IV ethanol. As shown in Fig. 1, the methanol levels gradually decreased over a five-day period, with resolution of all clinical symptoms. An ophthalmology consultation did not demonstrate any obvious optic atrophy. The infant had normal visual responses for his age. He was fed a standard formula (Enfamil, Mead Johnson, Princeton, NJ) and discharged after two weeks. A specimen of blood from the previous admission at the John Dempsey Hospital was recovered and contained a methanol concentration of 52 mg/dL.

Due to the suspicious nature of this intoxication (and no accidental source of methanol exposure could be found in the home) police and child protection agencies were contacted and an investigation was begun. The child was placed in protective custody and discharged to a foster home. Criminal charges have been filed.

TABLE 2—*Summary of laboratory results at admission from Hartford Hospital.*

Test	Result
sodium	147 mmol/L
potassium	4.1 mmol/L
chloride	110 mmol/L
CO_2	12 mmol/L
anion gap	21 mmol/L
osmolality	585 mOsm/kg
calculated osmolality[a]	304 mOsm/kg
osmolal gap	281 mOsm/kg
glucose	97 mg/dL
creatinine	0.6 mg/dL
urea nitrogen	12 mg/dL
pH	7.34
PCO_2	23 mmHg
PO_2	100 mmHg (room air)
bicarbonate	13 mmol/L
ethanol	0 mg/dL
salicylate	15 mg/L
urine	positive for methanol

[a]Formula used: (1.86[Na^+] + [glucose]/18 + [BUN]/2.8)/0.93 [*8*].

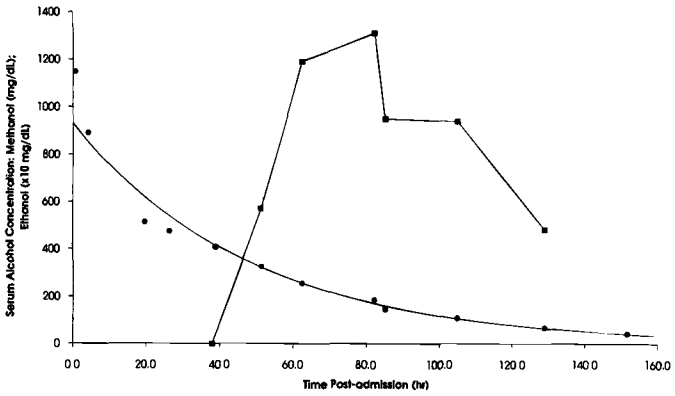

FIG. 1—*Serum methanol and ethanol levels in the case report. (●), methanol, (■), ethanol.*

Materials and Methods

Blood samples were collected by puncture of fingers and heels into low volume blood collection tubes (Microtainer, Becton Dickinson, Rutherford, NJ). Serum was assayed following centrifugation of blood. Because methanol was not initially recognized as the intoxicating agent, the initial five samples were assayed retrospectively. All subsequent samples were assayed prospectively when ordered. Urine was also collected for methanol analysis.

Specimens were assayed for methanol by three different procedures. The initial assay was performed using a direct-injection gas chromatographic assay (Model 5890, Hewlett-Packard, Palo Alto, CA), with a 5% Carbowax column (6′ × 1/8″), and a flame ionization detector. 1-Propanol was used as the internal standard. Samples were also assayed using an enzymatic assay as described by Vinet [*6,7*]. This assay makes use of alcohol oxidase coupled to formaldehyde dehydrogenase:

$$\text{methanol} + O_2 \xrightarrow{\text{alcohol oxidase}} \text{formaldehyde} + H_2O_2$$

$$\text{formaldehyde} + H_2O + NAD^+ \xrightarrow{\text{formaldehyde dehydrogenase}} \text{formic acid} + NADH + H^+$$

TABLE 1—*Summary of laboratory results from the John Dempsey Hospital.*

Test	Result
pH	7.35
pCO_2	29 mm Hg
pO_2	48 mm Hg
bicarbonate	16 mmol/L
organic acids	No unusual organic acids
amino acids	All normal except:
methionine	1993 nmol/mg creat (174–1090)
lysine	997 nmol/mg creat (189–850)
pyruvate	23 μmol/L (34–80 μmol/L)
non-esterified fatty acids	0.26 mmol/L (0–2.3)

The reaction was monitored by the increase in absorbance at 340 nm. Although other alcohols react with this oxidase, the specificity of the assay is determined by the coupling reaction, as formaldehyde is produced only from methanol. Studies have shown that this assay is not affected by other alcohols or other commonly prescribed drugs.

Serum and urine samples were also assayed by GC/MS. Ten microliters of plasma were diluted with 80 μL of reagent grade water and analyzed on a HP 5890/5988 GC/MS (Hewlett Packard). One microliter volumes of the diluted solutions were injected onto a FFAP (25 m × 0.18 mm, 2.0 μ) capillary column at a flow rate of 0.67 mL/min and a 1:44 injector split flow. The injector temperature was operated at 120°C and the interface line to the mass spectrometer was at 175°C. During the analysis, the column temperature was held at 40°C for 1 minute and then ramped to 80° at 10°C/min and held for 1 minute. After the analysis, the column temperature was increased to 140°C and held for 5 minutes prior to reequilibration a 40°C. The mass spectrometer was operated in the full-scan mode collecting spectral data from *m/z* 10 to 300 at 1.2 scans/sec. Aqueous standard solutions of methanol (50, 100, 200, 1000, and 2000 μg/mL) were analyzed along with a diluted negative plasma control, a diluted positive plasma control (80 mg/dL acetone, 40 mg/dL methanol, 80 mg/dL isopropanol and 150 mg/dL ethanol) and the diluted patient's plasma. The patient's plasma was analyzed after the negative plasma control and with reagent grade water analyzed between each sample.

Formic acid concentrations were assayed by the Nichols Institute Laboratories (San Diego, CA) on two serum samples collected at 4.3 and 51.3 h after admission.

Results

Independent evidence demonstrated the presence of methanol in the serum of this patient. Figure 1 shows the GC-FID results for methanol vs. time after admission. These data suggest an acute intoxication of some low molecular weight compound. A patient with an inborn metabolic disease would be expected to have more of a steady state concentration of a specific organic or amino acid. Figure 2 shows that the metabolism of this substance was linear when plotted on a semilogarithmic scale. This data is consistent with a first-order rate of elimination, with an estimated $t_{1/2}$ of 33 hours.

Results of serum samples collected at 3.5, 19.0, 26.6, and 38.3 h after-admission and assayed by the enzymatic procedure specific for methanol (Table 3). Results are within experimental error from values obtained from the GC-FID assay.

GC/MS was performed on samples collected at 26.6 and 51.3 h after admission and provided further documentation of the presence of methanol. All samples tested for methanol contained a chromatographic peak with a retention time relative to the internal standard that was within 2% that of the reference methanol standard analyzed at the same time. Figures 3 and 4 show the GC/MS data of the patient's serum sample collected at 26.6 h after admission (*A*), compared to that of the quality control sample containing acetone, methanol, isopropanol, and ethanol (*B*), and the aqueous methanol standard (*C*). In both of the patient's sample, the retention time of the peak was within 0.6% of that of the standard. The mass spectrum for each of the two patient samples matched that of the methanol standard with a cross correlation of 0.999.

Other data supporting the presence of methanol in this case include the osmolality, osmolal gap, and formate concentrations. The osmolal gap (Table 2) was 281 mOsm/kg, which is consistent with the presence of a low molecular weight substance at high concentrations. The corresponding methanol concentration on this sample was 890 mg/dL. This contributes 278 mOsm/kg to the osmolal gap. Other alcohols such as ethanol, isopropanol, and ethylene glycol were ruled out by their absence on the gas chromatogram. The formic acid concentrations on blood collected at 4.3 and 51.3 h after admission were 55 and 28 mg/dL (Table 3). These data taken together give undisputable evidence that methanol was present and likely caused toxic sequelae in this case.

Discussion

This case is the highest reported serum methanol concentration, and among the youngest of victims, with poisoning beginning at 5 weeks of age. Toxicity resulting from methanol intake has been attributed to the onset of metabolic acidosis caused by increases in blood formic acid concentrations. This highlights the role of "lethal synthesis" usually associated with methanol and other alcohols such as ethylene glycol. The parent compound causes little inherent toxicity. Methanol is sequentially oxidized first to formaldehyde by alcohol dehydrogenase (ADH) and then to formic acid. Formic acid is further oxidized to carbon dioxide by the tetrahydrofolate cycle. If the rate of methanol oxidation to formic acid

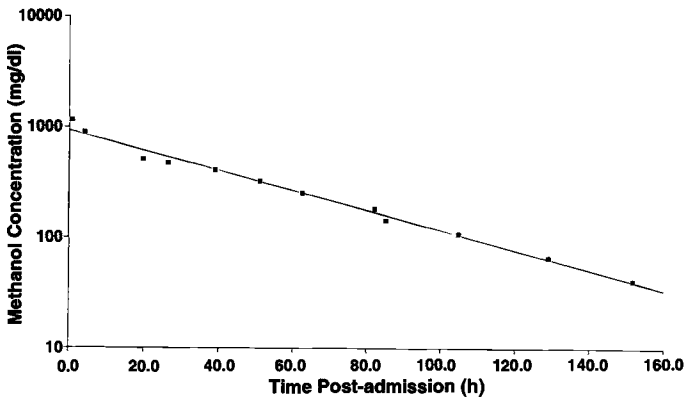

FIG. 2—*Semilogarithmic plot of methanol concentrations vs. time after admission to the hospital.*

TABLE 3—*Results of methanol and metabolites.*[a]

Time[b]	Methanol, GC-FID	Methanol, enzymatic	Formic acid	Ethanol, enzymatic
0.8	1148	—	—	NA[c]
4.3	890	752	55	NA
19.8	512	534	—	NA
26.6	473	—	—	NA
39.1	408	485	—	NA
51.3	324	369	28	57
62.6	253	—	—	119
82.3	183	—	—	131
85.3	145	—	—	95
105.1	108	—	—	94
129.1	66	—	—	48
151.8	41	—	—	discontinued

[a]All results in mg/dL.
[b]Time in hours from admission to blood collection.
[c]Ethanol not administered.

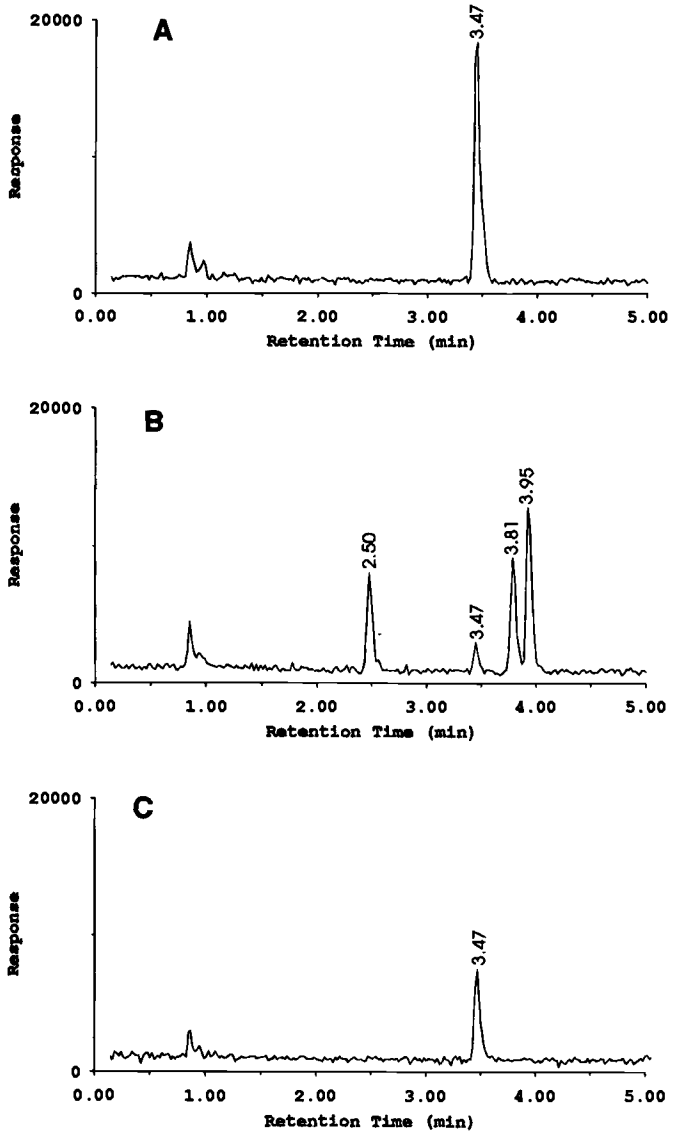

FIG. 3—*Total ion gas chromatograms of* (A) 1/9 *dilution of patient's plasma collected at 26.6 h after admission (methanol concentration 473 mg/dL);* (B) 1/9 *dilution of control plasma containing 80 mg/dL acetone (*R_t 2.50 min), 40 mg/dL methanol (R_t 3.47), 80 mg/dL isopropanol (R_t 3.81), 150 mg/dL ethanol (R_t 3.95) and (C) *200 mg/dL aqueous methanol standard.*

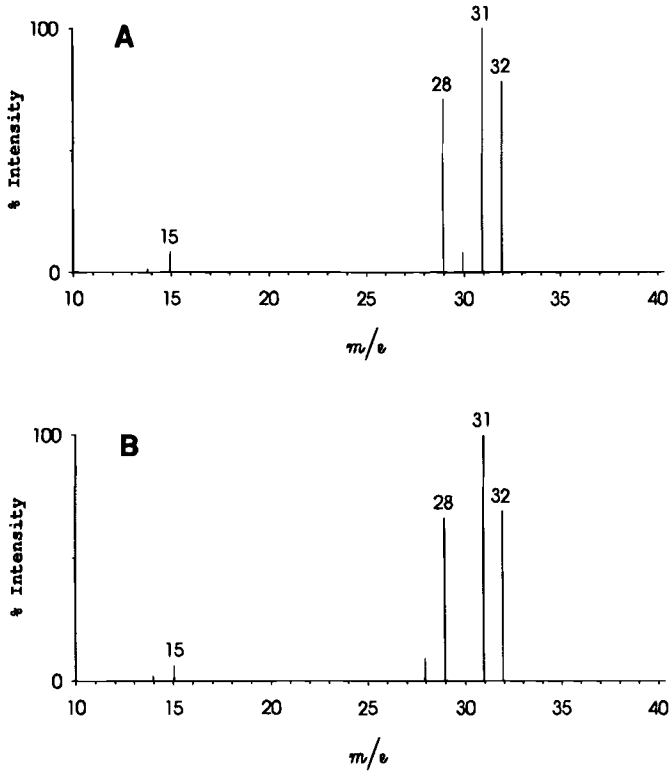

FIG. 4—(A) *Mass spectrum of compound in patient's plasma with a retention time of 3.47 minutes and* (B) *mass spectrum of the methanol reference standard.*

exceeds the rate of its subsequent oxidation to CO_2, blood formic acid concentrations will increase. Formate accounts for most of the toxic effects of methanol intoxication, such as mental status changes, severe anion gap metabolic acidosis, and retinal changes with visual loss [*8*]. Mathieu showed that base deficit and decreases in total CO_2 as a direct result of format accumulation, were correlated to the development of ocular sequelae [*9,10*].

Kinetic experiments in non-human primates [*11*] and case studies of human methanol intoxications [*12*] have shown that methanol normally follows zero-order elimination kinetics. Hepatic metabolism is the major route of elimination. Estimates for methanol elimination by pulmonary exhalation and renal excretion are insignificantly low compared to hepatic oxidation [*13*]. In non-human primates the K_m for alcohol dehydrogenase (ADH) using methanol as a substrate was 28 mg/dL (with a V_{max} of 8.0 mg/dL/h) [*14*]. The rate of formic acid oxidation in non-human primates has been estimated to be 5.5 mg/dL/h. From these kinetic data, blood methanol concentration exceeding about 35 mg/dL should result in zero-order metabolism for methanol, with subsequent accumulation of formic acid in the blood [*13*].

In this case, the serum methanol concentration greatly exceeded saturating concentrations for hepatic ADH. Nevertheless, the rate of methanol metabolism appeared to follow a first-order rate. Moreover, there was minimal accumulation of formic acid. Closer examination of the plot in Fig. 1 might suggest the presence of two first-order phases: one before and one after initiation of ethanol therapy. Although it is possible that the first specimen was obtained prior to full absorption and distribution of methanol, the clinical presentation of a 5-hour period of symptoms prior to admission does not support this. It is more likely that sample integrity may have accounted for deviations from this fit, as early samples were collected for other purposes and were not assayed prospectively for methanol. For example, serum collected at 19.8 and 26.6 h may have lost methanol producing falsely low results.

Although first-order elimination kinetics have been described previously in patients with high concentrations of ethanol [*15,16*], this is the first report of this rate for methanol. The average rate of methanol elimination between 4.3 and 51.3 h post-admission was 12 mg/dL/h (3.8 mmol/L/h). The formic acid concentration over this period decreased at a rate of 0.6 mg/dL/h (0.13 mmol/L/h). If the elimination of methanol was entirely due to oxidation to formic acid, then the rate of formic acid oxidation to CO_2 during this time would have been 17.9 mg/dL/h. This is considerably higher than the rate observed in non-human primates (5.5 mg/dL/h) [*13*]. The ability to limit the concentration of blood formic acid

concentration in this patient undoubtedly was responsible for his lack of serious physical injury.

This case report raises two important questions. *Why did methanol metabolism follow first-order kinetics?* Based on previous published reports, ADH cannot alone explain the observed first-order kinetics of methanol clearance in this patient. Pikkarainen and Raiha have shown that infants aged 9 days to 2 months had 80% less ADH activity for ethanol than older children and adults [*17*]. Moreover, the V_{max} for ADH with ethanol as a substrate is about 6 times lower in neonates than in adults. Methanol has been described as having 10% of the affinity of ethanol for ADH [*13*].

The high rate of methanol metabolism in this case suggests the presence of an alternate non-saturated mechanism of elimination. Catalase is another enzyme capable of oxidizing methanol to formaldehyde. Studies in ADH-deficient deer mice have shown that hepatic methanol oxidation proceeds by catalase [*18*]. This enzyme is rate limited by the availability of the substrate, hydrogen peroxide. However through lipid peroxidation, higher rates can be achieved by dietary supplement of palmitic or oleic acids [*19*]. If catalase (or some other alcohol oxidizing enzyme) has a high K_m for methanol, first-order elimination kinetics might occur. At low methanol concentrations, catalase activity may be low compared to ADH and contributes little to the elimination of methanol. However, as the concentration of methanol increases, ADH becomes rate limiting while the rate of oxidation by catalase might continue to increase. First order elimination kinetics for methanol would result if the V_{max} for catalase exceeds the V_{max} for ADH, or if catalase is present at much higher amounts relative to ADH.

In this case, ethnic variations in ADH isoenzyme content [*20*] are unlikely to account for the observed first-order elimination kinetics, as the ADH activity was probably low due to the age of the subject. Rather, low ADH activity in neonates might mimic the ADH-deficient deer mouse model [*18*], and suggesting the role of catalase for metabolism of methanol. The child was placed on a milk formula supplemented with linoleic acid, which may have made increased the availability of H_2O_2 as the substrate. Furthermore, the child was previously given methanol, as evidenced in the Case Report, which may have induced hepatic catalase activity.

Why was the rate of formic acid oxidation so high? If the elimination of methanol over this period of time was due to oxidation to formic acid, then the rate of formic acid oxidation to CO_2 must have been accelerated. The rate of formic acid oxidation by the tetrahydrofolate cycle is rate limited by the availability of folic acid [*13*]. Since the child's formula was also supplemented with folic acid at a level that was twice that of breast milk, blood folic concentration should have been higher than in normal adults or neonates. Even higher folic acid concentrations would be expected in this child relative to chronic alcoholic patients who intentionally ingest methanol, as they are often deficient in dietary folate and vitamin B12. Folate supplementation may be an important factor in the accelerated rate of formic acid oxidation that is postulated in this child. Unfortunately, folic acid concentrations were not obtainable because of the instability of folic acid in stored samples.

The beneficial effects of ethanol administration in this patient are unclear. Ethanol is often given to compete against methanol to retard its rate of elimination by ADH. The affinity of ADH is much greater for ethanol than for methanol, and several investigators have shown that serum ethanol concentrations as low as 20 mg/dL are effective in completely blocking methanol oxidation in adults with low (<10 mg/dL) serum methanol concentrations [*21*]. The recommended target ethanol concentration of 100 mg/dL was followed in this case. Although the rate of methanol metabolism was faster during the hours prior to ethanol therapy, nevertheless, methanol metabolism continued under first-order kinetics after therapy. The patient described by Brent et al. [*1*] also did well clinically without ethanol therapy. For pediatric patients poisoned with methanol, folate supplementation may be critical in avoiding accumulation of formate.

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