Journal of Nephrology & Therapeutics
ISSN: 2161-0959

Buller et al., J Nephrol Therapeut 2012, S10
DOI:10.4172/2161-0959.S10-004

Review Article Open Access

The Role of Hemodialysis and Fomepizole in Ethylene Glycol Intoxication

Gregory K. Buller*, Craig B. Moskowitz and Karen Eckardt

Department of Internal Medicine, Saint Mary's Hospital, Waterbury, Connecticut, USA

Abstract

Ethylene glycol is one of the most common toxic alcohol ingestions requiring hemodialysis for treatment. With the FDA approval in 1997 of fomepizole (4-methylpyrazole), the indications for hemodialysis in addition to fomepizole for ethylene glycol poisoning have been examined in recent articles and case reports. Fomepizole, a competitive inhibitor of alcohol dehydrogenase, binds to the same site on the enzyme as ethanol, however the pharmacokinetics of fomepizole are more predictable, and with fewer side effects compared to ethanol. Current guidelines cited in the literature for the use of hemodialysis in ethylene glycol poisoning include patients with severe metabolic acidosis (pH 7.3), serum ethylene glycol level 50 mg/dL, acute kidney injury, and deteriorating vital signs despite intensive care. This article is a review of the current literature with regard to the use of fomepizole as monotherapy for ethylene glycol poisoning, as well as the indications for hemodialysis in ethylene glycol poisoning.

Introduction

Ethylene glycol is present in many common substances such as antifreeze, de-icing substances, detergents, lacquers, and polishes [1]. Ethylene glycol itself is not toxic; rather the metabolites, glycolic acid and oxalic acid exert their toxic effects. Three stages of toxicity from ethylene glycol are classically identified: 1) CNS stage, 30 min to 12 hours after ingestion with features of altered mental status, ataxia and slurred speech; 2) cardiopulmonary stage, 12-24 hours after ingestion with hypertension, tachycardia, congestive heart failure, and adult respiratory distress syndrome; 3) renal stage, 24-72 hours after ingestion with flank pain, calcium-oxalate crystalluria, and oliguria [1]. Of interesting note, two forms of oxalate crystals can be present in the urine in ethylene glycol poisoning, one more specific than the other. A dumbbell shaped monohydrate crystal is most common, however the dihydrate form is most specific, as the monohydrate form can be present in those who consume large quantities of vitamin C as well as diets high in urate. The dihydrate form also requires a higher concentration of oxalate to be present, and is thus more indicative of ethylene glycol poisoning [2].

Fomepizole

Fomepizole (4-methylpyrazole) was approved by the FDA in 1997 for the treatment of ethylene glycol (EG) toxicity. Fomepizole is a potent competitive inhibitor of the enzyme alcohol dehydrogenase, thus preventing the toxic metabolites of EG from being formed. In the past, patients with suspected EG toxicity were treated with ethanol infusions because of its competitive binding to the enzyme alcohol dehydrogenase. However, fomepizole has since replaced ethanol and is currently first line therapy for the treatment of EG poisoning. Fomepizole treatment is often used in conjunction with cofactors such as thiamine and pyridoxine, which aid in converting the toxic metabolites of EG into nontoxic forms [1]. Indications for treatment with fomepizole include: documented plasma concentration of EG ≥20 mg/dL, recent ingestion history of EG with osmolal gap >10 mOsm/L, or suspected EG ingestion with (at least three of the following) arterial pH <7.3, serum carbon dioxide <20 mmol/L, osmolal gap >10 mOsm/L, and oxalate crystalluria [3]. Administration of fomepizole or other alcohol dehydrogenase inhibitors should continue until the serum EG concentration is less than 20 mg/dL and the patient is asymptomatic with a normal arterial pH [1]. In EG intoxication, the serum level of the toxin can be estimated by multiplying the osmolar gap by 6.2 [2].

Hemodialysis

Hemodialysis has also been an important treatment in EG poisoning, especially in patients with severe metabolic acidosis and acute kidney injury. Hemodialysis removes glycolate (metabolite of EG) and EG from the blood effectively and corrects the acidosis [4]. Glycolate is the main toxic metabolite of ethylene glycol and produces the high anion gap acidosis [2]. With respect to HD, current guidelines recommend that patients be dialyzed if serum EG concentrations are >50 mg/dL, presence of severe metabolic acidosis, and renal failure [5]. Refractory serum hyperosmolality and a glycolic acid level greater than 10 mmol/l have also been described as indications [6]. Dialysis is undertaken with a bicarbonate dialysate bath until the toxic alcohol level is <20 mg/dL [7]. A peak serum concentration of 20 mg/dL or greater has been cited as potentially toxic, however, data from human studies regarding this is lacking. Based on the few available case reports of patients presenting early with serum concentrations <20 mg/dL, it seems reasonable. It is important to note that this serum concentration does not take into account for pre-existing renal failure [8]. More aggressive treatment consisting of both HD and fomepizole would be reasonable in these patients.

The current literature with regard to EG poisoning suggests that in many cases, fomepizole has obviated the need for HD in patients with normal renal function and in those who are not acidodic. This is especially true for patients who present early after ingestion of EG, irrespective of the plasma EG level. However, most researchers agree that if a patient with a high serum EG level is to be treated with fomepizole alone, acid-base status should be monitored closely and HD be instituted if metabolic acidosis develops [3]. The benefit observed with hemodialysis appears to be a shorter length of hospital

***Corresponding author:** Gregory K. Buller, Department of Internal Medicine, Saint Mary's Hospital, Waterbury, Connecticut, USA, E-mail: gbuller@stmh.org

Received March 30, 2012; **Accepted** May 19, 2012; **Published** May 21, 2012

Citation: Buller GK, Moskowitz CB, Eckardt K (2012) The Role of Hemodialysis and Fomepizole in Ethylene Glycol Intoxication. J Nephrol Therapeutic S10:004. doi:10.4172/2161-0959.S10-004

stay, and decreased cost, rather than improved patient outcomes. The risks associated with HD include but are not limited to hypotension, dialyzer reactions, and infections.

There is no role for the use of activated charcoal, cathartics or gastric lavage in the treatment of EG intoxication [2].

Length of Stay and Comparative Cost

Vasavada et al. [9], demonstrated the comparative pharmacokinetics of fomepizole with and without hemodiaylsis (HD), which showed that the half-life of EG was 15.3 (hrs) and 3.15 (hrs) when fomepizole was used without HD and with HD respectively. The data is from two patients, one treated with fomepizole plus HD, and the other with fomepizole without HD, both patients had normal renal function. For HD alone, the clearance of EG is 200-250 mL/min and for glycolate 170 mL/min at blood flow rates of 250-200 mL/min [6]. The half-life of glycolate is reduced by a factor of six with HD [4].

Cost estimates based on a case study in a given patient with normal renal function and initial serum EG concentration of 284 mg/dL, normal arterial pH, and hemodynamically stable, show that treatment with fomepizole alone is more expensive compared to fomepizole plus HD. The length of stay was 72 hours for the patient if treated with fomepizole alone with a cost of $5897 compared with a 24 hour stay with one session of HD at a cost of $3804 for the 24 hour hospital stay (HD session of eight hours required) [1]. The increased cost in those treated with fomepizole alone is due to the longer duration of hospitalization and increased amount of fomepizole without dialysis. The authors concluded that cost factors may favor alcohol dehydrgenase (ADH) inhibition plus HD in patients that only one HD session and one day of hospitalization would be required [1].

Fomepizole as Monotherapy

There are numerous case reports of patients with EG poisoning being successfully treated with fomepizole alone. The case reports have in common patients with EG poisoning presenting with normal renal function and normal arterial pH. One case study demonstrates a 61year old patient who presents with a serum EG concentration of 202 mg/dL, arterial pH of 7.17, and normal creatinine of 0.9 mg/dL. This patient was aggressively hydrated with normal saline (four liters every four hours), and given sodium bicarbonate (200 mmol over six hours), and a total of six doses of fomepizole (15 mg/kg x 2 and 10 mg/kg x 4 every 12 hours) [10]. Bicarbonate is indicated for patients with pH below 7.3 [2]. The patient's renal function remained normal, and HD was not required. This case demonstrated that even in the setting of EG levels > 50 mg/dL with metabolic acidosis, fomepizole plus supportive care can still be effective and obviate the need for HD [6]. Four additional cases of patients with ethylene glycol concentrations as high as 320 mg/dL and pH as low as 7.12 have also been successfully treated with fomepizole alone [4]. The main determinates as to the appropriateness of fomepizole as monotherapy include: Time of presentation post-ingestion, degree of acidemia, and of renal function [11]. The highest serum EG concentration treated with fomepizole monotherapy was 706 mg/dL, in a patient with normal creatinine and arterial pH [7]. These case reports highlight the evidence that even in the presence of metabolic acidosis, patients with normal renal function would likely not require HD in EG poisoning, regardless of the EG concentration [12].

Conclusion

From 1985 to 2005, cases of poisoning requiring HD increased to 707 per million calls to poison control centers from 231 per million, with lithium and EG being the most common toxins removed by HD over this period [7]. Fomepizole was approved by the FDA in 1997 for the treatment of ethylene glycol intoxication. The current trend in the literature is to not use HD in patients with EG intoxication as long as renal function is normal, acidosis is not refractory, and the patient is not deteriorating with fomepizole and supportive care alone. There are a number of case reports of patients being successfully treated with fomepizole alone, even with a pH <7.2. The difference between the patients being treated with fomepizole alone and the patients requiring HD is time of patient presentation post ingestion of the EG. The serum EG level, based on numerous case reports is not a good predictor of patient outcome, and should not be used solely to decide whether or not to treat a patient with HD [2]. Ethylene glycol is osmotically active and before being metabolized by alcohol dehydrogenase (ADH), gives rise to high osmotic gap. Once EG is metabolized by ADH down to glycolic acid (glycolate), the osmotic gap closes, and the glycolate gives rise to an anion gap. Thus, in patients presenting with an osmotic gap and either a history of ingestion, or high suspicion for ingestion of EG, this would likely signify an earlier presentation, and fomepizole monotherapy may be appropriate. Patients presenting with a history of EG ingestion or highly suspicious for EG ingestion, with only an anion gap, this may be a sign of a late presentation. More glycolate and oxalic acid may have already formed giving rise to the high anion gap, and the absence of an osmotic gap signifying most of the osmotically active EG has been metabolized. This patient may be more prone to acute kidney injury, severe metabolic acidosis, and HD with fomepizole may be indicated. This explains why EG levels are a poor predictor of outcome, because a high level indicates early presentation in most cases, and less toxic metabolite formation.

Case reports previously highlighted above have demonstrated the successful treatment of EG poisoning with fomepizole alone, despite severe metabolic acidosis. Thus, in patients presenting with EG poisoning with metabolic acidosis, in the absence of acute kidney injury, HD can likely be delayed (possibly not needed entirely) and fomepizole monotherapy initiated. The acid-base status would need to be frequently monitored, as well as neurological, cardiac, and pulmonary status monitored. The indication for HD in EG poisoning appears to be mainly determined by the presence of acute kidney injury, electrolyte imbalances that do not respond to conventional therapy, as well as deteriorating vital signs despite intensive care [7].

References

1. Church AS, Witting MD (1997) Laboratory testing in ethanol, methanol, ethylene glycol, and isopropanol toxicities. J Emerg Med 15: 687-692.

2. Abramson S, Singh AK (2000) Treatment of the alcohol intoxications: ethylene glycol, methanol, and isopropanol. Curr Opin Nephrol Hypertens 9: 695-701.

3. Brent J (2009) Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med 360: 2216-2223.

4. Baud FJ, Galliot M, Astier A, Bien DV, Garnier R, et al. (1988) Treatment of ethylene glycol poisoning with intravenous 4-methylprazole. N Engl J Med 319: 97-100.

5. Barceloux DG, Krenzelok EP, Olson K, Watson W (1999) American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. J Toxicol Clin Toxicol 37: 537-560.

6. de Pont, Anne-Cornélie JM (2007) Extracorporeal treatment of intoxications. Curr Opin Crit Care 13: 668-673.

7. Bayliss G (2010) Dialysis in the poisoned patient. Hemodial Int 14: 158-167.

8. Caravati EM, Erdman AR, Christianson G, Manoguerra AS, Booze LL, et al. (2005) Ethylene glycol exposure: an evidence-based consensus guideline for out-of-hospital management. Clin Toxicol (Phila) 43: 327-345.

9. Vasavada N, Williams C, Hellman RN (2003) Ethylene glycol intoxication: case report and pharmacokinetic perspectives. Pharmacotherapy 23: 1652-1658.

10. Najafi CC, Hertko LJ, Leikin JB, Korbet SM (2001) Fomepizole in ethylene glycol intoxication. Ann Emerg Med 37: 358-359.

11. Velez LI, Shepherd G, Lee YC, Keyes DC (2007) Ethylene glycol ingestion treated only with fomepizole. J Med Toxicol 3: 125-128.

12. Sivilotti ML, Burns MJ, McMartin KE, Brent J (2000) Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management. For the Methylpyrazole for Toxic Alcohols Study Group. Ann Emerg Med 36: 114-125.

This article was originally published in a special issue, **Dialysis** handled by Editor(s). Dr. R. Allan Jhagroo, University of Wisconsin, USA