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REVIEW

Diethylene glycol poisoning

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Introduction. Diethylene glycol (DEG) is a clear, colorless, practically odorless, viscous, hygroscopic liquid with a sweetish taste. In addition to its use in a wide range of industrial products, it has also been involved in a number of prominent mass poisonings spanning back to 1937. Despite DEG's toxicity and associated epidemics of fatal poisonings, a comprehensive review has not been published. *Methods.* A summary of the literature on DEG was compiled by systematically searching OVID MEDLINE and ISI Web of Science. Further information was obtained from book chapters, relevant news reports, and web material. *Aim.* The aim of this review is to summarize all main aspects of DEG poisoning including epidemiology, toxicokinetics, mechanisms of toxicity, clinical features, toxicity of DEG, diagnosis, and management. *Epidemiology.* Most of the documented cases of DEG poisoning have been epidemics (numbering over a dozen) where DEG was substituted in pharmaceutical preparations. More often, these epidemics have occurred in developing and impoverished nations where there is limited access to intensive medical care and quality control procedures are substandard. *Toxicokinetics.* Following ingestion, DEG is rapidly absorbed and distributed within the body, predominantly to regions that are well perfused. Metabolism occurs principally in the liver and both the parent and the metabolite, 2-hydroxyethoxyacetic acid (HEAA), are renally eliminated rapidly. *Mechanisms of toxicity.* Although the mechanism of toxicity is not clearly elucidated, research suggests that the DEG metabolite, HEAA, is the major contributor to renal and neurological toxicities. *Clinical features.* The clinical effects of DEG poisoning can be divided into three stages: The first phase consists of gastrointestinal symptoms with evidence of inebriation and developing metabolic acidosis. If poisoning is pronounced, patients can progress to a second phase with more severe metabolic acidosis and evidence of emerging renal injury, which, in the absence of appropriate supportive care, can lead to death. If patients are stabilized, they may then enter the final phase with various delayed neuropathies and other neurological effects, sometimes fatal. *Toxicity of DEG.* Doses of DEG necessary to cause human morbidity and mortality are not well established. They are based predominantly on reports following some epidemics of mass poisonings, which may underestimate toxicity. The mean estimated fatal dose in an adult has been defined as ~1 mL/kg of pure DEG. *Management.* Initial treatment consists of appropriate airway management and attention to acid–base abnormalities. Prompt use of fomepizole or ethanol is important in preventing the formation of the toxic metabolite HEAA; hemodialysis can also be critical, and assisted ventilation may be required. *Conclusions.* DEG ingestion can lead to serious complications that may prove fatal. Prognosis may be improved, however, with prompt supportive care and timely use of fomepizole or ethanol.

Keywords Diethylene glycol; 2-Hydroxyethoxyacetic acid; Metabolic acidosis; Ethanol; Fomepizole; Renal toxicity; Delayed neuropathies

Chemical properties and uses

Diethylene glycol (DEG) (CAS 111-46-6), 2,2′-oxybisethanol, has a molecular formula of $C_4H_{10}O_3$ and a molecular weight of 106.12 g/mol. It is a clear, colorless, practically odorless, viscous, hygroscopic liquid, with a melting point of −6.5°C, a boiling point of 245°C, and a vapor pressure of <0.01 mmHg at 25°C. DEG has a sharp sweetish taste.[1,2] It is miscible in water, alcohol, ether, acetone, and ethylene glycol.[2] These physical properties make it an excellent solvent for water-insoluble chemicals and drugs.[3]

DEG is used as a component in antifreeze formulations, brake fluids, cosmetics, lubricants, wallpaper strippers, artificial fog solutions, heating/cooking fuel, mould-release agents, inks, as a softening agent for textiles and as a plasticizer for cork, adhesives, paper, and packaging materials. It is also used as an intermediate in the production of DEG dinitrate, DEG ethers and esters, morpholine, and certain resins.[1]

Methods

An extensive literature review was performed by systematically searching ISI Web of Science (1900 to May 2009) and OVID MEDLINE (January 1950–May 2009). Bibliographies of identified articles were screened for additional relevant studies including nonindexed reports. In addition,

nonpeer-reviewed sources were also included: books, relevant newspaper reports, and applicable web material.

Epidemiology

Poisoning because of DEG is not a common occurrence. Most of the documented cases of poisoning have been epidemics where DEG was substituted in pharmaceutical preparations for the more expensive, but virtually nontoxic, glycols or glycerine constituents customarily used. As these episodes (numbering over a dozen) all involved multiple cases, the total numbers affected have been substantial (Table 1). Furthermore, these epidemics have mostly occurred in impoverished developing countries, where there are often not only substandard quality control procedures but also limited access to intensive medical care, with resultant high mortality rates.

The first and most infamous mass poisoning was the sulfanilamide-Massengill disaster in the United States in 1937. DEG (72%, v/v) was used as the solvent in an elixir of sulphanilamide. No toxicity testing had been conducted on either the ingredients or the finished product prior to marketing.[4,5] Shortly after it was distributed across the United States, chiefly in the southern states, reports of adverse effects and deaths were noted.[6,7] In total, 353 patients received the product with 105 deaths: 34 children and 71 adults.[4,8] This disaster was the impetus for the passage of the 1938 Federal Food, Drug and Cosmetic Act in the USA, which requires drug producers to demonstrate acceptable safety before marketing a product.[8–10]

Following the ingestion of an over-the-counter sedative (pronap or plaxim) in Cape Town, South Africa (1969), seven children died of renal failure. Subsequent investigations implicated DEG, which was found to have been substituted for propylene glycol.[11] In 1985, five patients being treated in a burns unit in Spain developed anuric renal failure and died, despite supportive treatment. The patients were all treated with a topical silver sulfadiazine ointment that was contaminated with 6.2–7.1 g/kg of DEG. Although DEG is poorly absorbed through intact skin, it was suggested that systemic toxicity occurred because of the combination of damaged skin in these patients, the large areas being treated, and repeated applications of the product.[12]

Twenty-one patients (from two separate incidents) died from renal failure in India, following the administration of industrial glycerine (containing 18.5%, v/v, DEG) as part of their treatment.[13] In the summer of 1990, 47 children who were admitted to the Jos University teaching hospital in Nigeria later died from renal failure; all had been given paracetamol (acetaminophen) syrup, contaminated with DEG, that was substituted for propylene glycol.[14] A similar contamination of this analgesic led to the death of 236 children in Dhaka, Bangladesh, between 1990 and 1992.[15] Contaminated paracetamol resulted in 88 confirmed deaths of young infants in Port-au-Prince, Haiti, in 1996 (a further 11 children were lost, however, to follow-up when they were taken home by their families and presumably died). DEG-substituted glycerine in Haiti was supplied by a Dutch distributor from a manufacturer in China although the point of contamination was never determined.[16–23] Contamination of propolis syrup in Argentina in 1992 led to the death of 29 people; the syrup was found to contain between 24 and 66.5% DEG.[24,25]

Following the ingestion of a locally manufactured cough expectorant in Guragon, India (1998), 36 children developed acute renal failure and 33 died despite treatment with peritoneal dialysis and supportive care. Epidemiological investigations discovered that the medicine was contaminated with

Table 1. Tabulated summary of incidents of mass poisoning resulting from exposure to pharmaceutical preparations contaminated with diethylene glycol

Year	Country	Contaminated product	Number of documented deaths	Reference(s)
1937	USA	Sulfanilamide	105	4, 6, 56
1969	South Africa	Sedatives	7	11
1985	Spain	Silver sulfadiazine	5	12
1986	India	Glycerine	21	13
1990	Nigeria	Acetaminophen	47	14
1990–1992	Bangladesh	Acetaminophen	236	15
1992	Argentina	Propolis	29	24, 25
1996	Haiti	Acetaminophen	88	16
1998	India	Cough expectorant	33	26
1998	India	Acetaminophen	8	28
2006	Panama	Cough syrup	78	29
2006	China	Armillarisin-A	12	33, 34
2008	Nigeria	Teething syrup	84	35–37

17.5% DEG.[26,27] A related incident was caused by paracetamol syrup contaminated with 2.3–23% (median 15.4%) DEG, leading to the death of eight children.[28]

In 2006 in Panama, an official estimate of 78 deaths[29] (though it could be as high as 365)[30] occurred as a result of unexplained renal failure accompanied by neurological dysfunction. It was later discovered that a cough syrup was contaminated with an average of 8.1% DEG. The syrup was manufactured from glycerine imported from China via a European broker and was contaminated with an average of 22.2% DEG.[29,31,32] Another outbreak in the same year, in China, led to the confirmed death of 12 patients, following the intravenous administration of contaminated armillarisin-A.[33,34] Most recently in November and December of 2008, 84 children died in Nigeria following the ingestion of a teething syrup contaminated with DEG.[35–37]

DEG has also appeared in other consumer products. Austrian wine was adulterated with DEG to give the wine a sweeter taste.[38–40] One reported case of acute renal failure may have been a result of ingesting this wine.[41] Fake Sensodyne brand toothpaste contaminated with DEG has appeared in the United Kingdom,[42] while toothpaste imported from China and sold in Spain, Costa Rica, Panama, Nicaragua, the Dominican Republic, and the United States has also been found to be contaminated with DEG.[43–45] No serious illnesses were reported from use of these adulterated toothpastes.

In addition to these epidemics, there have also been some isolated cases typically occurring with people ingesting DEG or DEG-based brake fluids or canned fuel for recreational purposes as an alcohol substitute, or in intentional suicide attempts.[46–52] Less commonly, child exploratory or accidental exposures have also been reported.[53–55] The majority of intentional ingestions involved patients taking large doses, with high mortality rates being reported.

Toxicokinetics

There is limited information available regarding the human kinetics of DEG. The majority of published information is derived from experimental studies.[56]

Absorption

DEG is readily absorbed following oral ingestion. Oral doses in rats are rapidly and almost completely absorbed with peak plasma concentrations achieved within 25–120 min.[57] Absorption by the dermal route can occur though the rate of delivery is low. Unsurprisingly, DEG absorption is greater through broken or damaged skin,[12] if contact is prolonged and extensive, or it involves a large surface area.[55] Dermal administration of DEG over a large surface of a rat (50 mg/12 cm^2) led to the cumulative recovery of 9% of the initial dose, by 72 h post-application.[58]

To the knowledge of the authors, there are no reports on the respiratory absorption of inhaled DEG. However, as DEG has a low vapor pressure (<0.01 mmHg at 25°C), the risk of inhalation leading to toxicity is likely to be low in most circumstances.

Distribution

In rats, DEG is widely distributed (predominantly within well perfused regions), with an estimated apparent volume of distribution of ~1 L/kg body weight.[57] Following the administration of acute oral doses, rapid distribution (within 2.5 h) was achieved in the major organs and tissues[57]; those with reported concentrations included, in rank order, kidney > brain > spleen > liver > muscle > fat.[57] Five days post-ingestion, approximately 0.25–3.1% of the administered dose was still evident in the body, with some present in most organs.

DEG rapidly crosses the blood–brain barrier, with a maximum concentration being found in rat brain within 3–4 hours post-dosing.[57] Narcotic effects in this species have been observed within 20 min following ingestion and have continued for a further 6–8 h.

Metabolism

Metabolism of DEG occurs principally in the liver. There is limited information on humans, but in rats DEG has been shown to be oxidized to 2-hydroxyethoxyacetaldehyde by nicotinamide adenine dinucleotide (NAD)-dependent alcohol dehydrogenase (ADH). This is followed by aldehyde dehydrogenase (ALDH) enzymatic metabolism to 2-hydroxyethoxyacetic acid (HEAA),[59,60] as shown in Fig. 1. In rats, 16–31% of the dose is purported to undergo metabolism.[59] DEG does not appear to be metabolized to ethylene glycol; one important metabolite of the latter is oxalate, but calcium oxalate crystal deposition is not a feature of DEG poisoning (further details are provided in "Mechanisms of toxicity").[57,60]

Elimination

Renal excretion of DEG and its known metabolites is the predominant route of elimination.[57,58] Recoveries of ^{14}C activity following oral administration of ^{14}C-DEG to rats were 80–84% in the urine, 0.7–2.2% in the feces, and 0.3–1.3% in expired air.[59] Similar values have been reported in other investigations.[57] In rats, 61–68% of the ingested dose of DEG was excreted as the parent chemical, with approximately 16–31% appearing as HEAA.[59] Another study with rats reported 80% unmetabolized DEG and 20% HEAA.[60] An investigation with dogs showed that 40–70% of the excreted dose remained unchanged.[61] There is some evidence to suggest that unmetabolized DEG and HEAA are partially reabsorbed from the renal tubules following glomerular filtration.[57]
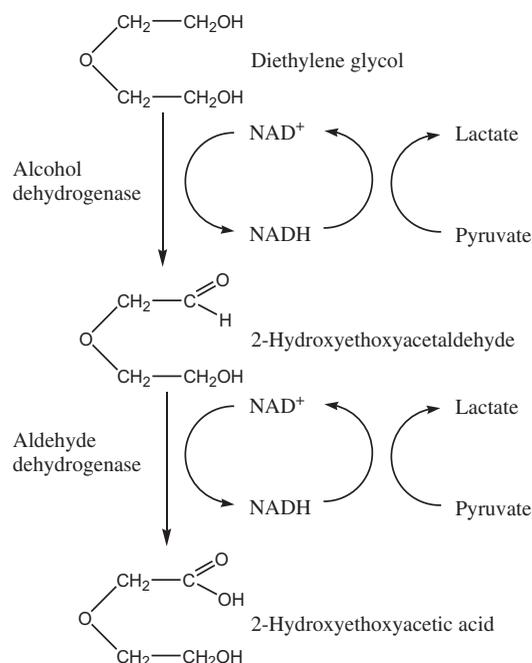
Fig. 1. Pathway of diethylene glycol metabolism by alcohol dehydrogenase oxidation to form 2-hydroxyethoxyacetaldehyde followed by aldehyde dehydrogenase oxidation to form 2-hydroxyethoxyacetic acid.

Mechanisms of toxicity

The precise mechanisms underlying DEG toxicity have not been fully elucidated. The molecule consists of two ethylene glycol molecules linked by a stable ether bond (Fig. 1). As ethylene glycol also causes acute renal failure, it was initially thought that DEG was metabolized by endogenous cleavage of the ether bond to form ethylene glycol, with the latter responsible for the adverse effects. Some experiments showing oxalate crystals in the urine of animals administered DEG were thought to prove that toxic effects were caused by the formation and subsequent metabolism of the cleaved ethylene glycol.[62–65] However, other conflicting studies in dogs[61] and rabbits[66] did not show any increase in urinary oxalate concentrations after oral dosing. Successive studies using radiolabeled DEG in rats and dogs confirmed these observations.[57–60] Additionally, patients poisoned by DEG have not displayed urinary oxalate formation,[12,18,24,48] lending further support to the argument that endogenous cleavage to ethylene glycol does not occur. Based on these results, it appears that DEG is not metabolized to two ethylene glycol molecules, most likely because of its metabolically stable ether linkage.[60,67] It has been hypothesized that those experiments suggesting oxalate formation may have involved products contaminated with ethylene glycol, which could have compromised their findings.[58,60]

Oxidation of the intact DEG molecule is the probable metabolic pathway leading to toxic effects.[67] Animal studies have demonstrated that DEG is metabolized by ADH oxidation to form 2-hydroxyethoxyacetaldehyde (Fig. 1), which is then rapidly metabolized by ALDH to HEAA.[57,59,60] Amounts administered to animals in these investigations covered a wide range of toxic to lethal doses (1, 5, 10, 12.5, 15, 17.5 mL/kg as 50% solutions).[57,59] Research suggests that HEAA does not undergo any further oxidation.[60] While concern has been raised that the parent compound may be directly toxic,[18] it appears that HEAA is the major contributor to the renal and neurological toxidromes.[60,68] This is based on animal experiments showing that pre-treatment with alcohol or ALDH inhibitors lessens the lethality of an LD_{50} dose[60] or even prevents signs of toxicity from occurring.[68]

Suggested mechanisms of cellular toxicity have included membrane destabilization via phospholipid or ion channel effects, and intracellular accumulation of osmotically active metabolites with associated transcellular fluid shifts.[48] Increasing concentrations of HEAA contribute to metabolic acidosis.[69]

DEG and its oxidized metabolite (HEAA) also appear to cause renal derangement, mild but typically resolving hepatic injury and delayed, and frequently lethal, neurological damage. One author has suggested that the two hydroxyl groups in the DEG molecule may account for much of the renal and hepatic hydropic degeneration.[18]

Toxicity of DEG

The minimum dose capable of causing toxic effects in humans has not been well established. Indeed, the range of doses reportedly required are wide (though overlapping), spanning in one instance more than two orders of magnitude.[4] They are based predominantly on reports following some epidemics of mass poisonings. Such doses were estimated by recollection of ingested volumes from family or relatives of patients, or the determined dose was based on maximum possible amounts ingested (i.e., it was assumed one patient ingested all the bottle's missing contents). Consequently, reported values may be an overestimate of doses necessary for morbidity and mortality, thereby underestimating toxicity.

From the sulfanilamide incident, the defined range in children for a cumulative nonfatal dose (1–14 years of age) was 2.4–84.7 g, whereas estimated cumulative fatal doses (7 months–16 years of age) ranged from 4.0 to 96.8 g.[4] There was, however, considerable overlap in these two ranges; doses in terms of mg/kg were not reported. The study did suggest that large doses can be survived with the mean estimated fatal dose in children being ~42 g.[4] In the same study, estimated cumulative nonfatal doses in adults ranged from 0.81 to 193 g, and the estimated cumulative fatal doses were from 16.3 to 193 g.[4] As with doses in children, there was considerable overlap; the minimum fatal dose of 16.3 g in some adults represented a dose that in other patients proved nonlethal. From this investigation, the mean estimated fatal dose in a adult was defined as ~71 mL (~80 g),[4] which in a "typical"

(~70 kg) adult represents ~1 mL/kg. Successive papers have subsequently reported this estimated value as a typical human lethal dose.

Overlap between reported nonfatal toxic doses and those without signs and symptoms has also been described following a recent mass poisoning of children in Haiti.[16] In children who developed symptoms, estimated doses ranged from 246 to 4,950 mg/kg (mean 1,500 mg/kg), whereas those who did not develop symptoms ingested a mean dose totaling 940 mg/kg.

Another recent study, reviewing the DEG contamination of propolis episode in Argentina reported surprisingly low doses in connection with some of the fatalities. Reported values (after dose calculations were corrected)[70] ranged from 14 to 174 mg/kg. The range was determined from two sets of data: fatal doses of 14–38 mg/kg or 56–174 mg/kg, depending on whether individuals were prescribed doses in volumes of 5 mL or 20 mL of the product.[25] The minimum estimated fatal doses were over two orders of magnitude less than the other published reports.

Doses that clearly do not cause poisoning have been reported following the accidental administration of contaminated polyethylene glycol used in the context of whole bowel irrigation. Patients showed no effects following an average dose of ~11 mg (range 2–22 mg) DEG.[71]

Defining a minimum dose capable of being either toxic or fatal is, as suggested above, difficult. One author suggests that all patients who have ingested above 10 (if children) or 30 mg (if adults) should be admitted to hospital for antidotal treatment.[72] There are no supporting data given for this recommendation (which in most cases would equate to <1 mg/kg), and any ingestion of reasonably concentrated forms would be above this amount. While likely conservative, given the uncertainties regarding minimum toxic doses (and often also amounts ingested), this guideline may well be currently appropriate, so that any ingestion would best be assessed and investigated at an emergency department.

Clinical effects

The reviewed literature in this section shows that the clinical effects of DEG poisoning can be divided into three characteristic intervals. The first phase primarily involves gastrointestinal symptoms and evidence of inebriation, as well as a developing metabolic acidosis. This interval is followed by a phase where metabolic acidosis worsens and evidence emerges of hepatic and particularly renal injury, which in the absence of appropriate supportive care, can lead to death. The final stage consists of delayed and sometimes lethal neurological effects including various neuropathies. However, some overlap can occur; the observed pattern can be modified by the dose ingested, other co-ingestants (e.g., ethanol), and the time elapsed before presentation.

Some symptoms usually manifest soon after ingestion, but the onset can in some instances be delayed for up to 48 h;[46,47] such delays are secondary to concurrent ingestions of substantial amounts of ethanol, which inhibits DEG metabolism.[46,47] Patients may present with gastrointestinal symptoms, such as nausea, vomiting,[4,6] abdominal pain,[4] and occasional diarrhea.[6] Anticipated early neurological symptoms are attributable to DEG inebriation and include an altered mental status,[6] central nervous system (CNS) depression, and coma.[50] Mild hypotension has also been reported.[51] An abnormal osmolal gap may develop, generally in advance of a later high anion gap metabolic acidosis (though the two may co-exist).[28,48,67] However, because of the relatively large molecular weight of DEGs, the osmolal gap may be insensitive (see below). Progression to the second phase is, however, dependent on the dose ingested. Small volumes may still result in mild gastrointestinal symptoms[4] and mild metabolic acidosis,[48] yet full resolution without further complications. In contrast, patients ingesting larger volumes may experience increasingly severe gastrointestinal symptoms requiring medical attention;[48,49,53] they may also present with severe metabolic acidosis. Such symptoms more often progress to the life-threatening second phase.

This phase typically develops 1–3 days following exposure. The hallmark is acute renal failure, heralded by progressive oliguria with or without flank pain, increasing serum creatinine concentrations, and eventually anuria.[11,16,18,47–49,53] In untreated cases, death typically occurs 2–7 days after the onset of anuria.[6] Patients with renal failure who do survive usually remain dialysis-dependent.[47,49,53] The degree of renal injury is considered a predictive indicator of the risk and severity of delayed neurological symptoms, which constitute the next phase. Renal injuries appear to arise mainly from tubular degeneration, principally involving the proximal convoluted tubules and are thus localized to the cortical regions alone. Degeneration of proximal tubules manifests as cortical infarctions and/or necrosis, with hemorrhage and severe vacuolation; profound swelling of the tubular epithelium can cause complete obliteration of the lumen.[7,28,41,50,56,73,74] Abdominal imaging and renal ultrasound in intoxicated patients have, in some cases, demonstrated enlarged "swollen" kidneys,[18] whereas other patients have exhibited marked atrophic kidneys with severe cortical thinning[49] and/or cortical necrosis.[47]

Mild to moderate hepatotoxicity is often reported, in the form of hepatomegaly and/or hepatocellular injury, as evidenced by moderate elevation of serum hepatic transaminases.[18,47,49] Other key hepatic indicators appear to remain normal.[49] Hepatic injury appears histologically as centrilobular degeneration and necrosis with ballooned hepatic cells.[7,56,74] One report showed glomerular periodic acid-Schiff-positive (showing evidence of large carbohydrates such as glycogen) arteriolar hyalinosis at the vascular pole along with hydropic necrosis of centrolobular areas in the liver.[24]

Patients can also develop hypertension,[46] tachycardia,[14] cardiac dysrhythmia,[29] pancreatitis,[18] hyperkalemia,[14,26] and mild hyponatremia.[46] However, some of these effects can be secondary to acidosis and/or renal failure. Leukocytosis has

also been described in an early report,[4] though this might have arisen secondary to fluid loss in this case; it is also a nonspecific finding in ethylene glycol and other poisonings and is probably because of demargination of white cells.

The final phase largely involves neurological complications, which can be delayed until at least 5–10 days post-ingestion.[18,47,48,53] Initially, patients may experience progressive lethargy[49,53] that can progress to facial diparesis (bilateral facial paralysis), dysphonia, dilated and nonreactive pupils, loss of the gag reflex, and loss of visual and auditory functions.[47–49,53] They may become quadraparetic and unresponsive.[47,49]

Peripheral neuropathies are a common occurrence subsequent to substantial DEG intoxications.[47–49,53] In one autopsy, severe histological changes were reported in peripheral nerves including the sural, popliteal, and femoral nerves, the lumbosacral and midthoracic level nerve trunks bilaterally, as well as the left upper thoracic nerves.[47] Neuropathies of the cranial nerves may also be anticipated, with evidence of involvement of the 6th,[18] 3rd and 5th,[53] and 9th to 12th (bulbar palsy)[48] cranial nerves. Facial diparesis[48,49] also suggests involvement of the 7th cranial nerve (Fig. 2). In addition to sensorimotor injuries, there is also evidence of CNS involvement;[18,47–49,53] an MRI of one patient identified abnormal foci in the left parietal lobe, and both occipital lobes and cerebellar hemispheres, possibly as a result of either edema or infarction.[48]

Acute and widespread denervation in muscles of the limbs has been demonstrated with electromyography (EMG) and nerve conduction velocity (NCV) studies.[18,47–49,53] EMG/NCV analysis, as well as histopathological evidence, have in some cases,[47,49] but not in others,[18,48] shown evidence of nerve demyelination. Delayed investigation following an intentional ingestion revealed elevated myelin in the cerebrospinal fluid by 10 days and EMG/NCV evidence of a demyelinating neuropathy on day 13.[47] Another study

Fig. 2. Facial diparesis injury to cranial nerve 7), subsequent to diethylene glycol poisoning. With permission, Angel Franco/The New York Times.[30]

showed reduced motor response amplitudes with preserved conduction velocities (and minimally prolonged distal motor latencies) at 8 days post-ingestion, suggestive of a primary axonopathy, with reduced nerve conduction velocities occurring at day 45;[53] these authors proposed that demyelinating neuropathy may be a later effect, possibly secondary (and in addition) to an acute axonal neuropathy. In the former case, demyelinating lesions (particularly affecting peripheral myelin) were more predominant than axonal damage at autopsy.[47] In contrast, elevated protein concentrations in the cerebrospinal fluid, suggestive of demyelination, were not evident in a further case report,[18] and a limited autopsy in another study found no evidence of central demyelination.[48]

Inspiratory muscle weakness with respiratory depression and even arrest can be anticipated, with an associated risk of aspiration pneumonia.[47–49] Patients may develop coma from which they may not recover. The clinical course during this phase is unpredictable, with long-term resolution in some patients, whereas others can incur permanent neurological damage or fulminant cerebral injury with a fatal outcome.[18,47,48,52]

Diagnosis

The measurement of DEG serum concentrations is the most definitive means of diagnosing poisoning. Serum concentrations are typically measured using gas chromatography–mass spectrometry.[54,75,76] Unfortunately, serum determination is labor intensive, relatively expensive, and is not readily available in most hospital laboratories.[77]

The presumptive diagnosis of DEG intoxication is more often made on the basis of the patient's history and clinical presentation. If there is no clear history of DEG ingestion, the diagnosis of poisoning becomes difficult and relies mainly on abnormalities in the patient's biochemistry. A possibly helpful diagnostic test is the osmolal gap, which defines the difference between the measured serum osmolality and the calculated osmolality;[78,79] serum osmolality should be measured by freezing point depression while calculated osmolality is determined from the following equation:

$$2 \times \text{sodium} \, (\text{mmol}/\text{L}) + \text{glucose} \, (\text{mmol}/\text{L}) + \text{BUN}$$
$$(\text{blood urea nitrogen}) \, (\text{mmol}/\text{L}) + \text{ethanol} \, (\text{mmol}/\text{L}).^{[79]}$$

This difference is normally less than 10 mOsm/L.[80] Nontoxicological causes of an increased osmolal gap are generally associated with only modest elevations, up to about 20 mOsm/L,[80] whereas a large gap, in excess of 20 mOsm/L, suggests the presence of low-molecular-weight compounds including alcohols and glycols. However, the absence of an increased osmolal gap does not necessarily exclude a toxic alcohol or glycol intoxication, and this may apply particularly for DEG, which has a lower serum osmolality per unit

concentration than several other alcohols/glycols (due to its higher molecular weight), resulting in a lesser osmolal gap.[80]

As DEG is metabolized and/or eliminated, any elevated osmolal gap will return to normal. The reason for normalization is associated with the formation of HEAA; present as a negatively charged ion at physiological pH (7.4), it will be associated with the sodium counter ion. Both are already accounted for in the calculated osmolality (see above equation).

In contrast, blood biochemistry will indicate an increasing anion gap metabolic acidosis. This gap, defining the difference in concentration between certain measured serum cations (sodium) and anions (chloride plus bicarbonate), is normally ~7 ± 4 mmol/L.[81] It will increase, due to the accumulation of DEG metabolites, in the form of (unmeasured) organic acid anions, which result in a decrease in bicarbonate concentration. Such metabolic acidosis ranges from mild to severe following DEG metabolism and is usually present if patients are seen at or after 24 h post-ingestion.[80] Reported DEG anion gap values have exceeded 38 mmol/L.[48]

Both tests are possibly important diagnostic tools that support diagnosis, but as noted, the absence of such elevated gaps does not rule out evidence of DEG toxicity, as there can be large variations in these parameters in the normal population.[79]

When investigating possible toxic causes, a presumptive diagnosis of DEG poisoning should be considered when there is a history or suspicion of ingestion plus any two of the following parameters: arterial pH < 7.3, serum bicarbonate <20 mmol/L (20 mEq/L), or osmolal gap >10 mOsm/L. Additionally, it should be considered in patients with a history or suspicion of ingestion within the last hour and osmolal gap >10 mOsm/L.[82] These criteria have only been validated for ethylene glycol poisoning and not for the diagnosis of DEG intoxication. In the absence of other validated guidelines, it is considered reasonable to adapt these criteria for DEG.

While the clinical course may be triphasic, DEG ingestion should also be considered if metabolic acidosis is present in conjunction with renal failure or if renal failure and paralysis develop subsequently. Finally, if adulteration of consumer products or medications is suspected as being involved in poisoning, it is worthwhile submitting the suspected product to be tested for the presence of DEG.[79]

Management

Stabilization

Patients may present to an emergency department subsequent to DEG poisoning in a critical condition; in these instances, stabilization becomes a priority. This consists of appropriate airway management including intubation and ventilation in obtunded patients, securing intravenous access, cardiac monitoring, and obtaining initial laboratory values. Any patient with an elevated osmolal gap and/or a high anion gap acidosis requires prompt and aggressive treatment. Management of

acid–base abnormalities with sufficient quantities of sodium bicarbonate may be required. Although case reports describing DEG toxicity often do not detail bicarbonate therapy, treatment involving patients ingesting other toxic alcohols has required more than 400–600 mmol of sodium bicarbonate in the first few hours.[83] Acid–base status, serum electrolytes, and fluid balance should be closely monitored.

Seizures should be managed initially with benzodiazepines; recommendations include lorazepam (0.05–0.2 mg/kg at 2 mg/min to a total initial dose of 8 mg) or diazepam (0.15–0.25 mg/kg in adults and 0.1–1 mg/kg in children at a rate no faster than 5 mg/min).[84] Phenobarbital 20 mg/kg, infused at a rate of 50–75 mg/min, may be necessary as second line therapy if seizures are refractory to benzodiazepines.

Hypotension will generally respond to fluid resuscitation, though catecholamines, such as dopamine or dobutamine, may occasionally be required.[51] Cardiac dysrhythmia should be treated with standard advanced cardiac life support. Management of renal dysfunction can be critical. Patients who initially demonstrate normal renal function should be administered IV fluids to maintain good urine volumes to maximize urinary elimination of DEG.[54] Careful monitoring to detect evidence of early renal failure is required. These include monitoring urine output, and serum urea and creatinine concentrations.

Decontamination

The benefits of gastric decontamination are unproven, and the risks potentially out-weigh gain. Nasogastric aspiration of gastric contents has been proposed after the ingestion of a substantial amount of DEG, if undertaken within 1–2 h of ingestion.[72] As this procedure may increase the risk of vomiting and pulmonary aspiration, the airway must be protected. Gastric lavage is an alternative with similar reservations.[85] The efficacy of oral activated charcoal in preventing DEG absorption is unknown; however, it has a low binding affinity to alcohols in general and therefore is not recommended.[86] Induced emesis with ipecac is not indicated.[87]

Antidote

It is believed that HEAA and possible other as yet unknown metabolites of DEG are predominantly responsible for renal toxicity.[68,69] The use of antidotes to reduce conversion to these toxic metabolites is therefore theoretically sound and generally recommended to prevent various aspects of toxicity.[48,54,68,69,80,88] The available antidotes, ethanol and fomepizole, act as a competitive substrate and inhibitor of ADH, respectively,[82] preventing ADH-induced formation of HEAA from DEG. There is some limited clinical evidence that suggests that both these agents can play a useful role to prevent host toxicity.[48,51,54,89] Fomepizole has an affinity for ADH over 8,000 times greater than that of ethanol in human liver extracts *in vitro*;[90] its use therefore is preferred to ethanol on

these and other grounds.[82] Although there is limited experience with fomepizole for DEG ingestions, it has proven efficacy in ethylene glycol poisoning.[91] Furthermore, fomepizole has also been shown to be efficacous in the treatment of DEG intoxication in an animal model.[68]

Recommended fomepizole dosing regimes includes a loading dose of 15 mg/kg diluted in 100 mL of normal saline or 5% dextrose in water, administered by IV infusion over 30 min.[92] Maintenance doses, consisting of 10 mg/kg every 12 h for 4 doses, and thereafter 15 mg/kg 12 hourly are necessary until the patient is asymptomatic and with a normal arterial pH. Furthermore, should testing be feasible, the glycol should no longer be detectable in the blood. Fomepizole is dialyzable and therefore the frequency of dosing should be increased to 4 hourly during hemodialysis.[92] Although these dosing regimes have been validated for ethylene glycol and methanol poisoning,[91,93] it is reasonable to assume that they should also be effective for DEG intoxication. Fomepizole has advantages over ethanol in that it has minimal adverse effects, and the standard treatment regimen maintains a constant serum concentration, which removes the need for constant monitoring.[91,94]

In the absence of fomepizole, ethanol can also be considered as an effective intervention for toxic alcohol and glycol poisoning.[95] It is successful as an antidote, as ADH has a higher affinity for ethanol than for DEG.[59] Pharmaceutical grade ethanol is employed, as either a 5 or 10% (w/v) solution in dextrose. To acceptably saturate the ADH enzyme and inhibit metabolism, the blood ethanol concentration should be maintained between 22 and 33 mmol/L (1,000–1,500 mg/L).[91,96] To achieve this, an initial loading dosage of 0.6–0.7 g ethanol/kg is required.[96] Subsequent maintenance doses are necessary; their rates are guided by regular measurement of blood ethanol concentrations. The average ethanol infusion rate is 110 mg/kg/h (1.4 mL of 10% ethanol/kg/h) but will vary according to individual differences in ethanol metabolism.[97,98] Patients typically require 66 mg /kg/h (0.8 mL 10% ethanol/kg/h), while alcoholic patients will require higher dosing, up to 154 mg/kg/h (2.0 mL 10% ethanol/kg/h).[96] As ethanol is readily dialyzable, if patients are undergoing hemodialysis, infusion rates must be increased two- to three-fold or ethanol added to the dialyzate.[100] Ethanol therapy should continue until the patient is asymptomatic, has a normal arterial pH, and, if blood levels are available, the glycol is no longer detectable.[96] The disadvantages of ethanol are its significant adverse effects including CNS depression, inebriation, hypoglycemia in pediatric or malnourished patients, and possible hepatotoxicity.[100] Additionally, because of its unpredictable kinetics, frequent dosage adjustments are often necessary, mandating frequent serum monitoring.

Although of questionable benefit, thiamine and pyridoxine are used as therapeutic adjuncts in ethylene glycol poisoning.[82,99] Because of their relative safety at commonly recommended doses, they have also been used in patients with DEG poisoning.[18,49] Although no data exist to demonstrate clear benefit for the latter, they may be of use in those with inadequate nutrition or a history of ethanol abuse.

Enhanced elimination

Hemodialysis and hemodialfiltration have been used successfully to treat both ethylene glycol and methanol toxicity. In contrast, there is limited information about its use following DEG intoxication. However, this diol has a relatively low molecular weight, and it is predicted to have a low volume of distribution and little or no plasma protein binding.[80] Theoretically, therefore, this should make DEG a suitable solute for hemodialysis removal. One report suggested successful removal of DEG by hemodialysis,[54] although it cannot be concluded that it played a significant role in this case. In addition, it is not known whether the toxic metabolite HEAA has been removed.[69] Nevertheless, hemodialysis should still be considered following poisoning to potentially remove both the parent molecule and its acidic metabolites.[80,88] Hemodialysis also has the advantage of ameliorating any other metabolic derangements and supporting renal function. This treatment may become more critical in patients presenting late, where the ADH blocking treatments are less relevant. Hemodialysis then becomes the only remaining key treatment available.

Further supportive care

Fluid and electrolyte imbalance

The large volumes of sodium bicarbonate used to treat metabolic acidosis may potentially lead to hypernatremia. Meticulous management of fluid and electrolyte balance is therefore required to avoid such derangements.[54] Renal failure may also contribute to electrolyte imbalance, predominantly hyperkalemia,[26] whereas prolonged dialysis may lead to hypophosphatemia,[96] though this is a rare occurrence.

Hepatotoxicity

Mild to moderate hepatotoxicity can occur, consequent to DEG exposure. Acetylcysteine has been tested for DEG poisoning.[49] Given its safety profile and routine use following other poisoning-induced hepatotoxicities, acetylcysteine could be useful if hepatitic transaminases are raised, although there are no supporting data.

Delayed neurotoxicity

Delayed central, peripheral, and cranial nerve impairment followed by severe CNS depression and coma may occur, consequent to DEG intoxication.[51] Impaired gag reflex and respiratory depression may necessitate intubation and assisted ventilation. Currently, there are no specific treatments available for other delayed neurological sequelae. Standard supportive care should be undertaken. The clinical course is variable; resolution of neurological symptoms may occur over time, though recovery can be incomplete and sometimes fulminant CNS damage occurs, which can be fatal.[47,48] Surviving patients may require appropriate follow up including further symptomatic treatment.

Prognosis

DEG can produce significant morbidity and mortality, especially in patients with delayed presentation or treatment.[46,47] Patients with renal failure who survive, more often than not, remain dialysis-dependent.[48,53] Reported mortality rates following epidemic poisoning have been high, and even intensive medical treatment may not improve outcome.[15,16,26] This, however, likely reflects the initially unsuspected nature of the ingestions, in many cases involving several doses, with associated delays in presentation, and limited access to the appropriate level of medical care, especially in timely fashion.

Conclusions

DEG has been responsible for outbreaks of mass poisoning, usually associated with contaminated pharmaceutical products. From these epidemics, it is believed that ~1 mL/kg body weight (and quite probably less) would be a lethal dose for some humans. Upon ingestion, DEG is rapidly absorbed and distributed mainly to well-perfused regions of the body; it is metabolized in the liver to form the toxic metabolite 2-HEAA, which is thought to be responsible for most toxic effects. Clinical effects appear soon after ingestion and may be divided into three stages. Initially the patient may experience inebriation, gastrointestinal distress, and developing metabolic acidosis. The second phase, subsequent to massive ingestion, may result in more severe metabolic acidosis and evidence of emerging renal injury, which, in the absence of appropriate supportive care, may become life-threatening. The final phase consists of delayed neuropathies and other neurological effects, sometimes fatal. Treatment consists of symptomatic management, timely administration of the antidotes ethanol or fomepizole, attention to acid–base abnormalities, hemodialysis, and potentially respiratory and other support in the event of neurological complications. With prompt supportive care, and timely use of fomepizole or ethanol, the prognosis for recovery is improved.

References

1. Cavender FL, Sowinski EJ. Glycols. In: Clayton GD, Clayton FE, eds. Patty's Industrial Hygiene and Toxicology. New York: John Wiley & Sons Inc.; 1994:4645–4719.
2. O'Neil M. The Merck Index. 14th ed. Whitehouse Station, NJ: Merck & Co; 2006.
3. Winek CL, Shingleton DP, Shanor SP. Ethylene and diethylene glycol toxicity. Clin Toxicol 1978; 13:297–324.
4. Calvery HO, Klumpp TG. The toxicity for human beings of diethylene glycol with sulfanilamide. South Med J 1939; 32:1105–1109.
5. Danby MY, Danby EB, Loranz CP. Deaths following elixir sulfanilamide massengill: report of the Secretary of Agriculture. South Med J 1937; 30:1231–1232.
6. Leech PN. (AMA Chemical Laboratory). Elixir of sulfanilamide-Massengill. JAMA 1937; 109:1531–1539.
7. Lynch KM. Diethylene glycol poisoning in the human. South Med J 1938; 32:134–137.
8. Wax PM. Elixirs, diluents, and the passage of the 1938 Federal Food, Drug and Cosmetic Act. Ann Intern Med 1995; 122:456–461.
9. Wax PM. Controversies in toxicology – elixir sulfanilamide-Massengill revisited (Reprinted From Mithridata, Vol 4, 1994). Vet Hum Toxicol 1994; 36:561–562.
10. Deaths following elixir of sulfanilamide-Massengill [Editorial]. JAMA 1938; 111:1567–1568.
11. Bowie MD, McKenzie D. Diethylene glycol poisoning in children. S Afr Med J 1972; 46:931–934.
12. Cantarell MC, Fort J, Camps J, Sans M, Piera L. Acute intoxication due to topical application of diethylene glycol [letter]. Ann Intern Med 1987; 106:478–479.
13. Pandya SK. Letter from Bombay. An unmitigated tragedy [letter]. BMJ 1988; 297:117–119.
14. Okuonghae HO, Ighogboja IS, Lawson JO, Nwana EJC. Diethylene glycol poisoning in Nigerian children. Ann Trop Paediatr 1992; 12:235–238.
15. Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ, Bennish ML. Fatal renal-failure caused by diethylene glycol in paracetamol elixir – the Bangladesh epidemic. BMJ 1995; 311:88–891.
16. O'Brien KL, Selanikio JD, Hecdivert C, Placide MF, Louis M, Barr DB, Barr JR, Hospedales CJ, Lewis MJ, Schwartz B, Philen RM, St Victor S, Espindola J, Needham LL, Denerville K. Epidemic of pediatric deaths from acute renal failure caused by diethylene glycol poisoning. Acute Renal Failure Investigation Team. JAMA 1998; 279:1175–1180.
17. Malebranche R, Hecdivert C, Lassegue A, Victor S, Derosena R, Denerville K, Amand CH, Severe D, Compas E, Cleophat P, Buteau JH, Fabien D, Colimon J, Verdier RI, Cayemitte MI, Placide MF, Hospedales J, Lewis M, Diouf MA, Garcia S, Parekh R, Bunchman T, Racusen L. Fatalities associated with ingestion of diethylene glycol-contaminated glycerin used to manufacture acetaminophen syrup–Haiti, November 1995–June 1996. MMWR Morb Mortal Wkly Rep 1996; 45:649–650.
18. Scalzo AJ. Diethylene glycol toxicity revisited: the 1996 Haitian epidemic. J Toxicol Clin Toxicol 1996; 34:513–516.
19. Woolf AD. The Haitian diethylene glycol poisoning tragedy: a dark wood revisited [Editorial]. JAMA 1998; 279:1215–1216.
20. Junod SW. Diethylene glycol deaths in Haiti. Public Health Rep 2000; 115:78–86.
21. Anonymous. Diethylene glycol poisoning associated with paracetamol liquid formulations. Adverse Drug React Toxicol Rev 1998; 17:207–208.
22. Wax PM. It's happening again – another diethylene glycol mass poisoning. J Toxicol Clin Toxicol 1996; 34:517–520.
23. Litovitz TL, Smilkstein M, Felberg L, Klein-Schwartz W, Berlin R, Morgan JL. 1996 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 1997; 15:447–500.
24. Drut R, Quijano G, Jones MC, Scanferla P. Pathologic findings in diethylene glycol poisoning [Spanish]. Medicina (B Aires) 1994; 54:1–5.
25. Ferrari LA, Giannuzzi L. Clinical parameters, postmortem analysis and estimation of lethal dose in victims of a massive intoxication with diethylene glycol. Forensic Sci Int 2005; 153:45–51.
26. Singh J, Dutta AK, Khare S, Dubey NK, Harit AK, Jain NK, Wadhwa TC, Gupta SR, Dhariwal AC, Jain DC, Bhatia R, Sokhey J. Diethylene glycol poisoning in Gurgaon, India, 1998. Bull World Health Organ 2001; 79:88–95.
27. Kumar A. Diethylene glycol poisoning in Gurgaon, Haryana, India, 1998. Bull World Health Organ 2001; 79:686–686.
28. Hari P, Jain Y, Kabra SK. Fatal encephalopathy and renal failure caused by diethylene glycol poisoning. J Trop Pediatr 2006; 52:442–444.
29. Rentz ED, Lewis L, Mujica OJ, Barr DB, Schier JG, Weerasekera G, Kuklenyik P, McGeehin M, Osterloh J, Wamsley J, Lum W, Alleyne C, Sosa N, Motta J, Rubin C. Outbreak of acute renal failure in Panama in 2006: a case-control study. Bull World Health Organ 2008; 86:749–756.

30. Bogdanich W, Hooker J. From China to Panama, a Trail of Poisoned Medicine.http://www.nytimes.com/2007/05/06/world/americas/06poison. html. Accessed 21 March 2009. New York: New York Times; 2007.

31. Barr DB, Barr JR, Weerasekera G, Wamsley J, Kalb SR, Sjodin A, Schier JG, Rentz ED, Lewis L, Rubin C, Needham LL, Jones RL, Sampson EJ. Identification and quantification of diethylene glycol in pharmaceuticals implicated in poisoning epidemics: an historical laboratory perspective. J Anal Toxicol 2007; 31:295–303.

32. Schier JG, Conklin L, Sabogal R, Dell'aglio D, Sanchez C, Sejvar J. 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 (Panama Follow-Up Investigation Workgroup). J Med Toxicol 2008; 4:40–42.

33. Lin BL, Zhao ZX, Chong YT, Li JG, Zuo X, Tao Y, Lou TQ, Gao ZL. Venous diethylene glycol poisoning in patients with preexisting severe liver disease in China. World J Gastroenterol 2008; 14:3236–3241.

34. Peng XM, Huang MX, Gu L, Lin BL, Chen GH. Characteristics of patients with liver disease intravenously exposed to diethylene glycol in China 2006. Clin Toxicol (Phila) 2009; 47:124–131.

35. BBC. Arrests in Nigeria Baby Poisoning. http://news.bbc.co.uk/2/hi/ africa/7884202.stm. Accessed 21 March 2009. London: BBC; 2009.

36. Polgreen L. 84 Children Are Killed by Medicine in Nigeria. http:// www.nytimes.com/2009/02/07/world/africa/07nigeria.html. Accessed 29 March 2009. New York: New York Times; 2009.

37. Riska O. Children are killed by poisoned drugs in Nigeria [Norweigan]. Tidsskr Nor Laegeforen 2009; 129:546.

38. Some Wine to Break the Ice [Editorial]. Lancet 1985; 2:254–254.

39. van der Linden-Cremers PM, Sangster B. Medical sequelae of the con- tamination of wine with diethylene glycol [Dutch]. Ned Tijdschr Geneeskd 1985; 129:1890–1891.

40. Sangster B. Diethylene glycol in wine [Dutch]. Ned Tijdschr Geneeskd 1985; 129:1457–1459.

41. van Leusen R, Uges DR. A patient with acute tubular necrosis as a con- sequence of drinking diethylene glycol-treated wine [Dutch]. Ned Tijdschr Geneeskd 1987; 131:768–771.

42. Fake toothpaste found. Br Dent J 2007; 203:68.

43. Pérez E, Limeres J, Tomas I, Diz P. Letter to the editor: toothpastes with diethylene glycol. Med Oral Patol Oral Cir Bucal 2008; 13:E222–E223.

44. Haller C. Made in China. J Med Toxicol 2008; 4:141–142.

45. FDA. US Food and Drug Administration. Imported Toothpaste. http:// www.fda.gov/oc/opacom/hottopics/toothpaste.html. Accessed 21 March 2009. Washington; 2007.

46. Doyle CR, Win N, Hodgman M, Krenzelok EP. Diethylene glycol abuse with resultant multiple fatalities [abstract]. J Toxicol Clin Toxicol 1998; 36:516–517.

47. Rollins YD, Filley CM, McNutt JT, Chahal S, Kleinschmidt-DeMasters BK. Fulminant ascending paralysis as a delayed sequela of diethylene glycol (Sterno) ingestion. Neurology 2002; 59:1460–463.

48. Alfred S, Coleman P, Harris D, Wigmore T, Stachowski E, Graudins A. Delayed neurologic sequelae resulting from epidemic diethylene glycol poisoning. Clin Toxicol (Phila) 2005; 43:155–159.

49. Marraffa JM, Holland MG, Stork CM, Hoy CD, Hodgman MJ. Diethyl- ene glycol: widely used solvent presents serious poisoning potential. J Emerg Med 2008; 35:401–406.

50. Wordley E. Diethylene glycol poisoning – report on 2 cases. J Clin Pathol 1947; 1:44–46.

51. Borron SW, Baud FJ, Garnier R. Intravenous 4-methylpyrazole as an antidote for diethylene glycol and triethylene glycol poisoning: a case report. Vet Hum Toxicol 1997; 39:26–28.

52. Bronstein AC, Spyker DA, Cantilena LJ, Green J, Rumack BH, Heard SE. 2006 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS). Clin Toxicol 2007; 45:815–917.

53. Hasbani MJ, Sansing LH, Perrone J, Asbury AK, Bird SJ. Encephalopa- thy and peripheral neuropathy following diethylene glycol ingestion. Neurology 2005; 64:1273–1275.

54. Brophy PD, Tenenbein M, Gardner J, Bunchman TE, Smoyer WE. Child- hood diethylene glycol poisoning treated with alcohol dehydrogenase inhib- itor fomepizole and hemodialysis. Am J Kidney Dis 2000; 35:958–962.

55. Kruger M, Regenthal R, Bohm R, Lindner D, Trauer H, Caffier P. Fatal diethylene glycol intoxication after misuse of Goldgeist (R) forte – a case report [German]. Anasthesiol Intensivmed 2002; 43:21–26.

56. Geiling EM, Cannon PR. Pathologic effects of elixir of sulfanilamide (diethylene glycol) poisoning. JAMA 1938; 111:919–926.

57. Heilmair R, Lenk W, Lohr D. Toxicokinetics of diethylene glycol (DEG) in the rat. Arch Toxicol 1993; 67:655–666.

58. Mathews JM, Parker MK, Matthews HB. Metabolism and disposi- tion of diethylene glycol in rat and dog. Drug Metab Dispos 1991; 19:1066–1070.

59. Lenk W, Lohr D, Sonnenbichler J. Pharmacokinetics and biotransfor- mation of diethylene glycol and ethylene glycol in the rat. Xenobiotica 1989; 19:961–979.

60. Wiener HL, Richardson KE. Metabolism of diethylene glycol in male rats. Biochem Pharmacol 1989; 38:539–541.

61. Haag HB, Ambrose AM. Studies of the physiological effect of diethyl- ene glycol: II toxicity and fate. J Pharmacol Exp Ther 1937; 59:93–100.

62. Durand A, Auzepy P, Hebert JL, Trieu TC. A study of mortality and urinary excretion of oxalate in male rats following acute experimental intoxication with diethylene-glycol. Preliminary report. Eur J Intensive Care Med 1976; 2:143–146.

63. Hébert JL, Fabre M, Auzépy P, Paillas J. Acute experimental poisoning by diethylene glycol: acid base balance and histological data in male rats. Toxicol Eur Res 1978; 1:2890–2894.

64. Morris HJ, Nelson AA, Calvery HO. Observations on the chronic toxic- ities of propylene glycol, ethylene glycol, diethylene glycol, ethylene glycol mono-ethyl-ether, and diethylene glycol mono-ethyl-ether. J Pharmacol Exp Ther 1942; 74:266–273.

65. Hébert JL, Auzepy P, Durand A. Acute human and experimental poi- soning with diethylene glycol [French]. Sem Hop 1983; 59:344–349.

66. Wiley FH, Hueper WC, Bergen DS. The formation of oxalic acid from ethylene glycol and related solvents. J Ind Hyg Toxicol 1938; 20:267–277.

67. Vale JA, Buckley BM. Metabolic acidosis in diethylene glycol poison- ing. Lancet 1985; 2:394.

68. Besenhofer LM, Cain MC, Latimer B, McMartin K. Metabolites of diethylene glycol (DEG) are responsible for the renal toxicity associ- ated with acute DEG poisoning. March 15–19. 2009. Toxicologist 2009; 108:103–104.

69. Vale A. Ethylene and diethylene glycol. Medicine 2007; 35:617–618.

70. Schep LJ, Slaughter RJ. Comments on diethylene glycol concentrations [letter]. Forensic Sci Int 2005; 155:233.

71. Woolf A, Pearson K. Presence of diethylene glycol in commercial polyethylene glycol (PEG) solutions. J Toxicol Clin Toxicol 1995; 33:490.

72. Raymond RW. Glycol ethers and diethylene glycol. In: Ford MD, Delaney KA, Ling LJ, Erickson T, eds. Clinical Toxicology. Philadel- phia, PA: Saunders Company; 2001:774–781.

73. Oliver J, Macdowell M, Tracy A. The pathogenesis of acute renal failure associated with traumatic and toxic injury; renal ischemia, nephrotoxic damage and the ischemic episode. J Clin Invest 1951; 12:1307–439.

74. Wilkinson DP. Diethylene glycol poisoning. Med J Aust 1967; 2:403–404.

75. Maurer H, Kessler C. Identification and quantification of ethylene gly- col and diethylene glycol in plasma using gas chromatography-mass spectrometry. Arch Toxicol 1988; 62:66–69.

76. Maurer HH, Peters FT, Paul LD, Kraemer T. Validated gas chromato- graphic-mass spectrometric assay for determination of the antifreezes ethylene glycol and diethylene glycol in human plasma after micro- wave-assisted pivalylation. J Chromatogr B Biomed Sci Appl 2001; 754:401–409.

77. Shin JM, Sachs G, Kraut JA. Simple diagnostic tests to detect toxic alcohol intoxications. Transl Res 2008; 152:194–201.

78. Smithline N, Gardner KDJ. Gaps – anionic and osmolal. JAMA 1976; 236:1594–1597.

79. Hoffman RS, Smilkstein MJ, Howland MA, Goldfrank LR. Osmol gaps revisited: normal values and limitations. J Toxicol Clin Toxicol 1993; 31:81–93.

80. Kraut JA, Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. Clin J Am Soc Nephrol 2008; 3:208–225.

81. Winter SD, Pearson JR, Gabow PA, Schultz AL, Lepoff RB. The fall of the serum anion gap. Arch Intern Med 1990; 150:311–313.

82. Brent J. Fomepizole for ethylene glycol and methanol poisoning. N Engl J Med 2009; 360:2216–2223.

83. Jacobsen D, McMartin KE. Methanol and ethylene-glycol poisonings mechanism of toxicity, clinical course, diagnosis and treatment. Med Toxicol Adverse Drug Exp 1986; 1:309–334.

84. Wallace KL. Toxin induced seizures. In: Brent J, Wallace KL, Burkhart KK, Phillips SD, Donovan JW, eds. Critical Care Toxicology: Diagnosis and Management of the Critically Poisoned Patient. Philadelphia, PA: Elsevier Mosby; 2005:225–239.

85. Vale JA, Kulig K. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position paper: gastric lavage. J Toxicol Clin Toxicol 2004; 42:933–943.

86. Neuvonen PJ, Olkkola KT. Oral activated charcoal in the treatment of intoxications. Role of single and repeated doses. Med Toxicol Adverse Drug Exp 1988; 3:33–58.

87. Seger D, Muelenbelt J. Position paper: Ipecac syrup. J Toxicol Clin Toxicol 2004; 42:133–143.

88. Daubert GP, Katiyar A, Wilson J, Baltarowich L. Encephalopathy and peripheral neuropathy following diethylene glycol ingestion. Neurology 2006; 66:782–783.

89. Auzépy P, Taktak H, Toubas PL, Deparis M. Acute ethylene glycol and diethylene glycol poisoning in adults. 2 cases with recovery [French]. Sem Hop 1973; 49:1371–1374.

90. Pietruszko R. Human liver alcohol-dehydrogenase – inhibition of methanol activity by pyrazole, 4-methylpyrazole, 4-hydroxymethylpyrazole and 4-carboxypyrazole. Biochem Pharmacol 1975; 24:1603–1607.

91. Brent J, McMartin K, Phillips S, Burkhart KK, Donovan JW, Wells M, Kulig K. Fomepizole for the treatment of ethylene glycol poisoning. N Engl J Med 1999; 340:832–838.

92. Antizol Medicines Datasheet, USA: Paladin Labs (USA) Inc. http://www.antizol.com. Accessed 22 March 2009. Dover, DL: Paladin Labs (USA) Inc; 2006.

93. Brent J, McMartin K, Phillips S, Aaron C, Kulig K. Fomepizole for the treatment of methanol poisoning. N Engl J Med 2001; 344:424–429.

94. Jacobsen D, Sebastian CS, Blomstrand R, McMartin KE. 4-Methylpyrazole – a controlled-study of safety in healthy-human subjects after single, ascending doses. Alcohol Clin Exp Res 1988; 12:516–522.

95. Wacker WE, Haynes H, Druyan R, Fisher W, Coleman JE. Treatment of ethylene glycol poisoning with ethyl alcohol. JAMA 1965; 194:1231–1233.

96. Barceloux DG, Krenzelok EP, Olson K, Watson W. American academy of clinical toxicology practice guidelines on the treatment of ethylene glycol poisoning. Ad Hoc Committee. J Toxicol Clin Toxicol 1999; 37:537–560.

97. Sidell FR, Pless JE. Ethyl alcohol: blood levels and performance decrements after oral administration to man. Psychopharmacologia 1971; 19:246–261.

98. Leung AK. Ethyl alcohol ingestion in children. A 15-year review. Clin Pediatr (Phila) 1986; 25:617–619.

99. Davis DP, Bramwell KJ, Hamilton RS, Williams SR. Ethylene glycol poisoning: case report of a record-high level and a review. J Emerg Med 1997; 15:653–667.

100. Brent J. Current management of ethylene glycol poisoning. Drugs 2001; 61:979–988.