

ACID-BASE AND ELECTROLYTE TEACHING CASE

Early and Late Presentations of Ethylene Glycol Poisoning

Stephen M.S. Ting, MRCP, Irene Ching, MRCP, Harikrishnan Nair, MRCP,
Gerald Langman, FRCPath, Vijayan Suresh, MRCP, and R. Mark Temple, MD, FRCP

INDEX WORDS: Ethylene glycol; anion gap; osmolal gap; oxalate nephropathy.

Ethylene glycol intoxication is uncommon, but can result in life-threatening metabolic acidosis, kidney failure, and death. Diagnosing such poisoning can be problematic in the absence of a clear history of ingestion, especially in patients who present with altered mental status or those who deny such consumption. Increased osmolal gap with a detectable serum ethylene glycol level is characteristic in patients presenting soon after ingestion, but increased anion gap metabolic acidosis without osmolal gap is seen in those who present late. Prompt institution of appropriate treatment can reduce the mortality and morbidity of poisoned patients, but requires clinicians to recognize these characteristic biochemical features according to whether presentation to the hospital is early or late after ethylene glycol ingestion. In cases of unexplained kidney failure, kidney biopsy may prompt the diagnosis by showing intratubular and intracellular calcium oxalate crystal deposition. We report 2 cases of ethylene glycol-induced acute kidney injury (AKI) with the diagnosis made after kidney biopsy. We discuss differences in laboratory results observed in these 2 patients because of timing of ingestion and coingestion of ethanol. We also review the toxic kinetics and clinical manifestations of ethylene glycol poisoning.

CASE REPORT

Clinical History

Case 1

A 53-year-old white man was referred by his general practitioner with suspicion of a transient ischemic attack. The patient reported acute onset of severe dizziness lasting 2 days. His wife described increased sleepiness and drowsiness for the previous 2 days associated with slurred and confused speech and recurrent falls because of an apparently weak left leg. During this time, he also was nauseated, with several episodes of vomiting. The patient had a history of chronic alcohol consumption of about 5 units daily for the past 10 years, but no history of cigarette smoking. He was investigated for weight loss 2 years previously, but upper gastrointestinal endoscopy and computed tomography (CT) of the chest and abdomen were normal.

On examination, the patient appeared underweight with a body mass index of 18 kg/m². He was fully conscious, but appeared mildly confused, with disorientation to time and place. Neurological examination of the cranial nerves and limbs was normal. Blood pressure was 136/78 mm Hg, and skin turgor was decreased. He was afebrile, but tachycardic, with a heart rate of 110 beats/min. Urinalysis found microscopic hematuria (2+) and proteinuria (1+). Laboratory results (Table 1) indicated AKI, with a serum creatinine level of 3.46 mg/dL (306 μmol/L). Four months before presentation, serum creatinine level was 0.71 mg/dL (63 μmol/L; estimated glomerular filtration rate > 90 mL/min/1.73 m² [>1.50 mL/s/1.73 m²]). He had normal anion gap metabolic acidosis with a serum bicarbonate level of 13 mEq/L (13 mmol/L). No abnormalities were found on head CT, chest X-ray, and renal tract ultrasound scan. Serum complement, antinuclear antibody, antineutrophil cytoplasmic antibody, anti-glomerular basement membrane antibody, and immunoglobulin levels were normal. No paraprotein was detected on serum electrophoresis. Liver enzyme levels were within normal limits. He was given intravenous fluids, predominantly 0.9% sodium chloride of approximately 4 L/d for 3 days, in addition to about 2 L of 1.26% sodium bicarbonate during the first 12 hours, followed by oral sodium bicarbonate, 1 g thrice daily, for 1 week. His confusion resolved by the second day of hospital admission. Urine output improved from 600 mL in the first 24 hours of admission to about 1,200 and 1,800 mL/d after 48 and 72 hours, respectively. This was accompanied by normalization of acid-base disturbances. Initially, he was believed to have acute tubular necrosis secondary to volume depletion. However, only modest improvement in serum creatinine levels was observed during 6 days (Fig 1), so a kidney biopsy was performed. He was discharged home after the kidney biopsy on day 7. Renal histological examination (Fig 2) showed a large number of oxalate crystals in tubules throughout the cortex, highlighted by their birefringence under polarized light. This was associated with focal

From the Renal Department, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham, West Midlands, UK.

Received August 8, 2008. Accepted in revised form December 12, 2008. Originally published online as doi: 10.1053/j.ajkd.2008.12.019 on March 9, 2009.

Address correspondence to Stephen M.S. Ting, Renal Unit, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham B9 5SS, West Midlands, UK. E-mail: stephenting@doctors.org.uk

© 2009 by the National Kidney Foundation, Inc.

0272-6386/09/5306-0024\$36.00/0

doi:10.1053/j.ajkd.2008.12.019

Table 1. Results of Laboratory Investigations

Investigations	Case 1		Case 2
	First Admission	Readmission	
Sodium (mEq/L)	133	147	130
Potassium (mEq/L)	4.8	5	6.4
Urea (mg/dL)	55.7	15.1	291.3
Creatinine (mg/dL)	3.46	2.31	36.82
Glucose (mg/dL)	99.1	138.7	108.1
Measured osmolality (mOsm/kg)	Not available	339	374
Osmolal gap (mOsm/kg)	Not available	32	4
pH	7.26	7.12	7.13
P _{CO} ₂ (kPa)	3.16	2.1	3.13
P _O ₂ (kPa); F _{IO} ₂	13.5 (0.2)	20 (0.6)	30 (0.8)
Bicarbonate (mEq/L)	13	9	10
Base excess (mEq/L)	-15	-21	-20
Lactate (mg/dL)	37.84	234.23	6.31
Chloride (mEq/L)	109	113	88
Anion gap (mEq/L)	11	25	32
Ethylene glycol (mg/L)	Not available	144	Undetectable

Note: Conversion factors for units: urea nitrogen in mg/dL to mmol/L, $\times 0.357$; serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 8.4$; glucose in mg/dL to mmol/L, $\times 0.05551$; lactate in mg/dL to mmol/L, $\times 0.111$; ethylene glycol in mg/L to $\mu\text{mol/L}$, $\times 16.11$. Serum sodium, potassium, bicarbonate, chloride, and anion gap expressed in mEq/L and mmol/L are equivalent. Osmolality expressed in mOsm/kg and mmol/kg is equivalent.

Abbreviation: F_{IO}₂, fraction of inspired oxygen.

acute tubular damage, whereas glomeruli were normal. No deposition of immunoglobulins or complement was seen on immunofluorescence.

The patient was brought back by his wife to the casualty department 1 week after his hospital discharge with a 24-hour history of drowsiness, confusion, and slurred speech. On readmission, blood pressure was 160/90 mm Hg, with sinus tachycardia of 120 beats/min, and he was tachypneic with a respiratory rate of 40 breaths/min. Four hours after

arrival, he became obtunded with a Glasgow coma scale of 4 (of 15). He was intubated and transferred to the intensive care unit. Biochemistry tests showed impaired kidney function (serum creatinine, 2.31 mg/dL [204 $\mu\text{mol/L}$]) with increased anion gap metabolic acidosis and lactate level of 234 mg/dL (26 mmol/L; normal, <19.8 mg/dL [2.2 mmol/L]); (Table 1). Serum amylase level and CT of the abdomen were normal. Toxicology screen for salicylates and paracetamol was negative.

Figure 1. Course of kidney function, timing of kidney biopsy, and duration of continuous venovenous hemofiltration (CVVH) in patient 1.

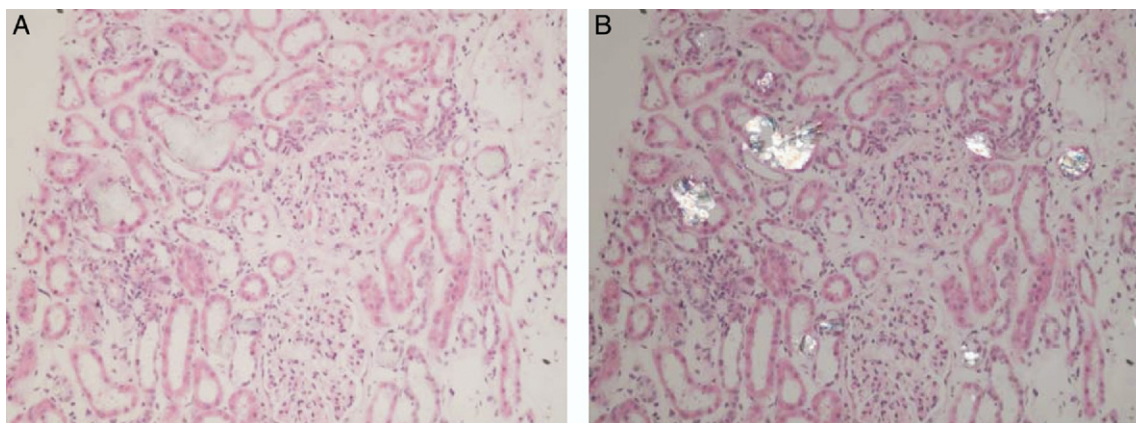


Figure 2. (A) Crystalline material is present in the tubules, (B) which is accentuated by the use of polarized light (hematoxylin and eosin stain; original magnification $\times 200$).

Case 2

A 49-year-old Asian man presented to the casualty department with a 2-day history of a macular-papular erythematous rash on his trunk and neck stiffness. His family described an acute onset of slurred confused speech about 10 days before admission lasting 48 hours, with subsequent increased lethargy and sleepiness for the rest of the week. The patient reported severe dizziness that persisted for 5 days. He had a history of multiple sclerosis diagnosed 10 years earlier, manifested by intermittent diplopia, but otherwise, he was not debilitated. There was a history of self-harm with paracetamol overdose 5 years previously, but he denied a recent overdose. He was not using any regular medications and did not consume alcohol or use tobacco. Clinically, he had a Glasgow coma score of 15. He was afebrile and blood pressure was 138/78 mm Hg, with a heart rate of 100 beats/min. There was left-sided torticollis. He had a longstanding bilateral internuclear ophthalmoplegia, but no other neurological deficit was found. Laboratory investigations showed severe AKI (serum creatinine, 36.82 mg/dL [$3,255 \mu\text{mol/L}$]), with increased anion gap of 32 mEq/L (32 mmol/L) and normal lactate level. Osmolal gap was normal at 4 mOsm/kg (4 mmol/kg) (Table 1). Urinalysis was not performed because of anuria. C-Reactive protein level was increased at 59 mg/L (reference value, $<10 \text{ mg/L}$), and there was mild leukocytosis of $12.4 \times 10^9/\text{L}$ (normal, $4 \text{ to } 11 \times 10^9/\text{L}$). Creatine kinase level was 483 U/L (normal, $<200 \text{ U/L}$), and liver enzyme levels were normal. Toxicology screen for salicylate, paracetamol, and ethylene glycol were negative. Head CT, chest X-ray, and renal tract ultrasound scan were normal. Cerebrospinal fluid analysis for virology and microbiology were also negative. He was started on intermittent hemodialysis therapy. Four days after admission, he developed a right-sided lower motor neuron seventh cranial nerve palsy. Immunology screen (serum complement, antinuclear antibody, antineutrophil cytoplasmic antibodies, anti-glomerular basement membrane antibody, and immunoglobulins) did not show abnormalities.

Additional Investigations

Case 1

The renal histological state of oxalate deposition in tubules (Fig 2) combined with the acute acid-base disturbance suggested acute ethylene glycol intoxication. Serum ethylene glycol level (measured by means of gas chromatography with flame ionization detection) 6 hours after presentation was 144 mg/L ($2,320 \mu\text{mol/L}$), with osmolal gap of 32 mOsm/kg (32 mmol/kg). Baseline serum ethanol was not measured by our laboratory.

Case 2

No ethylene glycol was detected in a blood sample obtained from the patient 1 hour after presentation. One week after hospital admission, a kidney biopsy was performed (Fig 3). This showed acute tubular necrosis with both degenerative and regenerative changes, accompanied by moderate deposition of oxalate crystals within the tubular lumina. Immunofluorescence and electron microscopy did not show immunostaining and electron-dense deposits within glomeruli, respectively.

Diagnosis

AKI caused by ethylene glycol poisoning was suspected in both patients. In patient 1, the diagnosis of acute ethylene glycol poisoning was confirmed by means of detectable ethylene glycol in serum. He subsequently admitted to ingesting automobile antifreeze in attempts to self-harm. About 100 mL of antifreeze mixed in a glass of cider apparently was consumed 3 days before the first admission, and about 150 mL of antifreeze (with an unspecified amount of cider) was consumed 24 hours before his second presentation.

Although no serum ethylene glycol was detectable in patient 2, he eventually admitted to drinking about 500 mL of antifreeze 10 days before presentation in an attempt to take his life because of depression.

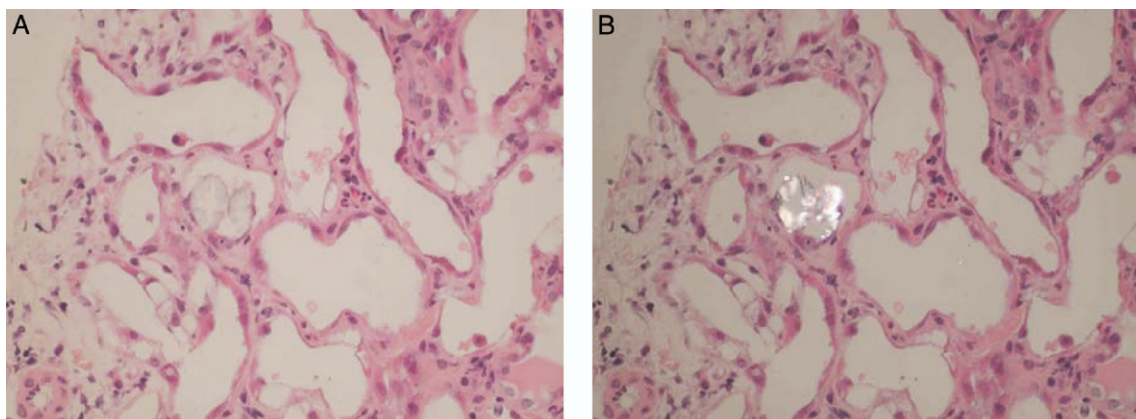


Figure 3. (A) A crystal within a tubule associated with flattening and necrosis of the tubular epithelium (B) shows birefringence under polarized light (hematoxylin and eosin stain; original magnification $\times 400$).

Clinical Follow-up

Patient 1 was started on continuous venovenous hemofiltration for 5 days until the acidosis was corrected. He received an intravenous ethanol infusion for 48 hours, maintaining a serum ethanol level of 100 mg/dL. Serum ethylene glycol became undetectable 48 hours after the simultaneous initiation of ethanol infusion and continuous venovenous hemofiltration. He subsequently made a complete renal recovery (Fig 1). However, patient 2, a late presenter, remains on hemodialysis therapy 7 months after the AKI.

DISCUSSION

Intoxication with ethylene glycol can be life-threatening. The cases presented illustrate the difficulty diagnosing ethylene glycol poisoning in the absence of a history of ingestion on presentation. Although both patients had symptoms characteristic of ethylene glycol intoxication, initial laboratory results differed (Table 1), primarily because of the pharmacokinetics of ethylene glycol and the periods between ingestion and presentation (Table 2). Kidney biopsy is rarely performed in these circumstances, but can lead to the diagnosis when intratubular oxalate crystals with positive birefringence under polarized light are seen on light microscopy (Figs 2 and 3). However, kidney failure associated with oxalate nephropathy can be caused by a number of conditions. In addition to ethylene glycol poisoning, ingestion of a large amount of ascorbic acid may increase the risk of calcium oxalate crystallization.¹ Autosomal recessive primary hyperoxaluria, seen commonly in the pediatric population, results in defective oxalate metabolism, often associated with systemic oxalosis.^{2,3} Mal-

absorption syndromes caused by ileal resection, Crohn ileitis, or jejunioileal bypass for morbid obesity also predispose patients to form calcium oxalate renal calculi.⁴⁻⁶ None of these conditions was present in our patients.

Ethylene glycol is the active ingredient in antifreeze for vehicle engines, but it also is found in various domestic or industrial cleaning products. The sweet taste of ethylene glycol, which is odorless and colorless, makes it palatable even in toxic quantities to both humans and animals; hence, its nickname “sweet killer.”⁷⁻¹⁰ Ethylene glycol ($\text{CH}_2\text{OH}-\text{CH}_2\text{OH}$) is rapidly and completely absorbed from the gastrointestinal tract and achieves peak concentration within 30 to 60 minutes after oral ingestion. The majority of absorbed ethylene glycol, which has a low molecular weight of about 62 Da, is metabolized by

Table 2. Comparison of Laboratory Features Seen in Patients Presenting Early and Later in the Course of Ethylene Glycol Poisoning

Laboratory	Early	Late
Anion gap	Normal or mildly increased	Increased
Osmolal gap	Increased	Normal
Serum ethylene glycol	Detectable	Not detectable
Oxalate crystalluria	May be present*	May be present†
Kidney function	Normal or mild AKI	Severe AKI

*May be seen 4 to 8 hours after ethylene glycol ingestion, up to 40 hours in the absence of acute kidney injury (AKI).

†Present up to 4 days with AKI.

the liver (80%) with a short half-life of 3 to 8 hours. The remaining 20% is eliminated by the kidneys, but the rate of excretion through this route is slow, with a half-life of 18 to 20 hours.^{7,8,9} The ethylene glycol molecule in itself is relatively nontoxic and produces clinical features similar to ethanol intoxication and central nervous system sedation, as observed in both our patients. In the liver, ethylene glycol is metabolized primarily by alcohol dehydrogenase (ADH) to produce glycoaldehyde, which is converted to glycolate by aldehyde dehydrogenase. The increased anion gap metabolic acidosis seen in patients with ethylene glycol poisoning is predominantly caused by glycolate and occurs 12 to 48 hours after ingestion. Further metabolism to glyoxylate and oxalate is relatively slow, which allows accumulation of glycolate, leading to worsening acidosis, increasing anion gap (Table 2), and cardiopulmonary decompensation.¹⁰⁻¹² Coingestion of ethanol may delay the onset of ethylene glycol toxicity because it also is metabolized by ADH. Ethanol has an affinity about 100 times greater for ADH than ethylene glycol. The presence of ethanol therefore will inhibit and delay the formation of toxic metabolites of ethylene glycol, which may explain the absence of increased anion gap metabolic acidosis in the initial admission of patient 1.^{7,8,13,14} High anion gap metabolic acidosis may be a characteristic biochemical feature of ethylene glycol poisoning, but it also can be seen in patients with severe renal failure. However, measurement of glycolate was not available in our institution to determine the cause of the high anion gap in patient 2, who presented late with severe AKI. Currently, intravenous infusion of ethanol is our standard therapy to saturate ADH, but fomepizole (4-methylpyrazole), a potent inhibitor of ADH, is an effective first-line antidote.^{15,16} Advantages over ethanol include a greater affinity for ADH of about 500 to 1,000 times, a lack of intoxicating effects, and more reliable achievement of therapeutic concentration. Fomepizole also may obviate the need for dialysis in patients who present early with increased serum ethylene glycol, but without significant acidosis.¹⁷

Marked lactic acidosis was seen in patient 1 during his readmission with shock, bowel ischemia, status epilepticus, and salicylate poisoning, all excluded as possible causes. An in-

creased lactate level can occur as an artifact because of the structural similarity of the lactate and glycolate molecules or misreading by certain chemical analyzers.^{18,19} However, the high serum lactate level in patient 1 probably was a true increase caused by inhibition of cellular metabolic enzymes by glycolate, causing lactic acidosis.^{8,11,20,21} This would have contributed to the significantly increased anion gap metabolic acidosis seen in patient 1 on his second presentation. The very mild lactic acidosis during the first admission could have been caused by a smaller amount of ethylene glycol consumed in the presence of ethanol, which further delayed hepatic oxidation to produce the toxic metabolite. Urine alkalization with sodium bicarbonate, administered during the first admission, helps promote renal excretion of both ethylene glycol and glycolate.

AKI usually takes 1 to 3 days to develop after ingestion of ethylene glycol. The mechanism of kidney failure is believed to be caused by glycolate-induced tubular cell necrosis with minimal glomerular damage. The characteristic histopathologic feature of ethylene glycol poisoning is the presence of intratubular and intracellular calcium oxalate crystals, with degeneration of tubular epithelium.²² Recent studies in rat models showed the accumulation of oxalate, the final metabolite product of hepatic ethylene glycol oxidation, in the form of calcium oxalate monohydrate crystals that were internalized by the proximal tubular cells, producing mitochondrial damage that resulted in cell death and tubular necrosis.^{23,24} Calcium oxalate crystals may be seen in the urine of poisoned patients up to 40 hours after ingestion of ethylene glycol in the absence of kidney failure and up to 4 days in kidney failure.^{8,25} However, their absence would not exclude the diagnosis because oxalate crystaluria often is seen late after ethylene glycol ingestion (Table 2).²⁵ In patient 2, no serum ethylene glycol was detected because the delay in presenting to the hospital meant that by then, all the parent alcohol had been metabolized. This explained the normal osmolal gap at presentation. Osmolal gap is derived from the difference between the laboratory measured and calculated serum osmolality and should not exceed 10 mOsm/kg (10 mmol/kg). Accumulation of any of the parent alcohols (ethanol, methanol, and ethylene glycol) will increase the measured serum

osmolality to greater than that of the calculated serum osmolality, producing an osmolal gap.²⁶⁻²⁸ Therefore, one would expect an increased osmolal gap with high serum ethylene glycol level in acute presentation (patient 1), but a normal osmolal gap with nondetectable serum ethylene glycol level in late presentation of ethylene glycol poisoning (patient 2). The significantly high osmolal gap of 32 mOsm/kg (32 mmol/kg) in patient 1 probably was caused by both the consumed ethanol and ethylene glycol. Incorporating serum ethanol measurement (if available) into the calculated serum osmolality would reflect the contribution of ethylene glycol to the increased osmolal gap.

Cranial neuropathies previously have been reported as delayed sequelae of ethylene glycol poisoning, with onset from 8 to 18 days after significant ingestion (up to 900 mL), especially in patients who presented late to hospitals.²⁹⁻³⁶ Patient 2 developed a right seventh cranial nerve palsy about 14 days after ingestion of ethylene glycol. Postmortem studies attribute this phenomenon to localized inflammation by oxalate microcrystals deposition, compromising the affected cranial nerve function. Partial or full recovery of the cranial nerve defects may take up to a year.^{32,35}

The 2 patients presented illustrate distinct biochemical features related to the time lapse between ethylene glycol ingestion and presentation to the hospital. Determination of the anion and osmolal gaps is fundamental to the assessment of patients with suspected ethylene glycol poisoning. Shortly after ethylene glycol ingestion, anion gap is normal, but osmolal gap is high. As ethylene glycol is metabolized, accumulation of the toxic acids leads to an increasing anion gap metabolic acidosis accompanied by a decreasing osmolal gap. Coingestion of ethanol can ameliorate the anion gap because of delayed production of toxic metabolites by competitive inhibition of the metabolizing alcohol dehydrogenase. With late presentation to the hospital, the ethylene glycol-poisoned patient can have a normal osmolal gap, no detectable serum ethylene glycol, and more severe AKI. Therefore, clinicians must consider ethylene glycol poisoning in the differential diagnoses of unexplained AKI. Ethylene glycol poisoning must be suspected in patients with a kidney biopsy specimen showing oxalate nephropathy. Prognosis is good in early presenters provided there is timely treatment with alkali

to combat acidosis, ethanol or fomepizole to prevent hepatic oxidation, and hemodialysis to effectively remove both the parent alcohol and its toxic metabolites.

ACKNOWLEDGEMENTS

We thank Kirsty Gordon, DipRCPath (Senior Clinical Scientist, Department of Clinical Biochemistry and Immunology, Heartlands Hospital, Birmingham, UK), who offered guidance on ethylene glycol sampling and analysis.

Support: None.

Financial Disclosure: None.

REFERENCES

1. Baxmann AC, De OG, Mendonça C, Heilberg IP: Effect of vitamin C supplements on urinary oxalate and pH in calcium stone-forming patients. *Kidney Int* 63:1066-1071, 2003
2. Danpure CJ: Advances in the enzymology and molecular genetics of primary hyperoxaluria type 1. Prospects for gene therapy. *Nephrol Dial Transplant* 10:S24-S29, 1995 (suppl 8)
3. Seargeant LE, deGroot GW, Dilling LA, Mallory CJ, Haworth JC: Primary oxaluria type 2 (L-glyceric aciduria): A rare cause of nephrolithiasis in children. *J Pediatr* 118:912-914, 1991
4. Nightingale JM: The short bowel syndrome. *Eur J Gastroenterol Hepatol* 7:514-520, 1995
5. McLeod RS, Churchill DN: Urolithiasis complicating inflammatory bowel disease. *J Urol* 148:974-978, 1992
6. Mole D, Tomson C, Mortensen N, Winearls C: Renal complications of jejuno-ileal bypass for obesity. *Q J Med* 94:69-77, 2001
7. Barceloux DG, Krenzelok EP, Olson K, Watson W: American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning. *J Toxicol Clin Toxicol* 37:537-560, 1999
8. Eder AF, McGrath CM, Dowdy YG, et al: Ethylene glycol poisoning: Toxicokinetic and analytical factors affecting laboratory diagnosis. *Clin Chem* 44:168-177, 1998
9. Sivilotti ML, Burns MJ, McMartin KE, Brent J: Toxicokinetics of ethylene glycol during fomepizole therapy: Implications for management. For the Methylpyrazole for Toxic Alcohols Study Group. *Ann Emerg Med* 36:114-125, 2000
10. Moreau CL, Kerns W II, Tomaszewski CA, et al: Glycolate kinetics and hemodialysis clearance in ethylene glycol poisoning. META Study Group. *J Toxicol Clin Toxicol* 36:659-666, 1998
11. Jacobsen D, McMartin KE: Methanol and ethylene glycol poisonings. Mechanism of toxicity, clinical course, diagnosis and treatment. *Med Toxicol Adverse Drug Exp* 1:309-334, 1986
12. Hess R, Bartels MJ, Pottenger LH: Ethylene glycol: An estimate of tolerable levels of exposure based on a review of animal and human data. *Arch Toxicol* 78:671-680, 2004
13. Wacker WE, Haynes H, Druyan R, Fisher W, Coleman JE: Treatment of ethylene glycol poisoning with ethyl alcohol. *JAMA* 194:173-175, 1965

14. Ammar KA, Heckerling PS: Ethylene glycol poisoning with normal anion gap caused by concurrent ethanol ingestion: Importance of the osmolal gap. *Am J Kidney Dis* 27:130-133, 1996
15. Baud FJ, Galliot M, Astier A, et al: Treatment of ethylene glycol poisoning with intravenous 4-methylpyrazole. *N Engl J Med* 319:97-100, 1988
16. Borron SW, Mégarbane B, Baud FJ: Fomepizole in treatment of uncomplicated ethylene glycol poisoning. *Lancet* 354:831, 1999
17. Brent J, McMartin K, Phillips S, et al: Fomepizole for the treatment of ethylene glycol poisoning. Methylpyrazole for Toxic Alcohols Study Group. *N Engl J Med* 340:832-838, 1999
18. Woo MY, Greenway DC, Nadler SP, Cardinal P: Artfactual elevation of lactate in ethylene glycol poisoning. *J Emerg Med* 25:289-293, 2003
19. Lindsay S, Akhtar J, Krenzelok EP, Brooks D: Artfactual elevation of plasma L-lactate in the presence of glycolate—A potential for misdiagnosis. *J Toxicol Clin Toxicol* 41:476, 2003 (abstr)
20. Bachmann E, Golberg L: Reappraisal of the toxicology of ethylene glycol. III. Mitochondrial effects. *Food Cosmet Toxicol* 9:39-55, 1971
21. Gabow BA, Clay K, Sullivan JB, Lepoff R: Organic acids in ethylene glycol intoxication. *Ann Intern Med* 105:16-20, 1986
22. Berman LB, Schreiner GE, Feys J: The nephrotoxic lesion of ethylene glycol. *Ann Intern Med* 46:611-619, 1957
23. Cruzan G, Corley RA, Hard GC, et al: Subchronic toxicity of ethylene glycol in Wistar and F344 rats related to metabolism and clearance of metabolites. *Toxicol Sci* 81:502-511, 2004
24. McMartin KE, Wallace KB: Calcium oxalate monohydrate, a metabolite of ethylene glycol, is toxic for rat renal mitochondrial function. *Toxicol Sci* 84:195-200, 2005
25. Jacobsen D, Hewlett TP, Webb R, Brown ST, Ordinario AT, McMartin KE: Ethylene glycol intoxication: Evaluation of kinetics and crystalluria. *Am J Med* 84:145-152, 1988
26. Glasser L, Sternglanz PD, Combie J, Robinson A: Serum osmolality and its applicability to drug overdose. *Am J Clin Pathol* 60:695-699, 1973
27. Abramson S, Singh AK: Treatment of the alcohol intoxications: Ethylene glycol, methanol, isopropanol. *Curr Opin Nephrol Hypertens* 9:695-701, 2000
28. Smithline N, Gardner KD: Gaps: Anionic and osmolal. *JAMA* 236:1594-1597, 1976
29. Mallya KB, Mendis T, Guberman A: Bilateral facial paralysis following ethylene glycol ingestion. *Can J Neurol Sci* 13:340-341, 1986
30. Factor SA, Lava NS: Ethylene glycol intoxication: A new stage in the clinical syndrome. *NY State J Med* 87:189-190, 1987
31. Berger JR, Ayyar RA: Neurological complications of ethylene glycol intoxication. Report of a case. *Arch Neurol* 38:724-726, 1981
32. Lewis LD, Smith BW, Mamourian AC: Delayed sequelae after acute overdoses or poisonings: Cranial neuropathy related to ethylene glycol ingestion. *Clin Pharmacol Ther* 61:692-699, 1997
33. Palmer BF, Eigenbrodt EH, Henrich WL: Cranial nerve deficit: A clue to the diagnosis of ethylene glycol poisoning. *Am J Med* 87:91-92, 1989
34. Spillane L, Roberts JR, Meyer AE: Multiple cranial nerve deficits after ethylene glycol poisoning. *Ann Emerg Med* 20:208-210, 1991
35. Anderson B, Adams M: Facial-auditory nerve oxalosis. *Am J Med* 88:87-88, 1990 (letter)
36. Fellman DM: Facial diplegia following ethylene glycol. *Arch Neurol* 39:739-740, 1982