PROPYLENE GLYCOL

BACKGROUND

Propylene glycol (or 1,2-propanediol) is an alcohol excipient used to solubilize many common medications in their topical, oral and intravenous forms. Physicians commonly review patients' medications for toxicity, but rarely consider the diluent as having the potential for harm. Propylene glycol is "generally regarded as safe" by the Food Drug and Administration, given its low toxicity in early animal studies. However, the medical literature contains many case reports of its toxicity after exposure.

In the commercial realm, propylene glycol can be found in a wide range of products, including antifreeze, deicing fluids, hair-coloring and moisturizing products and the solution used to create artificial smoke in nightclubs. Its preservative properties promote its use as a food additive. In agriculture, high concentrations of propylene glycol are added to the feed of dairy cattle to promote glycogen stores and prevent ketosis.

CLINICAL PHARMACOLOGY

Propylene glycol is an odorless, colorless, thick liquid. It is an aliphatic alcohol with a molecular weight of 76 daltons. After ingestion, the bioavailability of propylene glycol approaches one hundred percent. The volume of distribution is ~0.5 L/kg, suggesting that propylene glycol freely distributes throughout total body water. Following intravenous administration, the kinetics are non-linear with a saturable clearance. The plasma elimination half-life is reported as 2.3 ± 0.7 hours. The terminal elimination half-life after ingestion is approximately 4 hours. The elimination half-life in infants is much longer: 19.3 hours following parenteral administration and 16.9 hours after topical exposure.

Approximately 50% of propylene glycol is metabolized in the liver in the presence of alcohol dehydrogenase. This oxidation reaction proceeds via two separate pathways for free and phosphorylated forms of propylene glycol. While both reactions proceed via different intermediates, the end products are the same, namely lactate and pyruvate (see Figure 1). The remaining 50% of serum propylene glycol is excreted unchanged by the kidneys.

CLINICAL TOXICOLOGY

Propylene glycol toxicity may manifest itself as hyperosmolality and lactic acidosis. Almost 25 years ago, Bekaris et al implicated propylene glycol in two cases of significant hyperosmolality in burn patients receiving treatment with silver sulfadiazine cream. Since then, multiple cases of hyperosmolality with or without lactic acidosis have been reported. Propylene glycol contributes to serum osmolality as a low-molecular weight, osmotically active particle.

The production of lactate and subsequent acidosis are the frequently implicated in serious propylene glycol toxicity. While all of the metabolic derangements associated with acidosis may be seen, tachypnea has been problematic in the intensive care unit setting. The resulting respiratory muscle fatigue has created difficulty in weaning patients from ventilatory support. Serum lactate levels as high as 15.6 mg/dL have been reported in patients with propylene glycol toxicity.

Propylene glycol mimics ethanol's effects on the CNS. It acts as a CNS depressant that causes ataxia, dysarthria and confusion. Propylene glycol has also been implicated as the cause of new-onset seizures in an 11 year-old patient receiving an oral vitamin D preparation containing propylene glycol. His seizures remained refractory to anticonvulsants, but resolved after exposure to propylene glycol was discontinued. Case reports of propylene glycol toxicity in children describe CNS depression as a prominent feature. Hypoglycemia has been reported in one pediatric propylene glycol exposure and may contribute to CNS depression.

Patients with decreased creatinine clearance are at increased risk of hyperosmolality and lactic acidosis. In one study, patients with a creatinine clearance less than 30 mL/min had a significantly higher plasma serum propylene glycol level and osmolar gap than counterparts with normal renal function. Furthermore, propylene glycol itself can precipitate acute renal failure due to drug-induced renal tubular injury.
Infants are at high risk of propylene glycol toxicity. Standard parenteral solutions administered to infants rapidly exceed the 25 mg/kg/day guideline for safe propylene glycol intake as established by the World Health Organization. For example, the amount of propylene glycol in the loading dose of phenytoin appropriate for a 1 kg infant is approximately seven times greater than the World Health Organization standard. There is a case report of an 8-month-old treated with silver sulfadiazine topically for burns and desquamation over 78% of his body. He received approximately 9 g/kg/day of propylene glycol. The infant's course was complicated by cardiac arrest; acidemia secondary to propylene glycol toxicity was suspected as the cause. As in adults, there is evidence that use of propylene glycol-containing solutions in neonates is linked to an increased incidence of seizures. Caution is recommended in using any preparation containing propylene glycol in infants.

Exposure to propylene glycol may be oral, dermal, inhalational or, most commonly, parenteral. A partial list of parenteral medications that contain propylene glycol includes chlorzoxazone, diazepam, digoxin, esmolol, etomidate, hydralazine, lorazepam, nitroglycerin, phenobarbital, phenytoin and trimethoprim-sulfamethoxazole (see Table 1). Propylene glycol is also used as the vehicle for several oral vitamin preparations. Additionally, propylene glycol is used as an emollient and stabilizer in many creams, including silver sulfadiazine. In the case report literature, continuous infusion or large doses of benzodiazepines for sedation proves to be the most commonly cited reason for propylene glycol toxicity. In one report, lorazepam doses as low as 4 to 6 mg/hour via continuous infusion were found to cause propylene glycol toxicity.

In 2000, Glaxo-Wellcome issued a warning that the oral solution of ampanavir (Agenerase) may pose a risk to patients because of the large amount of propylene glycol it contains. As a result, use of ampanavir is contraindicated in the following populations: infants and children below the age of 4 years, pregnant women and patients with hepatic or renal failure. No cases of propylene glycol toxicity as a consequence of ampanavir use had been reported at the time of the warning. In ingestion, toxicity is most common following multiple exposures. However one case report describes a toddler who presented with obtundation, metabolic acidosis, and hyperosmolarity after chewing on disposable cleaning towels that contained propylene glycol. Another child presented with similar symptoms after ingesting hair gel.

Dermal exposure to propylene glycol may precipitate local effects, primarily dermatitis. However, systemic toxicity resulting from dermal application has been reported, particularly in pediatric and burn patients.

Parenteral exposure to propylene glycol may cause phlebitis and soft tissue injury. Hemolysis and hemoglobinuria have also been observed. Parenteral propylene glycol has also been implicated in cardiac arrhythmias and arrest. The phenomenon of ventricular arrhythmias seen with rapid intravenous infusion of propylene glycol is well documented. These same effects are less common with use of fosphenytoin, a pro-drug that contains no propylene glycol in its solution. Propylene glycol has been identified as the cardiotoxic agent.

### Table 1

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Propylene Glycol (V/V)</th>
<th>Grams per Average Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampanavir (oral solution)</td>
<td>Agenerase®</td>
<td>50%</td>
<td>57.75</td>
</tr>
<tr>
<td>Chlorzoxazone</td>
<td>Librium®</td>
<td>20%</td>
<td>0.08</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Vialium®</td>
<td>40%</td>
<td>0.4</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Lanoxin®</td>
<td>40%</td>
<td>4.8</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Brevilox®</td>
<td>25%</td>
<td>2.5 for 75 kg person</td>
</tr>
<tr>
<td>Etomidate</td>
<td>Amidate®</td>
<td>35%</td>
<td>0.35</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Alivan®</td>
<td>80%</td>
<td>0.64</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Tridil®</td>
<td>30%</td>
<td>0.3 over 24 hours</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Dilantin®</td>
<td>40%</td>
<td>4.8</td>
</tr>
</tbody>
</table>

**LABORATORY DATA**

The initial sign of propylene glycol toxicity in most patients will be either an anion gap or a metabolic acidosis. When propylene glycol is suspected, serum osmolality and serum lactate should be obtained. A serum propylene glycol level can be ordered for confirmation, but this study may take hours to days to return. Treatment must often be instituted before confirmatory testing is available.

The portion of the serum osmolar gap attributable to propylene glycol can be determined by dividing the serum propylene glycol concentration (mg/dL) by 7.6. Alternatively, the serum
propylene glycol level can be estimated from the osmolar gap using the formula \(84.6 + (7.8 \times \text{Osmolal Gap} \text{[mOsm/kg H2O]})\) per one author’s derivation. Serum propylene glycol levels do not correlate well with toxicity; levels between 18mg/dL and 1059 mg/dL have been reported in toxic patients. Of note, one case has been reported in which a gas chromatography peak initially interpreted as ethylene glycol was subsequently corrected to propylene glycol. These peaks are similar in their retention times, but distinct on gas chromatography. In this case report, the recommendation is made to notify laboratory personnel about propylene glycol exposure in any patient being evaluated for ethylene glycol exposure. A standard can be made using both compounds, thus avoiding the possibility of misidentification.

In patients receiving continuous infusion or large doses of medications containing propylene glycol, serial measurements of anion gap, osmolar gap and acid-base status may provide an indication of propylene glycol accumulation before clinical toxicity is evident.

**MANAGEMENT**

The most critical step in managing a patient with propylene glycol toxicity is the identification of propylene glycol as the etiology of their symptoms. Again, physicians rarely consider the excipient as a cause of systemic toxicity and many cases of propylene glycol toxicity may remain unidentified. Once propylene glycol toxicity is suspected, all medications containing propylene glycol must be discontinued and substituted with another medication, if necessary. This intervention should be sufficient to resolve symptoms and prevent further harm in patients with normal renal function. Other potential causes of lactic acidosis must be excluded, including exposure to other toxic alcohols, other medications that may increase serum lactate (e.g. metformin), and systemic hypoperfusion (e.g. sepsis).

**Supportive Care**

Initial assessment must, as always, begin with airway, breathing and circulation. Airway compromise secondary to CNS depression from propylene glycol toxicity may necessitate intubation. Tachypnea, as a compensatory mechanism for acidosis, may cause respiratory muscle fatigue and indicate the need for ventilatory assistance. An increased minute volume may be indicated to prevent a rapid fall in pH after intubation. Hypotension should be treated initially with intravenous fluid bolus therapy. Vasopressors may be necessary in cases of severe toxicity.

Seizures should be treated with benzodiazepines. The potential for exacerbation of CNS depression exists and appropriate monitoring is indicated. Midazolam, in contrast to lorazepam or diazepam, does not contain propylene glycol. Consequently, midazolam is preferred in the treatment of propylene glycol-induced seizures. Monitor serum glucose levels, as hypoglycemia is another complication of propylene glycol exposure. Sedation in the intubated patient may be safely achieved with midazolam or propofol continuous infusion as propylene glycol is not used as an excipient for either of these medications.

**Decontamination/ Enhanced Elimination**

There are currently no studies examining the use of activated charcoal for propylene glycol ingestion. Extrapolating from the limited role of charcoal in other alcohol ingestions, administration of charcoal should be reserved for cases in which a co-ingestion is suspected.

There are case reports documenting the use of hemodialysis for the treatment of propylene glycol toxicity. Hemodialysis may be considered to enhance elimination of propylene glycol. It should be considered in patients with decreased hepatic or renal function, severe acidosis or hypotension. A study by Parker documented serial propylene glycol and serum osmolality levels and documented a decrease in both following dialysis.

**Antidotes**

Theoretically, ethanol or fomepizole may provide some benefit by slowing the conversion of propylene glycol to lactate via inhibition of alcohol dehydrogenase, though there are no studies in which either of these antidotes has been evaluated for the treatment of propylene glycol toxicity.

**Disposition**

Due to the iatrogenic nature of most propylene glycol exposures, most patients with propylene glycol toxicity will already be in a setting in which appropriate care can be delivered. Patients with suspected toxicity in the outpatient environment may require admission for supportive care.

Kavita Babu, MD
Chief Resident, Brown University Residency in Emergency Medicine

Achul Dhupa, MD
Associate Director of Critical Care, Miriam Hospital
Assistant Professor, Department of Medicine, Brown Medical School

Angela Anderson, MD
Attending Physician/Toxicology Consultant, Pediatric Emergency Medicine, Hasbro Children’s Hospital
Associate Professor, Department of Pediatrics and Emergency Medicine, Brown Medical School
References (First-author only)
