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CASE REPORT

Use of Fomepizole in Pediatric Methanol Exposure: The First Case Report in Taiwan and a Literature Review

Tzu-Hua Chen [a,b], Chang-Hung Kuo [c,d], Chia-Tsuan Huang [a,c,e], Wei-Li Wang [c,f,g,*]

[a] Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[b] Department of Family Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan
[c] Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[d] Department of Pediatrics, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan
[e] School of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan
[f] Department of Emergency, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan
[g] Department of Pediatrics, True Generation Hospital, Kaohsiung, Taiwan

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Methanol poisoning is rare in the pediatric population, but a delay in diagnosis and intervention may cause severe morbidity and mortality. The current therapy for methanol poisoning is ethanol or fomepizole, which acts as a competitive inhibitor of hepatic alcohol dehydrogenase to inhibit the production of toxic metabolites derived from the oxidation of methanol. However, clinical experience in pediatric methanol poisoning is limited, and the safety profiles of the antidotes have not been established in children, especially in Asian populations. This is the first case to describe the use of fomepizole in a child with methanol exposure in Taiwan.

1. Introduction

Methanol is commonly used in antifreezes, solvents, and many other products. Methanol itself is not toxic, but it is oxidized by hepatic alcohol dehydrogenase to formaldehyde and then oxidized to formic acid, which is responsible

* Corresponding author. Department of Pediatrics, Kaohsiung Medical University Hospital, Number 100 Shih-Chuan First Road, Kaohsiung City 807, Taiwan.
E-mail address: fordrwang@yahoo.com.tw (W.-L. Wang).

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for metabolic acidosis and retinal toxicity.[1] Even small amounts of methanol ingestion may be fatal in children without timely treatment.[2] The traditional antidote is ethanol, a competitive inhibitor of alcohol dehydrogenase, to inhibit the metabolism of methanol. Fomepizole (4-methylpyrazole), a more potent competitive inhibitor of alcohol dehydrogenase, has been recommended as a superior antidote due to higher efficacy and less adverse effects than ethanol.[1] However, clinical experience of fomepizole use in children is limited,[3] and no cases have been reported in Asian populations. Herein, we report a case of pediatric methanol exposure with successful treatment of fomepizole.

2. Case Report

A 1-year, 5-month-old boy swallowed an unknown amount of alcohol paste (content = 80% methanol), which was a type of fuel of a chafing dish. He was sent to the emergency department 50 minutes after ingestion. Initial vital signs were stable. His consciousness was alert, but his activity was mildly to moderately decreased. His body weight was 10 kg. Physical and neurological examinations were normal. A blood gas analysis was as follows: pH, 7.176; PCO_2, 49.9 mmHg; PO_2, 104.4 mmHg; and bicarbonate, 18 mmol/L. Biochemical analyses of plasma revealed the following: sodium, 138 mmol/L; potassium, 4.4 mmol/L; chloride, 108 mmol/L; lactate, 2.1 mmol/L; blood urea nitrogen, 6.7 mmol/L; creatinine, 23.0 μmol/L; and glucose, 4.8 mmol/L. Anion gap was 12 mEq/L. The measured serum osmolality was 294 mOsm/kg, and the calculated serum osmolarity was 288 mOsm/kg, yielding an osmolal gap of 6 mOsm/kg. Serum concentrations of methanol and ethanol were measured, but the data could not be obtained immediately.

Initially, we performed nasogastric irrigation and fed the patient 45 cc of Shaoxing wine (content = 17% ethanol), and then we initiated fomepizole therapy. He received a 15 mg/kg loading dose of fomepizole and was then admitted to the pediatric intensive care unit.

Five hours after the loading dose, arterial pH level was 7.354, and serum bicarbonate level was 21 mmol/L. We continued to give him a 10 mg/kg maintenance dose of fomepizole every 12 hours, and we also administrated intravenous sodium bicarbonate to correct acidemia. Measurement of arterial blood gas, electrolytes, blood urea nitrogen, creatinine, glucose, and serum methanol concentration was followed up every 6 hours. Arterial pH and serum bicarbonate levels over time are shown in Figure 1. No visual deficits were found by the ophthalmologist on the 2nd day. After treatment, vital signs were stable, and no additional acidemia was noted, thus we discontinued fomepizole. He was transferred to the general pediatric ward on the 4th day and discharged on the 5th day. We obtained the following reports on the 9th day: serum concentration of methanol <0.1 mg/dL and ethanol <5 mg/dL on arrival to the emergency department and subsequent follow-up, respectively. No signs of methanol intoxication, no visual deficits, and no adverse effects of fomepizole were found at the outpatient department on the 10th day.

3. Discussion

Methanol is absorbed rapidly by the gastrointestinal tract and reaches peak concentration within 30–60 minutes.[4] The typical signs and symptoms of methanol poisoning include visual dysfunction, nausea, vomiting, abdominal pain, and central nervous system depression, with a latent period of 12–24 hours for methanol to oxidize to toxic metabolites.[2,4] Therefore, the antidotes should be administrated as soon as possible prior to formate formation, and early treatment may prevent fatalities and the need for hemodialysis.[2,5] Serum methanol concentration is unavailable immediately; moreover, clinical symptoms, visual impairment, and mortality correlate closely to the degree of metabolic acidosis rather than to serum methanol concentrations.[4] The indications of ethanol or fomepizole therapy are listed in Table 1 according to the guidelines of the American Academy of Clinical Toxicology.[4] Here, we report the first pediatric case of methanol exposure to be treated successfully with fomepizole in Taiwan.

Interestingly, the laboratory data of our patient were not typical of those found in patients with methanol poisoning, including high anion gap metabolic acidosis with high osmolal gap. Osmolal gap is an important biomarker in methanol poisoning, but its wide normal range makes it insensitive to small concentrations of methanol.[6] The reference range of osmolal gap is from 0 mOsm/kg to

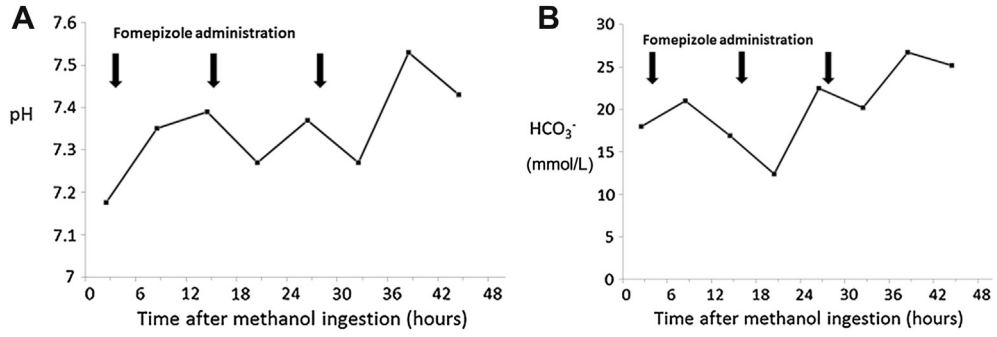

Figure 1 (A) Level of arterial pH over time after methanol ingestion. (B) Level of serum bicarbonate over time after methanol ingestion.

Table 1 Indications of ethanol or fomepizole therapy in methanol poisoning.

Criteria
Documented plasma methanol concentration >20 mg/dL or Documented recent history of ingesting toxic amounts of methanol and osmolal gap >10 mOsm/kg or History or strong clinical suspicion of methanol poisoning and at least two of the following criteria: (i) Arterial pH <7.3 (ii) Serum bicarbonate <20 mmol/L (iii) Osmolal gap >10 mOsm/kg

Note. From "American academy of clinical toxicology practice guidelines on the treatment of methanol poisoning," by D.G. Barceloux, G.R. Bond, E.P. Krenzelok, H. Cooper, and J.A. Vale. 2002, *J Toxicol Clin Toxicol*, *40*, p. 428. Copyright 2002. Marcel Dekker, Inc. Reprinted with permission.

10 mOsm/kg in a healthy adult, and from −13.5 mOsm/kg to 8.9 mOsm/kg in a healthy child.[7] As a result, a normal serum osmolal gap may be found in methanol poisoning in a child whose baseline osmolal gap is very low or negative. The increase of anion gap takes time because methanol metabolizes to formic acid gradually.[8] Our case was sent to the emergency department 50 minutes after methanol ingestion, thus serum anion gap may not have achieved a significantly high level in that time. It has been proposed that patients with methanol intoxication may present with high osmolal gap or high anion gap; however, few cases with osmolal gap and anion gap within the normal range have been reported.[8] In a study of toxicological case series of preschool children, some patients with symptoms had a negative serum methanol level.[9] In our case, the father witnessed the ingestion of alcohol paste, and its residue was found in the patient's mouth. Owing to the symptom of decreased activity and severe metabolic acidosis, which is most relevant to mortality of methanol poisoning, we prescribed fomepizole according to the antidote indication.

Ethanol is a traditional antidote for methanol intoxication. Oral ethanol is used as a temporizing antidote, and its kinetics is unpredictable due to high variability in individual metabolic rates and enteral absorption.[10] Intravenous ethanol is difficult to use because it requires central venous access due to hyperosmolarity. The adverse effects include hypoglycemia, hyponatremia, and cranial nervous system depression. In addition, it requires intensive care and close monitoring due to unstable serum ethanol concentration.[2]

Fomepizole was approved by the Food and Drug Administration (FDA) as an antidote for methanol poisoning in 2000.[1] It has been regarded as a more potent and safer antidote than ethanol. It is administrated conveniently via a peripheral venous line. The recommended loading dose is 15 mg/kg over 30 minutes, followed by a maintenance dose of 10 mg/kg every 12 hours for four doses. After 48 hours, additional doses of 15 mg/kg every 12 hours are given if necessary.[1] It has been suggested to discontinue therapy when the serum methanol concentration has decreased to below 30 mg/dL. A median of four doses of fomepizole was prescribed for methanol poisoning in prior clinical studies.[1] Its adverse effects include headache, nausea, dizziness, with rare reports of vomiting, seizure, and transient elevation of hepatic aminotransferase levels.[4,11] It is unnecessary to monitor serum fomepizole concentration due to its relative safety.[1]

The dosage regimen and clinical efficacy of fomepizole use has been well established in adults; nevertheless, clinical experience in pediatric patients is still limited. A review article reported 14 cases of pediatric ethylene glycol, diethylene glycol, butoxyethanol, and methanol poisoning with fomepizole therapy, and only four cases were younger than 2 years old, which highlights the limited data in the pediatric population.[3] We list an overview of all reported cases of pediatric methanol poisoning with fomepizole treatment in Table 2.[5,12–14] Fomepizole was given with the same dosage regimen as adults, and neither sequelae nor adverse effects were observed. According to the Taiwan antidote network, fomepizole is available in Taipei Veterans General Hospital, China Medical University Hospital, Kaohsiung Medical University Hospital, Buddhist Tzu Chi General Hospital, and Changhua Christian Hospital. The clinicians can contact the nearest hospital to obtain fomepizole.

In addition to antidote administration, we should also keep intravenous fluid supply to maintain adequate urine output to enhance the excretion of methanol.[2] Sodium bicarbonate administration is recommended for severe acidemia (pH < 7.3).[1] Hemodialysis should be considered for significant metabolic acidosis (pH < 7.25–7.30), vision impairment, unstable vital signs, renal failure, or electrolyte imbalance with poor response to treatment.[4]

In conclusion, fomepizole has been suggested to be an efficacious and safe antidote for methanol intoxication in adults, but there have been no reports in Asian children. In our case, we prescribed fomepizole for a 1-year, 5-month-old child with the dosage regimen the same as adults, and metabolic acidosis improved quickly, without any adverse

Table 2 Reported cases of pediatric methanol poisoning with fomepizole treatment.

Refs	Age, y	Ingested substance	Initial pH	Initial bicarbonate, mEq/L	Outcome	Adverse effects
Brown et al[12]	5	Windshield washer fluid	7.43	23	Normal	None
De Brabander et al[13]	3	Pure methanol	7.34	22	Normal	None
Rozenfeld and Leikin[5]	16	Windshield washer fluid	7.38	19	Normal	None
Leonard and Akhtar[14]	4	"Blue Thunder" model engine fuel (methanol and nitromethane)	Not reported	Not reported	Normal	None

effects or sequelae. Therefore, we report this successful experience for pediatricians as a valuable case in toxicological emergency.

Conflicts of interest

All authors declare that they have no potential conflicts of interest.

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