CORRESPONDENCE

Methemoglobinemia Due to Antifreeze Ingestion

TO THE EDITOR: Ingestion of antifreeze that contains ethylene glycol produces acidosis, nephropathy, coma, and cardiovascular collapse.[1] Previously, minimal increases in methemoglobin levels (to as high as 6%; normal value, <1.0% or <1.5%, depending on the assay) after ingestion of antifreeze have been reported,[2] with no known cause. We report a case of antifreeze ingestion that resulted in clinically significant methemoglobinemia caused by an identified agent.

Our patient, a 62-year-old man with a history of depression, presented to an emergency department 5 hours after ingesting antifreeze (Fleet Charge SCA Precharged Coolant/Antifreeze [Peak]). The bottle was recovered by paramedics. He had an arterial pH of 7.14 (normal range, 7.35 to 7.45), a serum bicarbonate level of 11 mmol per liter (normal range, 22 to 28), an osmolar gap of 167 mOsm per kilogram (normal value, <10), an anion gap of 17 mmol per liter (normal range, 3 to 11), and obtundation requiring intubation and mechanical ventilation. He was initially treated with intravenous sodium bicarbonate and fomepizole. Despite receiving mechanical ventilation, the patient had persistent pulse oximetry readings of 88% with the ventilator set to a fraction of inspired oxygen of 100% and a positive end-expiratory pressure of 15 cm of water. When his venous blood appeared brown in color despite an arterial partial pressure of oxygen of 502 mm Hg, the patient's methemoglobin level was tested and found to be 32.2%. The methemoglobinemia was successfully treated with methylene blue, and hemodialysis resolved the ethylene glycol poisoning with a favorable outcome.

On the basis of the patient's history and the results of urine gas chromatography–mass spectroscopy testing, no substance known to cause methemoglobinemia was present. The safety data sheet for the product that the patient ingested indicated a mixture of ethylene glycol (90 to 97%), diethylene glycol, water, and denatonium benzoate. Because only substances that comprise more than 1% of a given product are required by the Occupational Safety and Health Administration Hazard Communication Standard to be reported on the safety data sheet, a manufacturer's representative was contacted directly for further information. He disclosed the presence of nitrite (0.27%) and nitrate (0.08%) in the product. Nitrites and nitrates are used as anticorrosion agents in antifreeze[3] but are not universally included in all formulations, which may explain why methemoglobinemia has not been consistently observed after antifreeze ingestion.

On the basis of the concentration of ethylene glycol reported to be in the product, the patient's serum level of ethylene glycol at 5 hours after ingestion (835 mg per deciliter), and the patient's body weight (64 kg), we estimate that the ingested volume of antifreeze potentially exceeded 400 ml. This would contain the equivalent of 1.8 g of sodium nitrite, a toxic dose given that only 300 mg of medicinal sodium nitrite induces methemoglobinemia in the treatment of cyanide poisoning.[4]

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In conclusion, methemoglobinemia should be considered after a massive ingestion of antifreeze. More importantly, clinicians should be aware of the fact that because of the reporting limits allowed by the law, clinically significant poisons may not be listed on safety data sheets.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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Safety of Degludec versus Glargine in Type 2 Diabetes

TO THE EDITOR: In reporting the results of the Trial Comparing Cardiovascular Safety of Insulin Degludec versus Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE), Marso et al. (Aug. 24 issue)[1] report a lower risk of hypoglycemia among patients who received insulin degludec than among those who received insulin glargine, without significant differences in basal insulin doses, monitored plasma glucose or glycated hemoglobin levels, or concomitant medications. Although the use of prandial insulin was similar in the two groups, no information was provided on the actual doses administered. The distribution of risk factors for severe hypoglycemia, such as unawareness of hypoglycemia and hypoglycemia-associated autonomic failure, dietary practices, and exercise behavior, was also unclear.[2]

The authors attributed the between-group differences in the incidence of hypoglycemia to the "improved pharmacodynamic profile of degludec." However, the pharmacodynamic profile of insulin glargine is similar to that of regular human insulin[3] and degludec[4] with respect to counterregulatory responses during hypoglycemia. Thus, the mechanism of the seemingly large differences in rates of hypoglycemia reported for degludec versus glargine remains unclear, and the suggested explanation regarding the pharmacodynamic profile is not supported by the available data.

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TO THE EDITOR: In DEVOTE, patients with type 2 diabetes who received degludec had fewer episodes of severe hypoglycemia than those who received glargine (4.9% vs. 6.6%, P<0.001), with an average daily insulin dose of 0.7 U per kilogram of body weight. Studies have shown that steady-state plasma insulin concentrations are more than 20 times as high in healthy volunteers receiving a 0.4-U-per-kilogram daily dose of degludec as in those receiving glargine (2388 vs. 115 pmol per liter).[1,2] This increase in insulin concentration is probably due to protein binding.

The acute effects of highly protein-bound medication (e.g., phenytoin, valproic acid, furosemide, amiodarone, propofol, lorazepam, and propranolol) used in the emergency department