Ethylene Glycol Poisoning in a Child Treated With 4-Methylpyrazole

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ABSTRACT. *Objective.* **The alcohol dehydrogenase inhibitor 4-methylpyrazole (4-MP) is a new antidote of ethylene glycol (EG) intoxication. The purpose of the present case report was to demonstrate 4-MP efficiency in EG poisoning in a 4-year-old child.**

Method and Results. **4-MP Treatment was performed 7 hours after EG ingestion. Plasma EG and 4-MP concentrations were measured 2 hours after each infusion of 4-MP. Plasma 4-MP concentrations were in the range of the values reported to block EG metabolism. The efficiency of 4-MP treatment was confirmed by the rapid correction of metabolic acidosis without alkalization and by the increase in EG half-life. No adverse effect of 4-MP was observed.**

Conclusion. **This child ingested a potentially lethal dose of EG despite a high concentration of bittering agent in antifreeze. EG poisoning was treated efficiently by 4-MP without recourse to hemodialysis.** *Pediatrics* **1998;102(3). URL: http://www.pediatrics.org/cgi/content/full/102/3/e31; *4-methylpyrazole, ethylene glycol poisoning, denatonium benzoate.***

ABBREVIATIONS. EG, ethylene glycol; 4-MP, 4-methylpyrazole.

Ethylene glycol (EG) poisonings represent 0.15% of all calls to the Poison Center of Angers, with 70% of the confirmed cases occurring accidentally. In the period from 1991 to 1994, for a population base of 5.4 million inhabitants, 35 cases of EG poisonings were recorded and two deaths were noted. Exposure to EG typically is through the ingestion of automobile antifreeze. However, since 1995 in France, a minimum of 70 ppm of denatonium benzoate, a bitter agent, must be added to antifreeze to deter accidental ingestion.[1]

Clinical features of EG toxicity appear late and include hyperventilation, metabolic acidosis with elevated anion and osmolar gaps, and acute renal insufficiency. These are followed by convulsions, cardiac arrhythmias, and hypocalcemia. EG in itself is nontoxic, but it is metabolized in the liver by alcohol dehydrogenase, the enzyme responsible of the preliminary step in the hepatic metabolism of EG into glycolic acid, which causes a metabolic acidosis. Another metabolite, oxalic acid, precipitates with calcium, leading to the formation of oxalate crystals and is responsible for the organ toxicity of EG that results from the deposition of oxalate crystals in tissues. EG poisoning is usually treated by gastric lavage performed promptly after the ingestion, alkalization, and administration of ethanol. In severe cases with acute renal failure, the treatment include ethanol administration and hemodialysis to remove EG and its toxic metabolites.[2] The disadvantages of ethanol treatment are the difficulty of maintaining ethanol blood levels in the range of 1 to 2 g/L by frequent adjustments of dosage[2] and also the fact that ethanol may lead to a central nervous system depression, especially in children. An alternative therapy is the administration of 4-methylpyrazole (4-MP), which is a competitive inhibitor of alcohol dehydrogenase.[3] In France, the use of 4-MP has been reported in five adult EG intoxications, with favorable outcomes.[4–6] The patients were admitted early, before renal failure developed, which allowed for renal excretion of unchanged EG in the patients, eventually complicated by osmotic polyuria if hydration was not sufficient.[6] Only minor adverse effects of 4-MP were reported, and 4-MP treatment was noted to be easier to administer than ethanol.[5,6]

We report a case of massive EG poisoning in a child who was treated successfully by the new orphan drug 4-MP.

CASE REPORT

A 4-year-old girl, weighing 14 kg, accidentally ingested an unknown amount of antifreeze containing 41% EG and 113 ppm of denatonium benzoate (Bitrex, Macfarlan Smith, Edinburgh, UK). She vomited and was admitted to the hospital 4 hours later. Gastric aspiration was performed. One hour later, she was drowsy and hypotonic. Arterial pressure was 120/80 mm Hg, and the pulse was 100 beats per minute.

EG poisoning was confirmed by a metabolic acidosis, with an anion gap of 29 mmol/L and an osmolar gap of 50 mOsm/L (Table 1). Seven hours after ingestion, the metabolic acidosis increased and 4-MP treatment was prescribed as antidote after obtaining informed consent from the parents. No alkalization was prescribed.

Metabolic acidosis disappeared completely 7 hours after the beginning of 4-MP treatment, but a intracellular dehydration appeared (sodium 146 mmol/L). Renal function remained normal. No additional metabolic disturbances were recorded. Serum transaminases normalized the next day. During the hospitalization, a psychologic evaluation revealed that the child had a history of affective disorders, that she refused foods, and that she had previously ingested household products such as perfume and bleach. The child was discharged on the fourth day without metabolic, hepatic, renal, or hematologic disturbances. Nine days later, results of the clinical examination were normal, and biological parameters revealed no complications of EG poisoning nor of 4-MP treatment.

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TABLE 1. Biological Data of the Child at 4, 7, 22, and 70 Hours Postingestion of EG

	H 4	H 7	H 14	H 22	H 70
pH	7.29	7.25	7.47	7.46	
Total co_2 mmol/L	10.7	8.7	22.9	25.5	25.5
Sodium mmol/L	141	142	146	139	138
Potassium mmol/L	3.7	3.8	3.1	3.5	4.2
Chloride mmol/L	104	107		99	102
Total calcium mmol/L	2.75	2.8		2.25	2.4
Proteins g/L	80	77	68	62	61
ASAT UI/L (N 10–35)	38	31		25	29
ALAT UI/L (N 10–45)	5	5		7	8
Urea mmol/L	7.1	5.4	4.6	3.9	5.1
Creatinine μmol/L	52	40	44	39	32

Abbreviations: ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase.

METHODS AND RESULTS

Antidotal treatment in this child was performed 7 hours after EG ingestion by an intravenous loading dose of 15 mg/kg of 4-MP infused over 1 hour and 2 maintenance doses of 10 mg/kg infused 12 and 24 hours later. Pharmacie Centrale des Hôpitaux de Paris supplied 100 mg of 4-MP in an isotonic nonpyrogenic solution. 4-MP Was analyzed by reversed phase high-performance liquid chromatography.[7] Plasma 4-MP concentrations 2 hours after each infusion were 18.5, 17.5, and 12.5 mg/L, respectively.

EG was analyzed by gas chromatography after phenylboronic ester derivatization.[8] The first plasma EG concentration estimated from osmolar gap was 3.1 g/L (16.1 mOsm/L corresponds to 1 g/L). The estimated plasma EG half-life before 4-MP infusion was 4.4 hours and was prolonged to 10 hours during 4-MP treatment (Fig 1).

DISCUSSION

To our knowledge, no case of EG poisoning treated by 4-MP has been reported in the pediatric population. This antidote was used in the present case to avoid the central nervous system effects of ethanol.

The estimated initial plasma EG concentration of 3.1 g/L 4 hours after the ingestion of antifreeze revealed a potentially lethal dose of EG close to 1.4 mL/kg, assuming a volume of distribution of 0.4 to 0.6 L/kg.[3,6] The dosing schedule of 4-MP selected for this child was determined according to a mean plasma EG half-life of 12 hours during 4-MP treatment. Three infusions of 4-MP were prescribed every 12 hours in the case presented because three EG half-life periods were needed to decrease plasma EG concentration from 1.2 g/L to a nontoxic concentration <0.2 g/L. This dosing schedule, based on previous toxicokinetics of adult EG poisonings treated by 4-MP,[6] revealed to be initially well estimated because toxicokinetic data in the present case confirmed a plasma EG half-life prolonged to 10 hours with 4-MP treatment and a nontoxic plasma EG concentration at the end of 4-MP treatment. Moreover, plasma 4-MP concentrations observed were in the range of the values reported previously to block EG metabolism.[6] The efficacy of 4-MP treatment in this case also was demonstrated by the correction of metabolic acidosis without alkalization and by the absence of acute renal failure or other complications of

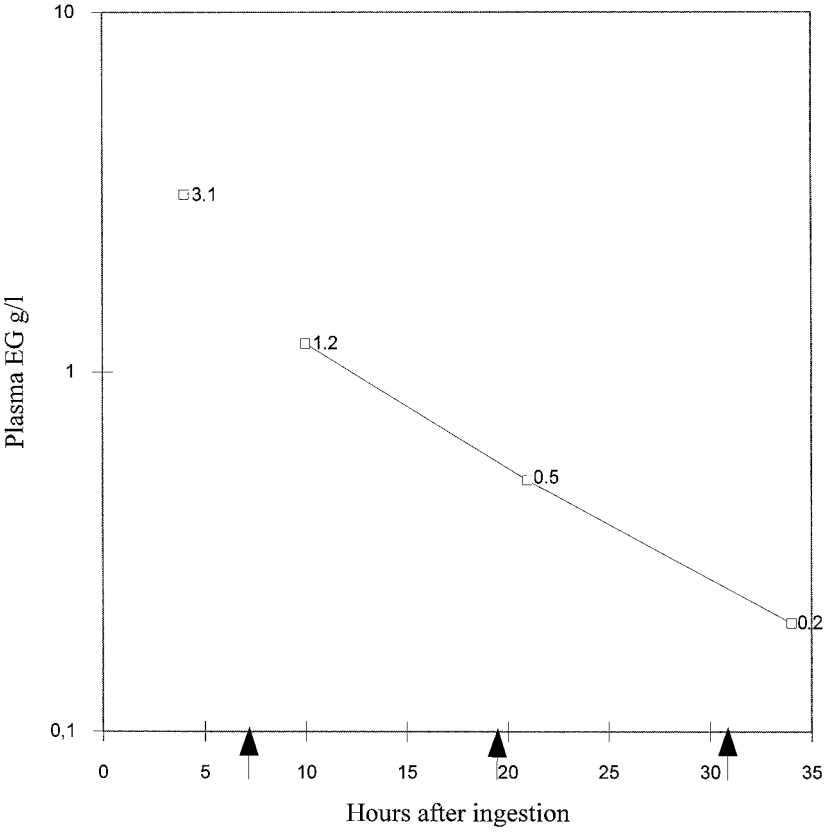

Fig 1. Plasma EG concentrations. Vertical arrows represents 4-MP infusions. EG half-life was prolonged to 10 hours during 4-MP treatment.

EG poisoning. No adverse effects of 4-MP were recorded, and serum transaminases returned in the normal range during 4-MP treatment.

The hypernatremia observed at H14 was probably attributable to EG osmotic polyuria, and this emphasizes the need for sufficient hydration during EG intoxication.[6]

In the present case, 4-MP treatment was confirmed to be easier to perform than the standard treatment with ethanol and hemodialysis.

The high concentration of the bittering agent denatonium benzoate (Bitrex, 113 ppm) in the antifreeze did not prevent ingestion of a potentially lethal dose by this child. Thus, we recommend that a child exposed to antifreeze, even that containing Bitrex, needs hospitalization for toxicologic evaluation. When EG poisoning is confirmed with normal renal function results, 4-MP antidote is indicated as the only treatment.

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