Rapid Communication

Mortality from Dermal Exposure to Tetramethylammonium Hydroxide

Chen-Long WU^{1,2,3}, Shih-Bin SU^{2,4}, Jin-Luh CHEN⁵,
Hung-Jung LIN^{6,7} and How-Ran GUO^{2,3}

¹Department of Occupational Medicine, Chi-Mei Medical Center, ²Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, ³Department of Occupational and Environmental Medicine, National Cheng Kung University Hospital, ⁴Tainan Science-based Industrial Park Clinic, Chi-Mei Medical Center, ⁵Southern Region Labor Inspection Office, Council of Labor Affairs, ⁶Department of Emergency Medicine, Chi-Mei Medical Center and ⁷Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taiwan

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Tetramethylammonium hydroxide (TMAH; $(\text{CH}_3)_4\text{NOH}$, CAS No. 75-59-2) was used mainly in research and development laboratories in the past, but recently has become widely used in the micro-electro-mechanical industries, *e.g.* in the manufacture of semiconductors and liquid crystal displays (LCDs)¹. It is considered to have a relatively low level of toxicity² although little toxicological information is available. In the literature, there are only a few reports of intoxication caused by the tetramethylammonium ion (TMA^+ ; $(\text{CH}_3)_4\text{N}^+$), a simple quaternary ammonium compound and cholinergic agonist resulting from the breakdown of TMAH, but not TMAH itself. Most of the intoxication cases were caused by eating food containing TMA, mainly gastropods, and the reported symptoms and signs were usually mild and self-limited³. However, industrial TMAH is in the form of a concentrated strong alkaline and thus might have severe hazardous effects. We here present a mortality case caused by dermal exposure to industrial TMAH at work.

Case

A 22-yr-old male engineer was accidentally drenched with concentrated TMAH solution (25%, pH 13.5) while conducting routine examination of the pipe system in a

plant manufacturing thin film transistor liquid crystal displays (TFT-LCDs). He was wearing a clean room suit with plastic goggles, but not a mask. As TMAH sprayed over his head, he closed the valve and took a shower at the nearby emergency shower facility immediately for decontamination. When he was found by a co-worker about 15 min later, he suffered from general weakness and moderate salivation but was still conscious enough to describe the accident. The paramedical team arrived about 30 min after the accident and found the patient losing his consciousness with a Glasgow coma scale of 6 ($\text{E}_1\text{V}_2\text{M}_3$). His pulse was weak and noted as 8 to 10 times per min, and miosis was also noted. He lost vital signs about half an hour later on the way to the hospital.

He was diagnosed as dead on arrival at the hospital, as neither pulse nor breath was found; no electroactivity was shown by the electrocardiogram, and miosis without reaction to light was noted. Multiple glossy and erythematous erosive wounds were noted over his perineum, all four limbs, and face except for the nares and mouth. After cardiopulmonary resuscitation with 2 mg epinephrine bolus injection and 500 ml normal saline challenge intravenously, his heart beats and blood pressure were restored, but he still needed invasive mechanical ventilation. Laboratory tests on the day of the accident revealed leukocytosis, hyperglycemia, and metabolic acidosis, but levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, and electrolytes were all within normal limits (Table 1). The results of chest X-ray examinations on admission and during follow-up excluded the diagnoses of inflammation airway and aspiration pneumonia. According to his family, he did not have any systemic diseases before this accident.

Because he had second-degree chemical burns on 24% of the total body surface area (TBSA) and third-degree burns on 5% of the TBSA (Fig. 1), he was admitted to the burn center for further management. He never regained consciousness and suffered from hypothermia, seizure, and electrolyte imbalance. He passed away eight days later.

Discussion

Using “tetramethylammonium hydroxide” or “TMAH” in searches, we could not find any previous reports of mortality cases due to industrial TMAH in PubMed, although several fatal cases occurred later in Taiwan⁴. Nowadays TMAH is used for thermochemolysis and facilitating the performance of polymerase chain reactions in laboratories. It is also used as a developer in photolithography, an anisotropic etchant of silicon, and a wafer cleaning solution in the micro-electro-mechanical industries¹. It has been regarded as non-toxic, non-flammable, and less harmful² and has been replacing other strong alkyls in the semiconductor and TFT-LCD

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Correspondence to: H.-R. Guo, Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, 138 Sheng-Li Road, Tainan 70248, Taiwan
(e-mail: hrguo@mail.ncku.edu.tw)

Table 1. Blood cell counts, biochemistry and arterial blood gas (ABG) analysis

Items	Results	Reference Level
White Blood Cell ($10^9/l$)	12.5	3.4 – 9.1
Red Blood Cell ($10^{12}/l$)	5.44	4.26 – 5.56
Platelets ($10^9/l$)	251	150 – 400
Glucose (mg/dl)	315.3	70 – 110
pH*	7.148	7.34 – 7.44
pCO ₂ * (mmHg)	39.3	35 – 45
pO ₂ * (mmHg)	359.6	75 – 100
O ₂ Saturation* (%)	99.7	95 – 98
Act cHCO ₃ * (mmol/l)	13.3	22 – 26
Base Excess* (mmol/l)	–14.9	–2.3 – 2.4

*Under mechanical ventilation with 50% FiO₂.

Fig. 1. The distribution of second to third degree burn injuries covering 29% of total body surface area.

industries. In Taiwan, more than two thousands tons of TMAH are used each month, and hundreds of thousands of workers have potential exposure to it.

TMAH is a colorless liquid with a strong amine odor. In the micro-electro-mechanical industries, it is usually transported as 25% solution (pH 13.5) in the pipe system, but is diluted to 2.38% solution when being used. In the present case, presentation of the burn wounds caused by TMAH was similar to those caused by other common alkalis. With the highly dissolubility, TMAH can introduce health hazards through its solution as a corrosive alkali as well as the product of its dissociation, TMA, which has caused several cases of accidental

intoxication³⁾. In the present case, the common causes of death in patients of chemical burns such as electrolyte imbalance and inhalation injury were excluded by the normal laboratory results and chest X-ray examinations. Whereas the possibility of burn shock could not be completely ruled out, it was unlikely because there was no evidence of organ failure or haemoconcentration. It is also uncommon for fluid and electrolyte imbalance or metabolic disturbances to cause death in one hour with a 29% TBSA burn injury. In general, the risk factors for burn mortality include large TBSA burns, more burn depth, older age, inhalation injury, and associated injury. Although it is hard to exclude the possibility that a 29% TBSA can be fatal, from previous epidemiology studies we know that the expected mortality rate for this size of burn injury by itself is minimal. For example, the abbreviated burn severity index (ABSI), which accounts for age, percent TBSA, sex, inhalation injury, and full thickness burns, was 3 for this case, corresponding to an expected mortality rate of less than 1%⁵⁾. In addition, another study observed 0% mortality from 21–30% TBSA burns in the 21–30 yr age group⁶⁾. Since the burn syndrome could not fully explain the death, TMA intoxication should be considered as the most likely one.

Most reported cases of TMA intoxication are due to eating food containing TMA, mainly gastropods. TMA is recognized as a cholinergic agonist that can bind to nicotinic and muscarinic receptors in the ganglion cells⁷⁾, skeletal muscles⁸⁾, smooth muscles⁹⁾, and cardiac muscles¹⁰⁾. Anthoni *et al.*³⁾ reviewed oral intoxication and pharmacotoxicology of TMA and concluded that TMA can induce transmission blockade on ganglions and long lasting depolarization blockade in neuromuscular junctions. TMA food intoxication may result in various signs and symptoms such as diplopia, impaired vision, photophobia, amblyopia, muscle twisting, reeling gait, weakness, nausea, vomiting, abdominal pain, dizziness, vertigo, headache, and urticaria, which are usually mild

and self-limited. In most cases, clinical presentations develop within one hour after exposure. Animal studies have demonstrated the induction of salivation, lacrimation, fasciculation and convulsion, motor paralysis, and finally cessation of respiration. After an extensive literature search, we found only one mortality case of TMA poisoning in human, which was due to the ingestion of the root of *Courbonia virgata*¹¹⁾. The oral lethal dose for an adult human was estimated to be 3 to 4 mg/kg¹¹⁾ or 250 to 1,000 mg¹²⁾. The paralysis of respiratory muscles has been proposed as the cause of death following TMA intoxication³⁾.

In the present case, salivation and miosis were noted by the paramedics, implying the possible muscarinic effects of TMA intoxication. The rapid loss of vital signs in the first hour might have been due to inhibition of the respiratory and cardiac systems. The respiratory failure could have resulted from paralysis of the respiratory muscles or ganglion nerve blockade, or both^{3, 12)}. The condition could have been further worsened by increased mucous secretion and constriction of the bronchia induced by muscarinic effects. The bradycardia noted within 30 min after the accident might have been the result of not only respiratory failure, but also inhibition of cardiac muscles by muscarinic effects, and sodium channel blockade¹³⁾ can not be ruled out. The hyperglycemia might have resulted from nicotinic effects. Although arterial blood gas analysis showed metabolic acidosis complicated with respiratory acidosis, it was hard to tell the results of circulation collapse from the respiratory inhibition after mechanical ventilation. Hypothermia, seizure, and electrolyte imbalance noted at admission to the burn center could have been related to the irreversible brain hypoxic damage caused during the absence of vital signs on arrival. As physical and chest X-ray examinations revealed no inhalation or oral cavity burn injuries, exposures to TMAH through these routes are thought to have been minimal, if any. Therefore, the most relevant exposure in the present case was dermal absorption, which could have been further facilitated by corrosive skin damage¹⁴⁾.

Conclusion

This case presents TMAH as a potentially fatal hazard to workers, which has never been reported. In contrast to the previous mild and self-limited reported cases caused by ingestion, this case exposed to industrial TMAH resulted in death. In spite of its growing popular use in the industry, currently there are no specific safety guidelines and regulations regarding TMAH in Taiwan, most likely because there are limited toxicological data and no related injuries have been reported. We suggest that hazard education, proper personal protecting equipments for strong alkali, and standard operation procedures should be emphasized as the prevention

strategies. Immediate irrigation with plenty of water for common chemical exposures should be applied to the emergency clinical first aid. The present case calls for further study of the toxicity of TMAH and the development of its treatment protocol, as well as safety guidelines and regulations in addition to those applied to strong alkalis in general. This case also warrants the attention of industrial hygienists and physicians to the fatal potential of TMAH exposures.

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