Medical Toxicology and Public Health—Update on Research and Activities at the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry

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The following is an update on research and activities in which clinical toxicologists are actively involved at CDC/ATSDR. The *Journal of Medical Toxicology* periodically will highlight some of these activities to illustrate the growing relationship between clinical toxicology and public health.

HEALTH STUDIES BRANCH, NCEH

The Health Studies Branch (HSB) is responsible for responding to domestic and international requests for assistance with suspected and known environmental-associated public health threats. The HSB employs personnel with a wide variety of educational backgrounds and professional training including epidemiology, medicine, statistics, and other environmental public health-related disciplines. This wide range of expertise is necessary to address the broad scope of potential environmental health threats. In addition to outbreak response activities, HSB scientists pursue research questions arising from these events. For example, research activities on the mitigation of aflatoxin-associated illness in Africa have been ongoing [1]. These activities are the result of a 2005 investigation into the largest aflatoxin-associated outbreak ever reported in Africa [1]. Another example is primary research into mercury levels in those who frequently consume fish caught in areas with elevated environmental burdens of mercury [2]. The HSB was also recently involved with investigating an outbreak of illness that was ultimately determined to result from diethylene glycol-contaminated cough syrup [3].

Prospective assessment of health effects in persons exposed to DEG in the Republic of Panama

Diethylene glycol (DEG) is a clear, odorless liquid often used in commercial and industrial processes and products. Exposure to DEG is known to cause severe acute effects in humans in both the renal and neurological systems, although the exact mechanism is unknown. Over the last 80 years DEG has been identified in a variety of different pharmaceutical products that were associated with several mass poisonings [4]. During October of 2006, the Centers for Disease Control and Prevention (CDC) assisted the Panamanian Ministry of Health to investigate an outbreak of renal and neurologic illness. On October 11, 2006, DEG was identified by CDC and United States Food and Drug Administration laboratories as a contaminant in cough syrup formulated in Panama and distributed to more than 30,000 residents. The

Note: The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry.

ingestion of this cough syrup was implicated in over 90 cases of acute renal failure, including 51 deaths. Substantial public health measures were taken by the Panamanian government and public health authorities to prevent further exposure to DEG, and no new cases were reported after October 28, 2006.

The acute short- and long-term adverse health effects of exposure to DEG are not well established. To the authors' knowledge, no detailed follow-up information on outcomes of DEG-poisoned patients exists, other than a brief report on a case series of five patients [5]. Of these five, three were severely ill on presentation, and one died shortly thereafter. The remaining two had improved neurologic function at 4–6 months after presentation, but remained dialysis-dependent and displayed persistent neurologic deficits at 26 months [5]. Considering the large number of potentially exposed individuals, it is conceivable that there might be a large future DEG-associated disease burden in the Republic of Panama. Therefore, on December 22, 2006, the Ministry of Health of Panama (MINSA) formally requested the assistance of scientists within the National Center of Environmental Health with the evaluation of clinical, laboratory, and diagnostic features of DEG exposure among both hospitalized and nonhospitalized persons over the course of approximately 24 months. Scientists from the CDC have partnered with MINSA and with representatives of the Pan American Health Organization, Gorgas Memorial Institute, the Caja del Seguro Social Hospital System, the Santo Tomas Hospital, and other in-country organizations to conduct a follow-up investigation.

The objectives of this investigation are (1) to provide information to the Panamanian Ministry of Health regarding the health status of individuals exposed to DEG that will guide health interventions and resource allocations, (2) to characterize and describe short- and long-term (clinical and subclinical) signs and symptoms of persons exposed to the implicated cough syrup that had high creatinine levels (>1.5 mg/dL) on follow-up screening, but who were not hospitalized at the time of the initial outbreak for acute illness, (3) to characterize and describe the health status of survivors who were initially hospitalized for acute DEG toxicity, and (4) to describe possible risk factors for the development of adverse health effects among hospitalized and nonhospitalized persons.

More than forty patients who are currently being followed fall into one of two categories: (1) those exposed to the DEG-contaminated cough syrup who manifested illness, were hospitalized, and recovered, and (2) those exposed to the DEG-contaminated cough syrup who did not manifest overt symptoms of DEG toxicity but were later found to have an elevated serum creatinine levels on follow-up creatinine screening conducted by the Panamanian government and health authorities. The following information is being collected on these patients: (1) reported signs, symptoms, and diagnosed medical conditions since exposure; (2) results of serial clinical examinations with an extensive neurological examination, including nerve conduction studies, by a board-certified neurologist; and (3) results of renal function and urine testing. Two evaluations, separated by a six-month period, of this cohort have occurred already; two additional evaluations are planned for 2008. Data collection and analysis are ongoing.

COMMENTARY

Diethylene glycol (DEG), or 2,2′-dihydroxydiethyl ether, is an alcohol produced by the condensation of two ethylene glycol (EG) molecules with an ether bond [5]. It was first isolated as early as 1869 and has been used in industry and manufacturing since 1928 [5]. Since then it has been used as an antifreeze solution; as a finishing agent for wool, cotton, silk, and other fabrics; and in dye manufacturing. DEG is chemically inert, does not ignite at normal temperatures, and has a higher boiling point than EG [6,7]. However, it has physical properties that are generally quite similar to EG, including a sweet taste [6,7]. DEG has been used as a hygroscopic agent for paper, glue, tobacco, gelatin, cheese, and gum drops; it has even been used as a solvent for food flavoring in products such as ice cream [7]. It is used as an intermediate in the production of polymers, higher glycols, morpholine, and dioxane [8]. It can be used in the dehydration of natural gas, production of polyurethanes and unsaturated polyester resins, and in solvent extraction processes in petroleum refining operations [9]. Although DEG has substantial inherent toxicity when ingested, its physical properties make it an excellent solvent for water-insoluble substances like drugs [6]. This fact, along with its overall cheaper cost compared to the safer and more expensive pharmaceutical grade diluents such as glycerin and propylene glycol, may explain its appearance in several medication-associated DEG mass poisonings over the last 70 years [2].

DEG is toxic primarily to the kidney and nervous system and can produce a wide variety of signs and symptoms after consumption. Patients typically develop acute renal failure (ARF) and may present with metabolic acidosis [5]. In several medication-associated DEG mass poisonings, the clinical picture included ARF and neurologic symptoms, including encephalopathy, coma, and death [10–12]. The lack of information on the short- and long-term effects of DEG exposure is matched by a scarcity of information on the manner in which DEG is metabolized and eliminated after ingestion and how it causes its specific end-organ effects in humans. Since DEG consists of two EG molecules linked together through an ether bond and since EG is known to cause ARF, early research efforts focused around the hypothesis that the ether bond was hydrolyzed, releasing two EG molecules.

The pathophysiology of EG-induced ARF is well understood. In the presence of EG, ARF results from metabolism of the parent compound to toxic metabolites. These toxic metabolites include glycolic acid, which contributes to the metabolic acidosis found in EG poisoning, and oxalic acid, which precipitates with calcium in the kidney to produce ARF [13–16]. Since DEG poisoning also causes ARF, this was a plausible mechanism, at least in theory, for its toxicity. Several early rat studies supported this notion and revealed evidence of oxaluria and calcium oxalate crystal formation in the renal tubules [13–16]. However, this appears to not be the case in DEG-induced ARF, at least in animal models.

The ether bond in the DEG molecule is likely stable and does not undergo endogenous cleavage. This was shown by Weiner et al. [17], who fed DEG containing radiolabeled carbon to rats, demonstrating that the principal urinary elimination products were 2-hydroxyethoxyacetic acid (HEAA) as well as DEG. Wiener then went on to document the absence of any EG and known metabolites of EG (glycolic acid, glycoaldehyde, glyoxylate, and oxalic acid) containing radiolabeled carbon [17]. Since earlier studies did not use DEG containing radiolabeled carbon, the true origin of the oxaluria in these reports cannot be definitively determined. Furthermore, commercial DEG production commonly uses EG in the manufacturing process. Therefore, the early reports of oxaluria and oxalate crystals in kidney tissue from animal experiments involving DEG containing nonradiolabeled carbon may have resulted from EG contamination of the DEG used in the protocols [17].

Weiner also reported that pretreatment with pyrazole (an alcohol dehydrogenase blocker) and diethyldithiocarbamate (an aldehyde dehydrogenase blocker) inhibited production of HEAA. This supports the notion that metabolism of DEG to HEAA occurs by alcohol and aldehyde dehydrogenase activity. He also reported decreased lethality when rats given an LD_{50} dose of DEG were pretreated with pyrazole, suggesting that HEAA may have some inherent toxicity [17]. Yip et al. [18] further reported on Wiener's work stating that the protective effect of pyrazole pretreatment in rats actually disappeared when fed a DEG dose of 1.25 times the LD_{50} [17,18]. This suggests that the parent compound has some inherent toxicity or some other, unidentified method of toxicity exists [18].

The exact pathophysiology of DEG-induced illness is still unclear. Limited evidence suggests that HEAA, the principal metabolite of DEG, is toxic, but this same work also suggests that it is not the only toxic agent. More work remains to be done on elucidating the pathophysiology of DEG-induced illness, as well as in clarifying short- and long-term outcomes of DEG-poisoned patients. A better understanding of DEG metabolism and pathophysiology will contribute to a better understanding of how to treat and manage the complications and manifestations of illness. The persistence of DEG-associated mass poisonings over the last century and now into the current one suggests that unless more work is focused on both the clinical and public health components of this problem, it will reoccur.

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