In the past decade a new trend seems to have emerged – namely, terrorists realize that there is no need to utilize sophisticated warfare agents to cause terror \[1,2\]. Toxic industrial compounds can achieve the same goal more rapidly and at lower cost. Terrorists can highjack a tanker or a transporting train to use for their nefarious purposes. On the other hand, an accidental spill such as those that can occur in fuel lines or air bases can still be the cause of a mass toxicological event. Hydrazine fits both scenarios, though an accident seems to be the more probable \[3\].

Hydrazine \((H_2N-NH_2, N_2H_4)\) is a water-soluble inorganic colorless diamine, with an ammonia-like odor, that evaporates at 113.5°C. Most people can smell hydrazine when present at concentrations of 2.0–8.0 parts per million. It is known for its corrosive and strong reducing properties. The chemical and its derivatives are highly flammable \[4\]. Its most familiar use is for emergency power supplies in fighter jets. Oxides of nitrogen, as well as ammonia and its derivatives are the main toxic combustion products of hydrazine \[5\]. They are also used in the manufacture of algaecides, fungicides, insecticides, agricultural chemicals and pharmaceuticals \[4\]. Human exposure to hydrazine and its derivatives may occur in aerospace research sites, fighter jet plane incidents, industrial facilities, or in hazardous material waste sites. People may also be exposed to small amounts of this chemical by chewing tobacco or smoking cigarettes (both active and passive smoking) \[5\].

Hydrazine is extremely irritating to skin and mucous membranes and may cause temporary blindness.

**Table 1. Summary of AEGL values for hydrazine**

<table>
<thead>
<tr>
<th>Time</th>
<th>10 min</th>
<th>30 min</th>
<th>60 min</th>
<th>4 hr</th>
<th>8 hr</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>AEGL 1 (ppm)</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>Eye and facial irritations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(in monkeys)</td>
</tr>
<tr>
<td>AEGL 2 (ppm)</td>
<td>23</td>
<td>16</td>
<td>13</td>
<td>3.1</td>
<td>1.6</td>
<td>Nasal lesions (in rats)</td>
</tr>
<tr>
<td>AEGL 3 (ppm)</td>
<td>64</td>
<td>45</td>
<td>35</td>
<td>8.9</td>
<td>4.4</td>
<td>Lethal (in rats)</td>
</tr>
</tbody>
</table>

Ref. [34]

* TWA (time-weighted average) is the term used in the specification of Occupational Exposure Limits to define the average concentration of a chemical to which it is permissible to expose a worker over a period, typically 8 hours.
** Ceiling value (CV) is the airborne concentration of a potentially toxic substance that should never be exceeded in a worker’s breathing zone.
*** IDLH refers to a concentration, formally specified by a regulatory value and defined as the maximum exposure concentration of a given chemical in the workplace from which one could escape within 30 minutes without any escape-impairing symptoms or any irreversible health effects. This value is normally referred to in respirator selection.
**** MRL (minimal risk level) is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.
******AEGL-1 (non-disabling) = notable discomfort, irritation, or certain asymptomatic non-sensory effects. The effects are transient and reversible upon cessation of exposure. AEGL-2 (disabling) = irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 (lethal) = life-threatening health effects or death.
The aim of this review is to highlight the clinical effects of hydrazine and the immediate medical support needed (including a specific antidote), and to present several case reports of hydrazine exposure in order to improve the knowledge of medical teams for the possibility of having to deal with such an event.

**Pharmacological properties**

Animal studies indicate that hydrazine is rapidly absorbed through the skin [9] and mucous membranes (ocular, respiratory and gastrointestinal tracts). The mechanism by which hydrazine is absorbed into the blood is poorly understood [6]. Data regarding its toxicokinetics are limited but suggest that absorption is rapid and is distributed to all body tissues. Metabolites are excreted largely in the urine or are released in expired air [6].

Several mechanisms have been proposed to explain hydrazine’s toxicity. The first involves covalent binding through a free amino group to key cellular molecules, such as α-keto acids, thus inhibiting oxygen consumption with mitochondrial substrates [10-12]. Furthermore, hydrazine and its derivatives react with vitamin B₆ derivatives, and so prevent functioning of the co-factors. Anemia, convulsions and dermatitis may be the result of vitamin B₆ deficiency [6]. This may account for the effectiveness of pyridoxine (one form of vitamin B₆) acting as an antidote. The second mechanism involves the formation of reactive species, oxygen radicals and the like [13,14].

**Clinical effects**

Health effects usually occur within an hour after exposure, but some may be delayed depending on the concentration and length of exposure. Hydrazine exposure is destructive to both skin and mucous membranes. Its vapor is extremely irritating to the eyes and can cause temporary blindness. The lungs, liver, kidneys and the central nervous system may be affected as well after inhalational or dermal exposure. Importantly, the anti-tuberculosis drug isoniazid embeds a hydrazine moiety in its core. The hydrazine molecule can be cleaved through hydrolysis or affect in situ. Therefore, it is not surprising that the side effects of isoniazid coincide with those of hydrazine toxicity and thus require similar treatment, including pyridoxine as an antidote. Interestingly, many of the recommendations regarding pyridoxine as an antidotal treatment for hydrazine exposure were derived from the experience with isoniazid.

There is no classic toxidrome, but the combination of respiratory difficulties with cutaneous manifestations and the smell of fish should alert us to suspect a suffocating agent. Life-threatening clinical manifestations include coma, seizures, hypotension, pulmonary edema, metabolic acidosis and methemoglobinemia [Table 2]. Most derivatives of hydrazine are carcinogenic in animals following oral and inhalational exposure [6]. Therefore, the International Agency for Research on Cancer and the American EPA consider hydrazine and its derivatives as Group 2B human carcinogens [15,16]. The major human clinical effects following an acute exposure are summarized in Table 2.

**Immediate and general medical care**

Initial treatment should focus on preventing further exposure and provide early aggressive supportive treatment. Victims should be removed from the contaminated area and should be decontami-
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Pyridoxine (a form of vitamin B₆) is considered an effective antidote to hydrazine and is given intravenously

Antidotal treatment
Pyridoxine (vitamin B₆) is considered an antidote to hydrazine poisoning, even 3–4 days after the exposure [18-21]. In mild to severe cases 25 mg/kg of pyridoxine should be administered intravenously. In case of a lack of response, the dosage may be increased periodically up to 5 g over a period of 30–60 minutes. Pyridoxine itself is inactive. It is converted in the body to its active form, pyridoxal-5-phosphate, in a two-step process involving phosphorylation and oxidation. Treatment with high dose pyridoxine presumably overcomes inhibition of pyridoxal kinase by hydrazine compounds to replenish PLP and restore GABA (γ-amino butyric acid) synthesis [20,22-25]. The decreased GABA formation reduces cerebral inhibition, which may contribute in part to seizures [21]. Both oral and intravenous doses of pyridoxine result in elevated PLP levels, but PLP production after i.v. infusion is much greater (lack of first-pass metabolism), suggesting that i.v. pyridoxine is the preferred route in cases of acute toxicity [26]. Pyridoxine also terminates seizures, corrects metabolic acidosis and reverses coma [21]. It is important to note that pyridoxine over-medication can produce severe peripheral neuropathy, even after a single i.v. administration [18].

Besides the antidotal treatment, victims should be immediately and aggressively treated symptomatically according to the affected organs [8,19-21,27].

Skin exposure
Since hydrazine can spontaneously ignite upon contact with clothes, clothing should be removed promptly. The exposed area should be washed thoroughly with soap and water. Dermal irritation and burns should be treated as any chemical burn. Patients may develop allergic contact dermatitis that should be treated with systemic or topical antihistamines and local corticosteroids [8,19-21].

Inhalational exposure
Casualties should be moved to fresh air and monitored for signs of respiratory distress. If cough or dyspnea develops oxygen should be administered. Bronchospasm should be treated with inhalation of β₂ agonists and parenteral corticosteroids. Despite the lack of data on the role of corticosteroids and nitric oxide in the treatment of acute lung injury following hydrazine exposure, we presume that it might have beneficial effects, as in other cases of irritant volatile compounds [28]. Thus, early anti-inflammatory therapy with corticosteroids is advised for all symptomatic patients [8]. Antibiotics should be administered only if there is evidence of infection [3,8]. If acute lung injury is suspected, early use of mechanical ventilation with positive end-expiratory pressure should be implemented [19,20,29].

Central nervous system effects
In case of seizures, benzodiazepines should be administered as soon as possible [8,19-21,29]. Benzodiazepines should be used to potentiate the antidotal effect of suboptimal doses of pyridoxine, if gram-for-gram replacement doses of the antidote are unavailable. The benzodiazepines act synergistically with pyridoxine, as well as possessing inherent GABA-agonist activity, but as single agents they may be non-effective in the treatment of acute isoniazid and hydrazine poisoning [21,22,30-32]. Phenytoin has no intrinsic GABAergic effect and is not recommended [22,33]. Barbiturates, which have potent GABA-agonist activity, are expected to be as effective as the benzodiazepines, although the risk of complications is greater with this class of anticonvulsant. The efficacy of propofol in terminating hydrazine and isoniazid-induced seizures has not been evaluated in humans [21].

Ocular exposure
Eyes should be washed with copious amounts of water for at least 15 minutes, after which the patient should be attended by a specialist [8,27].

Alimentary exposure
Patients should not be encouraged to vomit. They should be given water or milk to dilute the chemical. If possible, gastric lavage should be performed within one hour from the exposure and then activated charcoal may be used. Other symptomatic
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measure should be applied as needed (intravenous anti-emetic drugs, etc.) [8,27]. The alimentary exposure may be due to hydrazine-containing or releasing medications, like isoniazid. Although this is not the probable route employed by terrorists, it has clinical relevance in other cases.

Laboratory tests

Complete blood count should be taken due to possible hemolysis. Blood glucose levels should be carefully monitored. Electrolytes, urinalysis, blood methemoglobin levels (in case of nausea or in a fire scenario), liver function tests and renal function tests should be taken in cases of significant exposure. If respiratory tract irritation or respiratory depression is evident, arterial blood gases, chest X-ray, and pulmonary function tests should be performed [8,27].

Case studies

Because of its explosive qualities, hydrazine is considered suitable for explosive devices. Nevertheless, there have hardly been any attempts to use it deliberately. It is worth mentioning that in the Oklahoma City bombing in 1995, the authorities discovered that hydrazine was originally considered, but because the chemical could not be purchased, nitromethane was eventually employed. Tables 3 and 4 list several accidental and intentional events involving the use or the intention to use hydrazine.

Table 3. Accidents involving hydrazine on a miniature scale

<table>
<thead>
<tr>
<th>Year and place</th>
<th>Publication</th>
<th>Age</th>
<th>Gender</th>
<th>Source</th>
<th>Route</th>
<th>Time to onset</th>
<th>Clinical manifestations</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960, Germany</td>
<td>Drews A et al.</td>
<td>–</td>
<td>Male</td>
<td>6% aqueous solution of hydrazine</td>
<td>Oral</td>
<td>Immediate</td>
<td>Vomiting, weakness, somnolence, arrhythmia, slight but persistent leukocytosis, slightly elevated body temperature, hematuria, irregular breathing</td>
<td>Supportive only</td>
<td>Recovery 5 days after exposure</td>
</tr>
<tr>
<td>1965, West Africa</td>
<td>Reid FJ</td>
<td>–</td>
<td>Male</td>
<td>A cupful of hydrazine</td>
<td>Oral</td>
<td>Immediate</td>
<td>Vomiting, flushing, unconsciousness, mydriasis, coma, convulsions</td>
<td>Intubation under anesthesia, mechanical ventilation for 10 hours, treated with 10% dextrose and vitamin B6</td>
<td>Did not recover after several days. The final outcome is not mentioned</td>
</tr>
<tr>
<td>1986, place unknown</td>
<td>Harati &amp; Niakan</td>
<td>24 yrs</td>
<td>Male</td>
<td>A mouthful of hydrazine</td>
<td>Skin and inhalation</td>
<td>Immediate</td>
<td>Confusion, lethargy, restlessness, hepatic damage</td>
<td>Pyridoxine</td>
<td>Complete recovery within 5 days</td>
</tr>
<tr>
<td>1976, place unknown</td>
<td>Kirklin et al.</td>
<td>–</td>
<td>Male</td>
<td>Industrial hydrazine explosion</td>
<td>Inhalation</td>
<td>Immediate</td>
<td>22% of the body surface was burnt, comatose after 14 hrs, hyperglycemia, hematuria, respiratory difficulties</td>
<td>Pyridoxine</td>
<td>Recovery within 5 weeks</td>
</tr>
<tr>
<td>1965, India</td>
<td>Frierson WB</td>
<td>–</td>
<td>Two males</td>
<td>Aerozine 50 vapor via a leak in a fuel line</td>
<td>Inhalation</td>
<td>90 minutes</td>
<td>Headache, nausea, a shaky feeling, a sensation of burning of the face, sore throat, tightness in the chest, dyspnea, trembling, weakness, neurological disorders</td>
<td>Pyridoxine</td>
<td>Symptoms resolved after treatment</td>
</tr>
</tbody>
</table>

Table 4. Accidents involving hydrazine on a large scale

<table>
<thead>
<tr>
<th>Year and place</th>
<th>Description</th>
<th>Result</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991, Seaciff, California</td>
<td>A freight train derailed and 1666 liters of hydrazine were spilled at a freeway overpass</td>
<td>Coastal Highway 101 was closed for 5 days. No injuries were reported</td>
<td>A total of 20 people suffered from eye and skin irritation and breathing problems after exposure to the mixture. They were hospitalized and received medical treatment, but were released after a short time. This incident is considered to be a terror attempt though there were hardly any details published about it</td>
</tr>
<tr>
<td>2003, Deinze, Belgium</td>
<td>Ten letters containing phenarsazine chloride (adamisite, a former chemical warfare agent) and hydrazine, each with a card signed “The International Islamic Society,” were sent to the Prime Minister of Belgium and to the embassies of the USA, UK, and Saudi Arabia, to the Ministries of Justice and Foreign Affairs in Brussels, to the Airport Director in Ostend, and to two other business offices in Belgium. Two postal workers and five police officers discovered these letters in a routine mail inspection.</td>
<td>A total of 20 people suffered from eye and skin irritation and breathing problems after exposure to the mixture. They were hospitalized and received medical treatment, but were released after a short time. This incident is considered to be a terror attempt though there were hardly any details published about it</td>
<td></td>
</tr>
</tbody>
</table>

Ref. [18,36-39]
Summary

Hydrazine is considered a dangerous toxic compound. It is flammable, easily ignitable and may explode upon contact with different materials, including clothing. As a volatile liquid, it affects mainly the upper respiratory tract, mucous membranes and skin.

The characteristics and availability of this agent warrant our attention. Medical personnel should be familiar with its properties, major health effects and the treatment needed. The key principles in treating hydrazine victims include protection from further exposure and aggressive antidotal treatment with pyridoxine (vitamin B6), as well as supportive treatment as required. Finally, medical teams should also be equipped with the proper protection measures (appropriate suits, gloves and breathing apparatuses) in order to avoid secondary exposure of themselves and others.

References

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