**Abstract.** Ethylene glycol poisoning is a rare yet potentially fatal illness seen most commonly in association with ingestion by alcoholics or in suicide attempts. It is characterized by an elevated anion gap metabolic acidosis, osmolar gap, calcium oxalate crystals in the urine, and a well-defined clinical picture. Prompt treatment is crucial because effective intervention can prevent the neurologic, cardiac, pulmonary, and renal sequelae associated with ethylene glycol poisoning. Hemodialysis offers rapid clearance of ethylene glycol and its toxic metabolites. In this article, the case of a hemodialysis patient who suffered contamination of the dialysate solution with ethylene glycol, leading to altered mental status, coma, and severe anion gap metabolic acidosis, is reported. Despite prolonged dialysis and correction of the acidosis, the patient remained comatose and subsequently died. (J Am Soc Nephrol 8: 853–857, 1997)

Altered mental status is a rare complication of hemodialysis (HD), most often seen in dialysis dysequilibrium syndrome. It has also been described in association with technical difficulties and mishaps of dialysis (1). Acidosis is distinctly uncommon after dialysis because the dialysate has a bicarbonate concentration of 38 mEq/l. Ethylene glycol (EG) and its metabolites cause an increased anion gap metabolic acidosis. Familiarity with the differential diagnosis of an elevated anion gap metabolic acidosis (Table 1) is particularly important because EG poisoning is included in the diagnosis. Clarification of the importance of alcohol dehydrogenase and the toxic metabolites of EG have led to effective strategies designed to slow the metabolism of ethylene glycol and to decrease its subsequent toxic intermediates. Hemodialysis provides definitive therapy through clearance of EG and its toxic intermediates.

**Case Presentation**

A 56-yr-old female home-hemodialysis patient with ESRD secondary to hypertension presented to the University of Mississippi Hospital with acute mental status changes. Her dialysis session 2 days before this admission had been uncomplicated. On the day of admission, her family noted that she had developed mental status changes, including “babbling, slurring of speech and confusion” toward the end of her dialysis session. No seizure activity was noted. There was a distant history of alcohol abuse, but she had been abstinent in recent years. She became unresponsive shortly after arrival at the emergency department. At the time of presentation, her vital signs were: blood pressure, 147/86; pulse, 112; respiratory rate, 20; and temperature, 96.2°F. An eye examination revealed small, minimally reactive pupils and a negative doll’s eye sign. Her cardiac, pulmonary, and abdominal examinations were all unremarkable. Neurologic examination revealed her to be unresponsive to verbal, tactile, or painful stimuli. She had 1+ reflexes throughout, and it was noted that she had been able to move all extremities before arriving in the emergency department.

Laboratory examination at presentation revealed the following values: arterial blood gas on room air, pH 7.13; \( P_{\text{CO}_2} \) 23.9 mmHg; \( P_{\text{O}_2} \) 99 mmHg; white blood cell count, 7700; hematocrit, 35%; sodium, 148 mmol/l; potassium, 3.5 mmol/l; chloride, 100 mmol/l; serum bicarbonate, 7 mmol/l; BUN, 38 mg/dl; creatinine, 12.1 mg/dl, with an anion gap of 41. She had a calcium level of 10.5 mg/l, phosphorus level of 5.9 mg/l, and normal liver function tests. A computed tomographic scan of the brain was normal. A toxicology screen was performed to evaluate her elevated anion gap acidosis. Over the next several hours, she was given more than 350 mEq of sodium bicarbonate without significant improvement in her pH or bicarbonate level. She was intubated for airway protection, and HD was initiated to improve her severe metabolic acidosis. At the end of a 4-h HD session, she continued to have a severe acidosis with a bicarbonate level of 7 mmol/l and a pH of 7.12. Twelve hours after admission, an EG level of 392 mg/dl was reported. Hemodialysis was restarted, along with an infusion of ethanol at 5 mg/h. Her HD was discontinued after 6 h, when the EG level reached zero. Her arterial blood gas value had improved to a pH of 7.34 and a calculated \( P_{\text{CO}_2} \) of 20 mmol/l. Her level of consciousness slowly improved, and by the third hospital day, she was opening her eyes and moving all extremities spontaneously. However, her pupils remained sluggishly reactive and she was still verbally unresponsive. Intravenous antibiotic treatment was initiated on her third hospital day because of her fever of 101.5°F, which was associated with an elevation of her white blood cell count. She underwent dialysis during her fourth hospital day, without complication. Unfortunately, she was found later that same evening to be unresponsive and without a pulse; attempts to resuscitate her were unsuccessful. After finding an elevated EG level in our patient, we obtained fluid samples obtained from her home-hemodialysis machine.
Table 1. Causes of an increased anion gap metabolic acidosis

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<th>Cause</th>
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<td>Lactic acidosis</td>
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<td>Alcoholic ketoacidosis</td>
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<td>Diabetic ketoacidosis</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Ethylene glycol</td>
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<td>Salicylates</td>
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<td>Toluene</td>
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The fluid from the patient's dialysate-concentrate reservoir was negative for EG. However, the tube leading from the concentrate showed a level of 10.2 mg%. Samples taken from several points in the tubing prior to the dialyzer were all positive for EG (range, 5 mg% to 23 mg%). Two samples from the tubing after the dialyzer were also positive for EG (range, 4.3 to 5.8 mg%). Subsequent discussion with the family revealed that family members had been preparing for cold weather and were adding antifreeze to their cars. Our patient was known to use her own containers to hold the dialysate concentrate so that she could finish an entire session without changing containers. It appears that she had been running low on her dialysate concentrate solution, and a similar-appearing container of EG was accidentally either emptied into her reservoir or the dialysate intake line was placed into a container of EG.

Discussion

Ethylene Glycol Metabolism

Ethylene glycol itself has little or no toxic effects, other than causing inebriation. Metabolism of EO by the enzyme alcohol dehydrogenase leads to the formation of the toxic intermediates glycoaldehyde, glycolate, and glyoxylate. Oxalate is one of the metabolites of glyoxylate (Figure 1). Glycolate is the primary unmeasured anion, and its metabolism appears to be the rate-limiting step in the breakdown of ethylene glycol (2,3). It, along with glyoxalate and glycoaldehyde, accounts for most of the morbidity and mortality associated with EG ingestion (3–5). Inhibition of the alcohol dehydrogenase by ethanol helps to prevent formation of these toxic metabolites. Ethanol has a 100-fold greater affinity for alcohol dehydrogenase than does ethylene glycol. Thus ethanol in sufficient blood levels can significantly prolong the half-life of EG by competing for active binding sites, allow for its renal excretion, and decrease production of the toxic intermediates described above. Other less-proven interventions include thiamine and pyridoxine supplementation, which may promote metabolism of glyoxylate to less toxic end products (6). (Figure 1)

Clinical Presentation

Ethylene glycol intoxication should be suspected when a patient presents with altered mental status along with the presence of an increased anion gap metabolic acidosis. A high osmolal gap and calcium oxalate crystals in the urine warrant initiation of treatment. Detection of EG in blood or urine is diagnostic. Patients commonly present with altered mental status and appear inebriated without the characteristic odor of ethanol. In fact, the patient may appear to be suffering from ethanol intoxication, which can delay the treatment for ethylene glycol ingestion. Fluorescence of ethylene glycol in the urine or on the patient under a Wood’s lamp may provide rapid evidence of its ingestion (7).

A progression of clinical findings occurring in three stages (Table 2) has been described with EG ingestion (8,9). Stage 1, occurring between 30 min to 12 h after ingestion, primarily consists of central nervous system effects, including seizures, coma, and death in severe cases. It is not uncommon for nausea and vomiting to be present during this stage, and nonspecific physical findings can include cranial nerve VII, IX, and X abnormalities, along with depressed reflexes, nystagmus, and pupillary mydriasis (5,8). Although they are commonly described, calcium oxalate crystals in the urine may be absent. The second stage may manifest between 12 and 24 h after ingestion and consists of cardiopulmonary findings, including tachycardia, hypertension, tachypnea, adult respiratory distress syndrome, and, in more severe cases, cardiovascular collapse. The third stage is characterized by renal insufficiency and is usually apparent 2 days after the ingestion of EG.

![Figure 1. Ethylene glycol metabolism.](image-url)
### Table 2. Stages of ethylene glycol poisoning

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
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<tr>
<td>Stage 1</td>
<td>30 min to 12 h after ingestion</td>
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<tr>
<td>Stage 2</td>
<td>12 to 24 h after ingestion</td>
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<tr>
<td>Stage 3</td>
<td>apparent 2 to 3 days after ingestion</td>
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### Pathogenesis of Renal Failure

Calcium and oxalate form a poorly soluble complex that can deposit in renal, vascular, cardiac, pulmonary, and brain tissue. It was originally believed that deposition of calcium oxalate in renal parenchyma and tubules was the basis of renal insufficiency. However, in animal models, it appears that it is not simply the deposition of calcium oxalate but the toxic intermediates that are the etiology of renal failure (10). Acute tubular necrosis as a result of direct cytotoxicity of the intermediates, rather than simple mechanical obstruction, may be the cause of azotemia in most cases (11). In general, the renal failure associated with EG ingestion is transient, and renal recovery is expected.

### Pathogenesis of Osmolal Gap

Normal serum osmolality is between 285 and 290 mosmol/kg. The calculated osmolality is expressed as: $2 \times \text{serum } \text{Na}^+ + \text{glucose (mg/dl)}/18 + \text{BUN (mg/dl)}/2.8$. A normal osmolal gap is $10 \pm 4$ mosmol/kg and is the difference between the calculated and measured osmolality. A compound that is osmotically active, i.e., EG, ethanol, isopropyl alcohol, methanol, or mannitol, will cause an elevation of the normal osmolal gap because it is not accounted for in the equation. In the case of EG ingestion, the osmolal gap may give an indication of the blood level. However, a normal osmolal gap does not rule out EG ingestion even if a severe poisoning but may be an indication that the parent compound has been more completely metabolized. Because of this phenomenon, it is important to remember that EG intoxication can present in a fashion similar to that of lactic acidosis. It is not uncommon for patients to present with a severe metabolic acidosis with a blood pH of less than 7.0 and a serum bicarbonate level less than 10 mmol/l. In general, only EG and methanol are likely to cause a combined elevated osmolal gap and anion gap (Table 1).

### Diagnosis and Treatment

Management of EG intoxication includes general measures to protect the airway, cardiac monitoring, and intravenous access. Intravenous fluid administration may increase urine output and aid in the excretion of EG. The confirmation of an elevated EG level can be made by colorimetry, mass spectrometry, isotachophoresis, or HPLC. Unfortunately, many of these assays are time-consuming and do not yield results quickly. It is important to note that the blood level test results can be deceiving because metabolism of EG can result in negative or non-toxic levels if it has been more completely metabolized. Gas chromatography analysis of the urine may be helpful in this setting, because it is positive even when blood level tests are negative (12). Some laboratories also offer glycolic acid levels but this is not widely available.

Treatment (Table 3) should be initiated in patients found to have an EG level greater than 20 mg/dl or a known ingestion of 20 ml or more of EG. If the ingestion is known to have occurred very recently, a cathartic can be given; however, EG is rapidly absorbed through the gastric epithelium, and gastric emptying is not likely to benefit a patient with a distant time of ingestion. Although its use is controversial, activated charcoal can be given and may aid in the treatment if a coingestion is suspected. A dose between 25 and 50 g may be administered and has no significant toxicity. As already mentioned, ethanol has a 100-fold increased affinity for alcohol dehydrogenase, and administration should be initiated in the appropriate clinical setting while toxicology tests are performed. Depending on the level of consciousness of the patient, a loading dose of ethanol of 0.6 of 50% ethanol per kg body wt should be given either orally or intravenously (13). Appropriate serum levels of ethanol are between 100 and 200 mg/dl and can be maintained with either 20% oral or 5 to 10% intravenous ethanol administration (13). Hemodialysis is indicated with EG levels greater than 50 mg/dl, in association with renal failure, or to correct a severe anion gap metabolic acidosis or other electrolyte abnor-

### Table 3. Therapeutic options

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<th>Activated charcoal</th>
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<tr>
<td>Gastric lavage</td>
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<td>Ethanol infusion</td>
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<td>Hemodialysis</td>
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<td>Continuous renal replacement therapy</td>
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<tr>
<td>Thiamine</td>
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<td>Pyridoxine</td>
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mality. Hemodialysis offers rapid clearance of EG and its inter-
mediates, especially when high-flux hemodialysis mem-
branes are used (14,15). The length of dialysis time is some-
what controversial, with longer dialysis times being more
commonly recommended or until the metabolic acidosis is
resolved and the EG level is less than 10 mg/dl. Ethylene
glycol is lipid-soluble and can be released from adipose tissue
for up to 36 h after ingestion, leading to a rebound effect af-
after HD (16). This release from adipose tissue likely accounts
for the extended dialysis time required in some patients because
HD clearance rates of approximately 150 ml/min for EG and
greater than 100 ml/min for glycolic acid can be achieved
(14–16). In patients who have hemodynamic instability, con-
tinuous renal replacement therapy has been shown to be effec-
tive in EG removal (17). Although their effectiveness is un-
proven, the use of thiamine and pyrodoxine in doses of 100 mg
each is harmless and may increase the metabolism of toxic
intermediates to less harmful end products (Figure 1).

Conclusion

In this study, we present a unique case of EG poisoning. To
our knowledge, it is the only reported case of poisoning
through the HD procedure. Our patient was a stable patient
who performed her own HD for 8 yr, and there was no history
of psychiatric or other mental disorder to suggest that this was
an attempted suicide or that other foul play was involved.
Ethylene glycol was detected from the dialysis tubing prior to
any contact with the patient. Even though the EG in the
dialysate effluent could have been derived from the patient
after an oral ingestion, that of the dialysate affluent could not
be explained on that basis. This case and its tragic outcome
reinforce the need for a high degree of clinical suspicion and
early treatment in patients with a combined elevated anion gap
acidosis and osmolar gap, even in the absence of a known
ingestion. Unfortunately, our patient did not survive her poi-
soning even though treatment was initiated before the confir-
mation of an elevated EG level. Another important point from
this case was the patient’s history of using makeshift containers
to hold larger amounts of dialysate concentrate so she could
complete a 4-h dialysis session without having to switch con-
tainers. The unfortunate outcome of this practice, which had
been discouraged in the past, highlights the need for patients to
use meticulous care in preparing for HD and during the process
itself. Home HD patients and those who assist them should be
instructed not to use containers other than those specifically
approved for HD and to follow home training guidelines
strictly.

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The Nephrology Training Program at the University of Mississippi, headed by Dr. John Bower, offers fellows a diverse clinical and academic experience. Fellows rotate through general nephrology, consultative nephrology, and transplant nephrology at the University of Mississippi and the Jackson Veterans' Administration Medical Center. The outpatient dialysis facility is located near the University, and is adjacent to a home-training center. The first year of training consists of basic inpatient nephrology, transplantation, home-training experience, and consultative nephrology. The second year expands on the first, with time allocated to include both research and pediatric rotations.

In addition to clinical responsibilities, a variety of regularly scheduled teaching conferences are utilized to further the education of nephrology fellows. A clinical journal club and research conference are conducted monthly. A pathology conference with the nephrology faculty and a renal pathologist occurs weekly. Twice-monthly clinical conferences are presented by both faculty and fellows. A combined urology/nephrology clinical radiology conference takes place every other week. All fellows are expected to participate in a research project during their fellowship training. Clinical and basic research opportunities are available both in and outside the department of nephrology.

The University of Mississippi Nephrology Fellowship provides a strong, diversified clinical experience along with excellent research opportunities and prepares fellows for the broad range of career choices in renal medicine.