Accepted June 2014

CASE REPORT

Intoxication with ethylene glycol treated with fomepizole: a case report

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Keywords – **Ethylene glycol intoxication, fomepizole, ethanol, antifreeze**

Abstract

A woman was admitted to the intensive care unit after a severe intoxication with ethylene glycol. Her plasma level of ethylene glycol was extremely high. She was treated with ethanol infusion and with continuous-venovenous haemofiltration. Subsequently the ethanol was replaced by fomepizole. Her recovery was uneventful without end-organ damage. This case report describes the advantages of treatment with fomepizole compared with the well-known treatment with ethanol in case of ethylene glycol intoxication. We conclude that fomepizole should be considered in patients with severe ethylene glycol intoxications.

Introduction

In 2011, 89 intoxications with ethylene glycol were reported to the Dutch National Intoxication Centre (RIVM). Ethylene glycol ranks nine in the top ten intoxications with household products in persons older than 13 years.[1] Ethylene glycol intoxication is a life-threatening intoxication with a high risk of persistent end-organ damage. If untreated, the mortality rate is 28% with permanent visual impairment in 30% of the survivors.[2] It is important to initiate adequate therapy as soon as possible to prevent irretrievable organ damage.

Fomepizole (4-methylpyrazole) is an unfamiliar treatment modality for ethylene glycol intoxications. The cost of fomepizole, its limited availability and its unfamiliarity in the Netherlands are clear barriers for its usage. This case report, however, shows that fomepizole can be used as a suitable alternative treatment in a patient with ethylene glycol intoxication.

Case

A 52-year-old woman was admitted to the emergency department two hours after ingestion of 200 ml antifreeze suitable for temperatures until 36 degrees below Celsius (*figure 1*). On presentation she was restless but adequately conscious without neurological symptoms. Her vital parameters were initially normal. Additional analysis showed a respiratory compensated metabolic acidosis (pH 7.41, bicarbonate 16 mmol/l, CO_2 3.4 kPa, base excess -6.8 mmol/l). The anion gap (corrected for the albumin) as well as the osmolarity gap were increased (26 mmol/l and 82 mosm/kg, respectively). Her plasma level of ethylene glycol was extremely high (4000 mg/l).

Figure 1. Bottle with 20-year-old antifreeze.

Minutes after presentation the patient became more agitated and uncooperative. Because of the high risk of irretrievable end-organ damage we decided to sedate and intubate the patient for further treatment.

Subsequently the metabolic acidosis deteriorated to a pH 7.12. Ethanol 96% infusion, with a target plasma level of 1000-1500 mg/l, was started to prevent the formation of toxic metabolites. After four hours of treatment, the ethylene glycol plasma level was 3000 mg/l. We started continuous-venovenous haemofiltration (CVVH) in an attempt to reverse the rapid progression of the clinical symptoms. In addition, because of the extremely high plasma level and the clinical deterioration fomepizole replaced the ethanol infusion. Fomepizole was started at 780 mg in 45 minutes according to her weight. After 15 hours of treatment with fomepizole (1 mg/kg/h) her ethylene glycol level was 200 mg/l and the fomepizole was discontinued. One day later, her ethylene glycol level was below 200 mg/l and CVVH was also discontinued. Her further recovery was complete without end-organ damage.

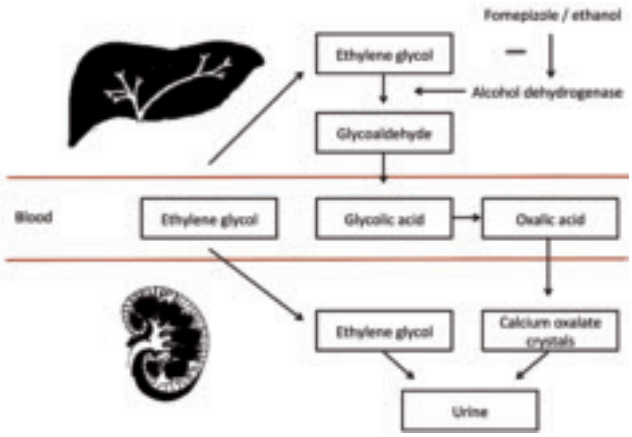
Discussion

The clinical presentation of ethylene glycol intoxication consists of three phases. The neurological phase starts (1-12 hours after ingestion) with symptoms varying from agitation to a comatose state and seizures. In the second phase (12-24 hours after ingestion) cardiopulmonary symptoms such as hypertension, tachypnoea, tachycardia, circulatory shock and acute cardiomyopathy can develop. In untreated patients, the second phase is responsible for the high mortality rate. In the third phase (24-72 hours after ingestion) acute renal failure can develop. Sometimes permanent haemodialysis is necessarily in cases of severe renal failure; however, in general there is a spontaneous recovery of the renal function.[3,4] Until two weeks after ingestion, neurological symptoms caused by cranial nerve involvement can occur.[3]

The cornerstone in the treatment of ethylene glycol intoxication is to inhibit alcohol dehydrogenase (ADH) and thereby prevent the formation of toxic calcium oxalate and other toxic metabolites (*figure 2*). Ethanol is used as a competitive inhibitor for ADH. Fomepizole is also a competitive inhibitor of ADH with a 500 to 1000 x greater affinity for ADH than ethanol.[5] Treatment with ethanol has a number of potential side effects. Not only does ethanol treatment require close monitoring with frequent measurement of the ethanol concentrations and adjustment of the dose, it also requires close observation of the patient because of the change in mental stage, risk of hypoglycaemia or hepatotoxicity and pancreatitis.[4,6]

We decided, in the heat of the moment, to treat our patient with fomepizole. This case report is a single observation with a number of limitations and confounding factors; however, our patient made a full recovery without any end-organ damage, possibly attributed to the administration of fomepizole.

Figure 2. Metabolism of ethylene glycol.



Fomepizole has fewer and less serious side effects in comparison with ethanol. In addition it has never been established whether the reported side effects of fomepizole are caused by fomepizole or just due to the ethylene glycol intoxication itself. The most common side effects are headache with nausea, dizziness, agitation and eosinophilia and seizures.[6]

Fomepizole is an expensive drug, especially when compared with the use of ethanol in the treatment of ethylene glycol intoxication. The costs of fomepizole are € 150 per 100 mg, while the costs of ethanol therapy are € 40 euro per 50 g. Converted to costs per patient per day, fomepizole therapy is 10 times more expensive than ethanol therapy. However fomepizole does not increase the half-life of ethylene glycol whereas ethanol increases the half-life by 14 hours. Therefore, treatment with fomepizole potentially decreases the days of treatment and admission.[7] Treatment with ethanol makes the rate of elimination less predictable so that frequent monitoring of blood levels is necessary in contrast to fomepizole.[8] In patients with ethylene glycol intoxication, treatment should be started as soon as possible. If fomepizole is the choice of treatment the best way to give it is intravenously. In simultaneous treatment with dialysis the dosage of fomepizole should be increased because it is ultrafiltrated by dialysis (*table 1*).[5,6] In addition, there are studies suggesting that due to the favourable toxicity profile of fomepizole and the reduced need of monitoring, treatment of patients with less severe ethylene glycol intoxication might not have to be in an intensive care unit.[2,9]

Furthermore, in serious ethylene glycol intoxication dialysis is an important treatment to eliminate toxic metabolites. Levine et al. showed in a retrospective study design that non-acidotic patients with normal renal function at presentation who were treated with fomepizole monotherapy had a good outcome without the need for renal replacement therapy.[3,10]

Multiple studies suggest that although fomepizole is an expensive drug, because of its advantages it also reduces costs by decreasing days of admission, preventing admission

Table 1. Dosage of fomepizole in serious ethylene glycol intoxication.[5,6]

Time	Without dialysis	With dialysis
Start	15 mg/kg in 100 ml glucose 5% or sodium chloride 0.9%	15 mg/kg in 100 ml glucose 5% or sodium chloride 0.9%
Maintenance	10 mg/kg every 12 hours (3 times) followed by 15 mg/kg every 12 hours	1 mg/kg/h When dialysis starts after > 6 hours, repeat start dosage
Stop	Ethylene glycol < 200 mg/l	Ethylene glycol < 200 mg/l

to an intensive care unit and fomepizole might even, when administered early after ingestion in a non-acidotic patient, make dialysis unnecessary.[7]

Recently, Rietjens et al.[9] concluded that there is no conclusive scientific evidence whether ethanol or fomepizole should be used as antidote in the treatment of ethylene glycol intoxication. Treatment with fomepizole is easier but also more expensive than treatment with ethanol. We believe that patient characteristics and the availability of fomepizole should be leading in the choice of treatment. However, ethylene glycol intoxication is an emergency situation and treatment should be started immediately after presentation at the emergency department to prevent end-organ damage.

Conclusion

In conclusion, based on this case report and the current literature, fomepizole could be considered in patients with ethylene glycol intoxication, especially in the non-acidotic patient who presents shortly after ingestion.

The use of fomepizole in the treatment of ethylene glycol may be cost-effective; however, there is no research to support this suggestion. Rapid initiation of therapy is essential in ethylene glycol intoxication and fomepizole is not yet directly available in Dutch hospitals. Therefore, first-line treatment in patients with ethylene glycol intoxication remains the use of ethanol infusion. Based upon patient characteristics, clinical presentation and availability fomepizole could be used as adjunctive therapy and may replace the initial ethanol infusion.

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