A Case of Poisoning by a Mixture of Methanol and Ethylene Glycol

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Arai, H., Ikeda, H., Ichiki, M., Iino, M., Kumai, M., and Ikeda, M. A Case of Poisoning by a Mixture of Methanol and Ethylene Glycol. Tohoku J. exp. Med., 1983, 141 (4), 473-480 — A fatal case of poisoning by a mixture of methanol and ethylene glycol is described. A 72-year-old man was hospitalized when he was found stuporous to semicomatose, and despite massive bicarbonate therapy, died 36 hr after the admission. While the presence of numerous oxalate crystals in urine strongly suggested ethylene glycol intoxication, the GC analysis of the liquid the patient ingested revealed that he presumably drunk about 150 to 200 ml of a mixture of methanol (80%) and ethylene glycol (20%), the amount well over the lowest lethal dose when the additiveness of toxicity was considered. Retrospective evaluation of the signs suggested that while some of them such as oxalate crystalluria, elevated CPK, hypocalcemia, renal failure are attributable to the toxicity of ethylene glycol, others including elevated serum amylase and cyanosis are indicative of methanol poisoning. Disturbed consciousness was considered to be of metabolic origin; the high anion gap observed (38.2 mEq/liter) may be due not only to lactic acidosis but also to acidogenicity of the two chemicals ingested. The importance of gas chromatographic analysis for identification of the causative chemical(s) is stressed. — ethylene glycol; GC analysis; methanol; poisoning

While the poisoning by either methanol (Bennett et al. 1953; Closs and Solberg 1970; Bohn et al. 1974; Chinard and Frisell 1976; Naraqi et al. 1979; Scrimgeour 1980; Lins et al. 1980; McLean et al. 1980; Swartz et al. 1981) or ethylene glycol (Hagstam et al. 1965; Ahmed 1971; Parry and Wallach 1974; Vale et al. 1976; Forycki et al. 1979; Stokes and Aueron 1980; Berger and Ayyar 1981) alone is well documented in the literature, no report has ever

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appeared, to the knowledge of the present authors, on the intoxication attributable to the mixture of these two organic chemicals popular in the community.

It is the purpose of the present communication to report a case of death after ingestion of a mixture of 80% methanol and 20% ethylene glycol. Clinical spectrum of the patient will be discussed to identify the symptoms and signs attributable to either methanol or ethylene glycol, or common to both, with special reference to the fact that both of the two chemicals are strongly acidogenic when metabolized in vivo (McMartin et al. 1975; Emmett and Narins 1977; Clay and Murphy 1977; anonymous 1979; Sirridge 1981; Smith et al. 1981; Smith et al. 1982). Emphasis is also given to the validity of gas chromatographic analysis for the causative agent to establish the diagnosis.

**Case Report**

A 72-year-old man with a history of alcohol abuse but otherwise noncontributory was admitted to our hospital on October 25, 1981, because of disturbed consciousness. Five hours prior to the admission, he was discovered by his daughter, who visited him on that day, to be badly drunk with decreased responsiveness and slurred speech. The daughter took him to her home by car, and he vomited on the way. The patient remained unresponsive even after he arrived at the daughter's home, and transferred to our hospital as the level of consciousness was declining unexpectedly.

On examination the patient was stuporous or semicomatose with deep breathing. His breath, however, had no odor of ethanol nor acetone. The skin was cold and livedo-like cyanosis was observed, although his cardiovascular function was well maintained, i.e., the blood pressure was 160/100 Torr and the pulse rate was 90 per minute. Neither cervical lymphadenopathy nor struma was detected, and there was no sign of head trauma. Heart sounds were clear and rales were not heard. On abdominal examination there was no hepatosplenomegaly. Neither tenderness nor muscle guarding was elicited. Neurological examination showed that the patient was severely confused. The eyes were situated in midposition and nystagmus was not recognized. The pupils were slightly miotic and constricted sluggishly on exposure to light. Optic fundi appeared normal. The extremities were flaccid and deep tendon reflexes were not elicited, nor Babinski's reflex.

Immediately after admission drip infusion of physiological saline was begun and hydrocortisone (2,000 mg) was also given. In the arterial blood taken while the patient was breathing with a nasal cannula (oxygen supply at ca. 2 liters/min), partial pressure of oxygen (P_{a}O_{2}) was 150 Torr, that of carbon dioxide (P_{a}CO_{2}) 12.5 Torr, plasma bicarbonate level (HCO_{3}^{-}) 2.3 mEq/liter, base excess (BE) -30.5 mEq/liter, and pH 6.89, indicating metabolic acidosis. Hematology and blood biochemistry studies disclosed the followings: Hematocrit, 51.9%, RBC, 4.52×
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10^6/mm³; WBC, 16,800/mm³ with 86% neutrophils and 11% stab cells; platelets, 187 x 10^4/mm³; sugar, 100 mg/100 ml; BUN, 20.1 mg/100 ml; Ca, 6.5 mg/100 ml; P, 6.6 mg/100 ml; NH₄OH, 91 μg/ml; fibrinogen, 252 mg/100 ml; lactate, 7.6 mEq/liter (normal range: 0.4–0.8); pyruvate, 0.35 mEq/liter; Na, 150 mEq/liter; K, 4.5 mEq/liter; Cl, 114 mEq/liter; GOT, 31 Karmen units (normal range: 9–40); LDH, 480 Wroblewski units (normal range: 50–400); CPK, 208 units (normal range: 10–80); amylase, 334 Caraway units (normal range: 60–160). Urinalysis revealed 46 mg protein/100 ml, but neither acetone nor glucose was detected. There were innumerable red blood cells and 8 white blood cells per high power field as well as numbers of crystals consistent with calcium oxalate in the sediment. An electrocardiogram demonstrated atrial fibrillation with the inverted T wave in II and V₃₋₆, flat T wave in I and aVL, and prolongation of Q-T interval. An X-ray film of the chest showed no abnormality. An ultrasound examination of the kidneys appeared normal.

After bolus intravenous injection of 100 ml of 7% sodium bicarbonate solution to correct metabolic acidosis, arterial blood taken while the patient was breathing oxygen-added air with the nasal cannula disclosed that \( P_{aO₂} \) was 176 Torr, \( P_{aCO₂} \) 13.1 Torr, \( HCO₃^- \) 4.6 mEq/liter, BE –21.8 mEq/liter and pH 7.16. Succeedingly, another 100 ml of 7% sodium bicarbonate was administered and the level of consciousness was improved to somnolent or drowsy state. Continuous drip infusion of 7% sodium bicarbonate solution was begun. Urinary flow was good. Although the metabolic acidosis had been gradually corrected by large volume of 7% sodium bicarbonate (total volume coming up to 1700 ml), the level of consciousness stayed no better than somnolent or stupor. About 30 hr after the admission, the patient became anuric and left-sided hemiconvulsion occurred repeatedly. The administration of 20% mannitol and 10% phenobarbital were ineffective. Hemodialysis was not available. No trial of ethanol therapy was made. The patient died with no definite diagnosis 36 hr after the admission. Autopsy could not be performed.

**GC Analysis of the Liquid Ingested by the Patient**

After the death of the patient, the patient’s wife brought us blue liquid which she said the patient was considered to have ingested. Accordingly, trials were made to identify the constituents of the liquid by gas chromatography (GC). The GC used was a Hitachi GC Model 163 equipped with FIDs, stainless steel columns (3 mm in diameter and 2 m in length, packed with 5% PEG-HT on Uniport-HP, 60–80 mesh) and connected with a Hitachi recorder Model 065. The temperature of the injection port and the columns was 230°C and 170°C, respectively. The supply of the carrier \( N₂ \) was at 30 ml per minute, while that of \( H₂ \) and air to FIDs were at 0.8 and 1.5 kg per cm², respectively.

When 2 μl of the sample liquid was injected, two peaks were detected which were clearly separated from each other as shown in Fig. 1. The comparison with
authentic reagents revealed that the first peak indicated methanol and the second one ethylene glycol. By calculating the area of each peak, it was estimated that the liquid ingested by the patient is a mixture of approximately 80% methanol and 20% ethylene glycol (V/V). The presence of methanol was further confirmed by GC with two FS-WCOT capillary columns (0.25 mm in inner diameter × 50 m in length) of Silicone OV 101 and PEG 6000. Diagnosis was made retrospectively that the patient was poisoned by a mixture of 80% methanol and 20% ethylene glycol to death.

DISCUSSION

As this case is an intoxication due to a mixture of 80% methanol and 20% ethylene glycol, the toxicity of each chemical should be considered to evaluate the clinical spectrum of the patient.

The most remarkable finding on admission was stuporous or semicomatose state of consciousness continued over a whole clinical course despite intensive alkali therapy. Six hr after the onset of acute renal failure which supervened 30 hr after the admission, the patient died. The most striking biochemical abnormality was severe, alkali-resistant metabolic acidosis; the blood pH was 6.89 immediately after admission, and was 7.16 after bolus intravenous injection of 100 ml of 7% sodium bicarbonate. On initial examination, gross inspection suggested cerebrovascular accident involving the brain stem and the reticular activating system. Hydrocortisone was administered to protect the patient from deteriora-
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deterioration of the general condition (anonymous 1979). Blood gas analysis, however, revealed an extraordinary feature of acid-base balance, i.e., severe metabolic acidosis with a high anion gap (Emmett and Narins 1977) of 38.2 mEq/liter (normal range: approximately 12 mEq/liter). The case of disturbed consciousness and other neurological signs were thus considered to be of metabolic origin, and not due to cerebrovascular damage. Worthy of noting is the fact that both methanol and ethylene glycol are acidogenic poisons (Parry and Wallach 1974; McMartin et al. 1975; Vale et al. 1976; Emmett and Narins 1977; Clay and Murphy 1977; anonymous 1979; Sirridge 1981; Smith et al. 1981; Smith et al. 1982). While lactic acidosis was present at an arterial lactate level of 7.6 mEq/liter, this level was not enough to explain the high anion gap observed. The formation of acidic compounds during the biotransformation of both methanol and ethylene glycol should be taken into accounts for the explanation of the remaining anion gap.

Although four clinical conditions, i.e., uremia, ketoacidosis, lactic acidosis and acidosis due to acidogenic poisons, are known to be associated with high anion gap metabolic acidosis (Emmett and Narins 1977; Sirridge 1981), the detection of number of oxalate crystals in urine strongly suggested that the case was ethylene glycol intoxication (Bunuan 1978; Bowen et al. 1978; Godolphin et al. 1980). The clinical spectrum of the case was further reevaluated retrospectively when the GC analysis for causative chemicals established the conclusive diagnosis of poisoning by a mixture of methanol and ethylene glycol. While some signs such as vomiting, drunkenness, disturbance of consciousness, severe metabolic acidosis are common to the toxicities of both chemicals concerned, flaccid extremities and areflexia (Pons and Custer 1946; Hagstam et al. 1965; Berger and Ayyar 1981), oxalate crystalluria and hematuria (Bunuan 1978; Bowen et al. 1978; Godolphin et al. 1980), elevation of CPK (Parry and Wallach 1974) hypocalcemia and hyperphosphatemia (Rajagopal et al. 1977; O'Connor et al. 1977; Bunuan 1978; Bowen et al. 1978; Godolphin et al. 1980), leukocytosis (Forycki et al. 1979), focal convulsion and renal failure (Hagstam et al. 1965; Parry and Wallach 1974; Vale et al. 1976; Forycki et al. 1979) in the late period are more clearly understood as signs of ethylene glycol toxicity.

Other abnormal findings included elevated serum amylase, miotic and sluggishly reactive pupils, and livedo-like cyanosis. Elevation of serum amylase may be explained by pancreatitis due to methanol. In fact, the elevation of serum amylase was reported to be the most striking abnormality in laboratory findings of methanol poisoning (Bennett et al. 1953) and frequently observed especially in fatal cases (Naraqi et al. 1979), e.g., pancreatic necrosis was detected in 13 of 17 cases of methanol poisoning at autopsy (Bennett et al. 1953). Amazingly enough, this patient had cyanosis although cardiovascular function was well maintained. While the mechanism of cyanosis remains unclear, this sign seems to be due to methanol, and not to ethylene glycol. Rφe (1946) called cyanosis seen in
cyanosis seen in methanol-intoxicated patients "a blend of rubeosis and cyanosis". Dilated, non-reactive pupils are characteristic of acute methanol poisoning (Rae 1946; Bennett et al. 1953; anonymous 1979). In the cases of ethylene glycol intoxication, pupils were reported to be normal-sized or dilated (Ahmed 1971; Michelis et al. 1976; anonymous 1979). The present patient, however, showed miotic pupils which could not be attributable to the toxicity of either methanol nor ethylene glycol (Fig. 2).

Judging from the amount missing from the bottle from which the patient had drunk the liquid, the amount ingested was estimated to be about 150–200 ml. Considerations were made whether or not this amount be lethal to the patient. Trial was made to estimate the lowest lethal dose (LDL) of the liquid consisting of 80% methanol and 20% ethylene glycol (V/V) on the basis of additive effect of these chemicals, utilizing Finney's formula (Finney 1952) to predict LDL of the mixture as follows:

$$\frac{1}{\text{LDL predicted}} = \frac{P_a}{\text{LDL of component A}} + \frac{P_b}{\text{LDL of component B}}$$

where $P_a$ and $P_b$ represent the proportions of component A and B in the mixture.
The lowest published lethal dose of methanol and ethylene glycol for man (National Institute for Occupational Safety and Health 1980) are 340 mg/kg (≈ 0.269 ml/kg) and 710 mg/kg (≈0.788 ml/kg), respectively. The calculation gives 0.310 ml/kg as the LDL of the mixture. When the body weight is assumed to be 60 kg, the estimate of the amount ingested (150–200 ml) would be about 10 times as large as the calculated LDL of 18.6 ml/60 kg.

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