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Case Report

Diethylene Glycol Poisoning From Transcutaneous Absorption

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A case of transcutaneous diethylene glycol poisoning with severe acute kidney injury, but a positive outcome, is described. A man without significant medical history was admitted to our hospital due to anuria, gastrointestinal symptoms, and hypertension. Ultrasonography excluded vascular damage and postrenal obstruction. Laboratory tests showed acute kidney injury and metabolic acidosis with increased anion gap; hemodialysis therapy was started. The brother of the patient reported that the patient had been smearing his skin with brake fluid containing diethylene glycol to treat a "dermatitis." Only supportive therapy was given due to the lack of a specific antidote. Continuous venovenous hemofiltration was performed. The kidney biopsy showed acute toxic proximal tubulonecrosis, without deposition of oxalate crystals. His neurologic condition worsened dramatically; supportive care was continued. Over time, acute kidney injury and neurologic damage gradually improved; 33 days after admission, he went to a rehabilitation unit for 5 months, with complete clinical recovery. Historically, diethylene glycol has been the cause of large-scale poisonings from ingestion of contaminated drugs. The clinical evolution is unpredictable. Treatment is not well defined; early hemodialysis treatment reduces levels of toxic metabolites, and fomepizole could be useful in cases with an early diagnosis. A comparison of the characteristics of diethylene glycol versus ethylene glycol poisoning is given.
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INDEX WORDS: Diethylene glycol; ethylene glycol; acute kidney injury; acute renal failure; poisoning; intoxication.

Diethylene glycol, a clear, colorless, and odorless substance present in many industrial products, causes toxicity if ingested. In the past, it has been substituted in pharmaceutical preparations in place of more expensive but nontoxic substances, causing mass poisoning 12 times during the last 70 years.[1-3] Diethylene glycol poisoning leads to kidney failure, peripheral neuropathy, and liver toxicity.[4]

This case report describes a rare case of transcutaneous diethylene glycol poisoning with severe clinical course.

CASE REPORT

A 29-year-old African man who was a nonsmoker, spoke Italian fluently, reported no misuse of alcohol or illicit drug use, and had no significant medical history came to our hospital experiencing nausea, abdominal pain, weakness, hyporexia, hypertension (blood pressure, 170/100 mm Hg), and anuria. Physical examination findings were unremarkable. Laboratory test results indicated severe kidney failure (serum creatinine, 15.5 mg/dL; estimated glomerular filtration rate, 4.3 mL/min/1.73 m^2 estimated using the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation[5]), metabolic acidosis (bicarbonate, 16.4 mEq/L) with mildly elevated anion gap (23 mmol/L), and high levels of serum lipase (3,027; reference, < 216 IU/L), transaminases (serum alanine aminotransferase, 98 IU/L; serum aspartate aminotransferase, 100; reference range, 5-50 IU/L), and C-reactive-protein (131; reference, <5 mg/L). Renal and Doppler sonography excluded chronic kidney disease, urinary tract obstruction, renal artery stenosis, and renal vein thrombosis. Laboratory test results for the more likely infectious and immunologic diseases were negative.

Hemodialysis therapy was started immediately. Due to a prolonged bleeding time, kidney biopsy was delayed until day 6 after admission. Soon after the biopsy, the patient's brother reported that the patient had been smearing his skin with brake fluid for the past few months to treat a "dermatitis." The patient confirmed this, but denied accidental or intentional ingestion. The brake fluid was class DOT3 (Department of Transportation), with a mean diethylene glycol concentration of 10%. Only supportive therapy was given due to the lack of a specific antidote for diethylene glycol. Over the next 3 hours, the patient developed progressive drowsiness, hypotension (systolic blood pressure, 100 mm Hg), and respiratory failure requiring intubation and ventilator support in the intensive care unit. Lumbar puncture excluded meningitis. Continuous venovenous hemofiltration was performed from days 7 to 12.

The kidney biopsy specimen exhibited normal glomeruli and vessels and acute toxic proximal tubular necrosis without oxalate crystals, findings that supported the differential diagnosis of diethylene glycol intoxication. Laboratory analyses found only traces of diethylene glycol in urine, but the samples had been collected after some dialysis sessions. Laboratory methods for detecting metabolites of diethylene glycol were not available.

Over the next several days, the patient's neurologic situation progressively worsened: ascending paralysis with disappearance of limb, head, and eye movements; areflexia; loss of corneal, vestibulo-ocular, and gag reflexes, and absence of auditory evoked potentials; electroencephalography showed depression of activity

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in the cerebral cortex; and Glasgow Coma Scale score was 3. Supportive care was continued. Later, progressive improvements in kidney and neurologic function occurred. At 33 days after admission, the patient's serum creatinine level was 1.26 mg/dL (estimated glomerular filtration rate, 89 mL/min/1.73 m^2) and the patient was transferred to a rehabilitation unit. At discharge, after 5 months, his neurologic recovery was almost complete, having recovered his ability to walk, speak, and hear.

DISCUSSION

Diethylene glycol has been involved in many medication-associated mass poisonings, mainly due to oral ingestion of acetaminophen or other contaminated drugs. The first report was in 1937 in the United States: 105 patients died after having ingested Elixir Sulphanilamide, which was marketed without a prior toxicity test.[6,7] This event led to creation of the Federal Food, Drug, and Cosmetic Act, which requires that drug producers must demonstrate safety before selling a product.[8] To our knowledge, there is only one report in the literature of topical intoxication; 5 patients with second- and third-degree burns involving 7% to 62% of the body surface area were treated with silver sulfadiazine cream for 4 to 24 days. Between days 3 and 6, they developed anuria and neurologic deterioration and died despite supportive care. The cream contained diethylene glycol and the autopsy revealed renal lesions suggestive of diethylene glycol intoxication.[3]

The kinetics of diethylene glycol in humans is not known: the available information derives from experimental studies in animals. Diethylene glycol is absorbed rapidly in the gastrointestinal tract; transcutaneous absorption is minimal through intact skin. No report of respiratory absorption is described. After absorption, diethylene glycol is distributed widely throughout the most perfused organs.

Diethylene glycol is metabolized in the liver. It is oxidized to 2-hydroxyetoxyacetaldehyde by alcohol dehydrogenase and then to 2-hydroxyethoxyacetic acid by aldehyde dehydrogenase. 2-Hydroxyethoxyacetic acid is oxidized further to diglycolic acid. Diethylene glycol is not metabolized to ethylene glycol; this is why calcium oxalate crystals, typical of ethylene glycol intoxication, are not found after diethylene glycol poisoning (Tables 1 and 2).[1,9-12]

The clinical course of diethylene glycol poisoning has 3 phases. The first phase is characterized by altered mental status and gastrointestinal symptoms, such as vomiting, nausea, abdominal pain, and sometimes diarrhea.

The second phase usually starts after 1 to 3 days, depending on the diethylene glycol dose and other coingestants (eg, ethanol inhibits diethylene glycol metabolism). Oliguric or anuric acute kidney failure with metabolic acidosis is typical. Death can occur 2 to 7 days after the onset of anuria in untreated patients; the other patients usually remain dialysis dependent. Renal ultrasound shows enlarged or swollen kidneys and, less frequently, atrophic kidneys. The degree of kidney injury can predict the neurologic evolution. The coexistent hepatic damage is expressed by transaminase level elevation. Hypertension, tachycardia, and pancreatitis are frequent.

Table 1. Chemical and Physical Characteristics of Ethylene Glycol and Diethylene Glycol

	Ethylene Glycol	Diethylene Glycol
Molecular formula	$C_2H_6O_2$	$C_4H_{10}O_3$
Structure	HO-CH_2-CH_2-OH	HO-CH_2-CH_2-O-CH_2-CH_2-OH
Molecular weight (Da)	62.07	106.12
Solubility	Water soluble	Water soluble
Appearance	Viscous hygroscopic liquid; colorless; odorless; sweetish taste	Viscous hygroscopic liquid; colorless; odorless; sweetish taste
Contained in	Automobile coolants; heat transfer fluids; precursor to polyester (bottle); used in bottling; runway deicers	Antifreeze; brake fluids; cosmetics; lubricants; paper; inks; textiles; adhesives; packaging materials; adhesives, solvents

The third phase is characterized by neurologic damage, mainly of the peripheral nervous system (eg, areflexia, loss of visual and auditory functions, and motor deficit). Sometimes inspiratory muscle weakness with respiratory depression or coma occurs.

The clinical evolution is unpredictable: long-term resolution, permanent neurologic or kidney damage, fulminant ascending paralysis, and death have been described.[1,13-16]

Renal damage in diethylene glycol poisoning is due to necrosis of the proximal tubules of cortical nephrons. Severe vacuolation and swelling of epithelial cells cause obstruction of the lumen.[1,17,18] The mechanism of renal diethylene glycol toxicity is not completely known. The oldest studies hypothesized that it was not due to diethylene glycol itself, but to its metabolites, 2-hydroxyethoxyacetic acid and diglycolic acid.[19,20] Diglycolic acid has a molecular structure similar to some endogenous compounds; therefore, after glomerular filtration, it is transported into the proximal tubular cells by apical sodium dicarboxylate transporters (NaDC-1) or organic anion transporters. Diglycolic acid reaches elevated concentrations in the tubular cells, where it inhibits a citric acid cycle enzyme, thus blocking adenosine triphosphate (ATP) production and causing cell death. Inhibition of diglycolic acid transporters in tubular cells blocks diglycolic acid–induced toxicity.[4,21] This