The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Medication-Associated Diethylene Glycol Mass Poisoning — A Preventable Cause of Illness and Death

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Despite increasing scrutiny of the pharmaceutical industry at both the national and international levels, Gambia recently faced a medication-associated diethylene glycol mass poisoning (MDMP).[1] Why do such tragedies continue to happen?

During the past 80 years, there have been more than 14 MDMPs reported in 14 countries — including Nigeria, Panama, Haiti, and others — which have often affected children; there may have been more that have gone undetected.[1,2] As in most outbreaks in resource-constrained settings, the true numbers of cases of diethylene glycol (DEG) poisoning in these events are unclear. In addition, the true number of people exposed to toxic but sublethal amounts of DEG who did not seek health care will never be known. Identifying this latter population is of public health importance because DEG poisoning can cause chronic kidney disease in survivors of acute poisoning.[3,4]

This data gap most likely results from the fact that public health authorities in low- and middle-income countries (LMICs) have inadequate resources to support core public health activities for MDMPs, such as surveillance for acute kidney injury of unknown origin, education of clinicians about how to recognize DEG poisoning, and clinical follow-up of cases. Further complicating management of this problem is the lack of resources for clinicians to diagnose and manage DEG poisoning. Many countries have few, if any, laboratories that can rapidly confirm DEG ingestion, and they lack appropriate and timely treatment options (which include relatively expensive antidotes such as alcohol-dehydrogenase–inhibiting drugs) and access to extracorporeal treatments.

DEG is miscible in water, alcohol, ether, and acetone, which makes it an effective solvent for water-insoluble chemicals.[3,4] It has numerous industrial uses: as a brake fluid, antifreeze, wallpaper stripper, lubricant, fuel, softening agent, plasticizer, and many others.[3] Although there are multiple instances of injury (both fatal and nonfatal) from DEG ingestion (both intentional and unintentional), DEG as a toxic chemical is responsible for an unusually high number of poisonings, owing to its consumption as an inappropriate excipient — an inert ingredient commonly

used as a diluent or vehicle for delivering one or more biologically active ingredients in a medication.[2]

DEG poisoning is reported to cause a wide range of adverse health effects in multiple organ systems,[3] but nephrotoxicity is its hallmark feature.[3,4] Although we have incomplete data on the effects in humans, the nephrotoxicity most likely originates from a DEG metabolite, known as diglycolic acid (DGA). In sufficient amounts, DGA is a potent nephrotoxin that is concentrated in the proximal renal tubule, causing mitochondrial dysfunction and cell damage.[4] If affected persons survive long enough to recover from acute poisoning, they remain at risk for neurotoxic effects that may manifest in bilateral facial paralysis, peripheral neuropathy, quadriparesis, and other neurologic signs and symptoms.[3]

Hypotheses about the mechanism of these effects include tissue damage due to DGA production by DEG metabolism. Therefore, current management therapies for DEG poisoning include inhibiting DGA production by blocking alcohol dehydrogenase enzymes using a drug such as fomepizole or ethanol. Supplemental or complementary treatment regimens include extracorporeal treatments such as hemodialysis.[3,4] Both treatment options should ideally be guided by serial measurements of blood DEG concentrations, but these are not routinely available tests.

We believe that promotion of evidence-based public health practices as well as adherence to drug-manufacturing best practices and regulatory enforcement can have the greatest impact in preventing these avoidable events. The reported historical association of MDMPs with the excipients glycerin and propylene glycol[2] offers opportunities for targeted, preventive public health action. Drug manufacturers can fulfill their responsibility to ensure that their products meet Current Good Manufacturing Practice requirements by means of tailored adherence to guidance set forth by national regulatory authorities such as the Food and Drug Administration[2] or international public health authorities such as the World Health Organization (WHO) and by providing appropriate quality assurance. Such adherence includes routine testing of raw ingredients used in the manufacturing of active and inert components, as well as of finished product batches, to ensure that they meet specifications for identity, purity, strength, and quality. The identity of manufacturing and distribution supply-chain vendors, which include source-ingredient providers and repackaging distributors, can be confirmed, and mandatory programs can be put into place to ensure that product lots undergo quality-control procedures and checks. This process can also include deployment of regulatory strategies for identifying and interdicting counterfeit medications. Establishing postmarketing surveillance programs and encouraging reporting of adverse events may facilitate early detection, which in turn can mitigate morbidity and mortality attributable to mass poisoning.

It is also important to briefly highlight the larger public health problem of global inequity in resources dedicated to the prevention, control, and management of poisoning by toxins (e.g., drugs or chemicals). Worldwide, poisoning causes hundreds of thousands of deaths each year, including in LMICs.[5] In many countries, poison centers (PCs) play an important public health role in poisoning-prevention activities, providing training and information to clinicians and the public on the recognition and management of poisoning, and supporting pharmacovigilance networks and the development of relevant laboratory capacity for toxicology.

Despite the fact that poisoning and chemical exposures are included in the International Health Regulations (2005) and the 70th World Health Assembly Roadmap, the WHO has estimated that only 47% of all WHO member states have a functioning PC. Formally trained clinical toxicologists are few, and they primarily practice in North America, Europe, and other high-income countries and regions. Access to formal toxicology training and "short-course" modular training for clinicians and public health professionals in LMICs is a critical need.

Despite a dearth of clinicians formally trained in clinical toxicology, all health care staff can play an important part in poisoning-prevention work by, for example, counseling patients about medication safety and appropriate use. Public health authorities can conduct educational campaigns and outreach to clinicians about the importance of preventing poisoning by discouraging the purchase of medications outside of licensed pharmacies or retail stores and warning people against using medications prescribed for someone else or for another indication. Finally, such campaigns can also include focused education for clinicians

about how to recognize potential early indicators of mass poisonings by toxicologic agents, which can be different from indicators of infectious disease outbreaks.

Although the root causes of MDMPs are unclear, DEG continues to sporadically appear in medications that normally contain appropriate excipients, such as pharmaceutical-grade propylene glycol and glycerin.[2] The most common explanations for the recurrence of MDMPs include unintentional or intentional adulteration of medications at some point in the manufacturing or distribution supply chain and poor quality-control procedures and processes during manufacturing (often attributable to cost-saving efforts).[2] The current multinational nature of pharmaceutical ingredient manufacturing may be contributing to the increased potential for missteps on the way to manufacturing of the final product.[2,4] MDMPs are a recurring public health problem, but guidance already exists regarding identification of affected ingredients and final products that are likely to cause a mass poisoning. Following this guidance is a critical way to prevent MDMP-associated illnesses and deaths.

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure forms provided by the authors are available at NEJM.org.

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This article was published on March 2, 2023, at NEJM.org.

1. Bastani P, Jammeh A, Lamar F, et al. Acute kidney injury among children likely associated with diethylene glycol–contaminated medications — The Gambia, June–September 2022. MMWR Morb Mortal Wkly Rep 2023;72:217-22.
2. Schier JG, Rubin CS, Miller D, Barr D, McGeehin MA. Medication-associated diethylene glycol mass poisoning: a review and discussion on the origin of contamination. J Public Health Policy 2009;30:127-43.
3. Schep LJ, Slaughter RJ, Temple WA, Beasley DM. Diethylene glycol poisoning. Clin Toxicol (Phila) 2009;47:525-35.
4. Brent J. Lessons learned from yet another episode of diethylene glycol poisoning: it happened before and it happened again. JAMA Intern Med 2014;174:918-9.
5. Neumann NR, Thompson TM. Medical toxicology education and global health: it is still a world of limited resources in low- and middle-income countries. J Med Toxicol 2020;16:358-60.

DOI: 10.1056/NEJMp2215840