

BRIEF COMMUNICATION

Tetramethylammonium hydroxide poisoning

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Introduction. Tetramethylammonium hydroxide (TMAH) is widely used as a developer or etchant in semiconductor and photoelectric industries. In addition to alkalinity-related chemical burn, dermal exposure to TMAH may also result in respiratory failure and/or sudden death. The latter toxic effect has been of great concern in Taiwan after the occurrence of three fatalities in recent years. To better understand the toxicity following dermal exposure to TMAH, we analyzed all cases with TMAH exposure reported to the Taiwan Poison Control Center (PCC-Taiwan). **Case reports.** In total, there were 13 cases of such exposure, including three patients who died after being exposed to 25% TMAH. A worker also developed severe effects manifesting muscle weakness, dyspnea, hyperglycemia, and chemical burn (28% of total body surface area) shortly after an accidental exposure to 2.38% TMAH. He received endotracheal intubation with assisted ventilation for 2 days and survived. **Conclusion.** Skin corrosive injury related to the alkalinity of TMAH and the ganglionic toxicity of tetramethylammonium ion might contribute to the clinical manifestations that occurred after dermal TMAH exposure. Thorough skin decontamination followed by prompt respiratory support should be the mainstay in the management of dermal TMAH exposure. Preventive strategies are warranted as well to decrease future occupational TMAH exposures.

Keywords Chemical burn; Tetramethylammonium; Tetramethylammonium hydroxide; Respiratory failure

Introduction

Tetramethylammonium (TMA⁺), a well-known ganglionic blocker, was first isolated and identified by Ackermann et al. from a sea anemone in 1923.¹ It had been widely used in research laboratories as a pharmacological agent.² Nowadays, its hydroxyl salt tetramethylammonium hydroxide (TMAH) is commonly used in semiconductor and photoelectric industries as a developer or an agent for silicon anisotropic etching, a key technology for the fabrication of various microelectromechanical system devices that integrate mechanical elements, sensors, actuators, and electronics on a common silicon substrate. In Taiwan, more than 2000 tons of TMAH are used every month.

TMAH is a colorless to light yellow solution that is miscible with water.³ It has an amine odor at room temperature; the information regarding its volatility, however, is unknown. According to the Material Safety Data Sheet of TMAH, the

main hazards of this quaternary ammonium salt were limited to its high alkalinity only, which can cause corrosive injury after exposure.³ However, its other toxic mechanisms have been of particular concern in Taiwan in recent years after the occurrence of mortality among three workers who had dermal exposure to 25% TMAH without extensive corrosive injury.^{4,5} To better understand the toxicology of TMAH, we analyzed all such exposures reported to the Taiwan Poison Control Center (PCC-Taiwan).

Methods

We conducted an observational case series study by using the data reported to the PCC-Taiwan. We first searched the computerized database of the PCC-Taiwan for the following terms: TMA and TMAH in both English and Mandarin. All relevant inquiries made to the PCC-Taiwan between January 1986 and August 2009 were independently reviewed by two trained clinical toxicologists. Records only of unrelated exposure and information inquiries were excluded. TMAH exposure was diagnosed by the exposure history and verification of the implicated agents by the treating physicians. After carefully reviewing the case records, detailed exposure history, clinical manifestations, laboratory findings, and outcome were abstracted onto a standardized form.

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Case reports

Illustrative case

A 33-year-old maintenance worker (case 1 in Table 1), together with his three coworkers (cases 2–4 in Table 1), was accidentally exposed to 2.38% TMAH in an incident. He was sprayed by TMAH over his whole body when he was checking a leaking valve of the TMAH supply system in a wafer factory. He did not wear appropriate personal protective equipment and was thus exposed. He reached the automatic flushing system for decontamination 10 min after the exposure because of pain over exposed areas. Despite thorough wash with tap water, he experienced general weakness, salivation,

and dyspnea within 10 min. He was sent to a local hospital where limb paralysis, severe muscle twitching, vomiting, and poor gag reflex were noted. Physical examinations did not reveal any evidence of chemical burn of oral cavity or upper airway. After receiving endotracheal intubation, he was referred to our service 2 h post-exposure.

On arrival, the patient was alert and had stable vital signs under assisted ventilation (blood pressure 129/83 mmHg, heart rate 68/min). Physical examinations disclosed first-to-second degree chemical burns on 28% of total body surface area (TBSA), including bilateral lower limbs (18%), anterior chest wall (6%), genital organ (1%), forehead (1%), and left hand (2%). The most severely affected area was scrotum, which had multiple shallow ulcers and spot hemorrhage on it.

Table 1. Summary of 13 patients with dermal tetramethylammonium hydroxide (TMAH) exposure in Taiwan

Case no. ^a	Age/sex	Concentration of TMAH (%)	Exposed BSA	Elapsed time to decontamination	Clinical manifestations	Laboratory abnormalities	Treatment/outcome ^b
1	33/M	2.38	28% BSA	10 min	Second to third degree chemical burn, dyspnea, salivation, respiratory failure, weakness	Leukocytosis, hyperglycemia	Supportive, endotracheal intubation, intensive care/survived
2	36/M	2.38	5% BSA	<10 min	First to third degree chemical burn, dermal pain, skin rashes	None	Supportive/survived
3	?/M	2.38	<1% BSA	<10 min	None	None	Supportive/survived
4	?/M	2.38	<1% BSA	<10 min	None	None	Supportive/survived
5	34/M	2.38	18% BSA	Unknown	First to second degree chemical burn	None	Supportive/survived
6	36/M	2.38	5% BSA (face)	<1 min	Limb weakness, skin rashes	None	Supportive/survived
7	29/M	2.38	1% BSA (finger)	2 h	Dermal pain and swelling, skin rashes	None	Supportive/survived
8	61/M	2.38	Eye	<1 min	Conjunctivitis	None	Supportive/survived
9	33/M	2.38	2% BSA	<1 min	First to second degree chemical burn, dermal pain, skin rashes	None	Supportive/survived
10	31/M	25	3% BSA	<30 min	Second to third degree chemical burn, dermal pain, skin rashes	None	Supportive/survived
11	28/M	25	7% BSA	<1 min	Second to third degree chemical burn, coma, dyspnea, shock, ventricular tachycardia	Hyperglycemia, leukocytosis, metabolic acidosis	ACLS, intensive care/died due to OHCA
12	35/M	25	7% BSA	<1 min	Second to third degree chemical burn, coma, dyspnea, shock	Hyperglycemia, leukocytosis	ACLS, intensive care/died due to OHCA
13	22/M	25	29% BSA	>30 min	Bradycardia, second to third degree chemical burn, coma, miosis, shock, salivation, weakness	Hyperglycemia, leukocytosis, metabolic acidosis	ACLS, intensive care/died due to OHCA

^aCases 1 through 4 were exposed to TMAH in an incident; while cases 8 and 9, and cases 11 and 12 were simultaneously involved in another two incidents. The clinical details of case 13 had previously been published.⁴

^bSupportive therapy includes skin decontamination and/or symptomatic treatment. ACLS denotes "advanced cardiac life support"; OHCA stands for "out-of-hospital cardiac arrest" after exposure.

His pupils were isocoric (sized 2 mm) with prompt light reflex. Chest X-ray revealed patchy pulmonary alveolar infiltrates over bilateral perihilar regions. Laboratory examinations, including hemogram, serum biochemistry, and arterial blood gases, showed significant leukocytosis (WBC 19,200/cumm), hyperglycemia (135 mg/dL), and slight elevation of creatinine phosphokinase (324 U/L). A series of RBC and plasma cholinesterase measurements were all within normal limits.

The patient was admitted to the intensive care unit for ventilatory support. Nine hours post-exposure, his maximum inspiratory pressure was noted to be 52 cm H₂O (normal range 80–100 cm H₂O). He was weaned successfully 1 day later. Pulmonary function tests performed on day 4 showed normal ventilatory function with mild reduction of gas exchange. Electromyogram and nerve conduction velocity studies were unremarkable. He was discharged on the day 7. The skin lesions completely resolved 3 weeks later.

In addition to case 1, another 12 workers involved in 9 incidents of various amount of TMAH exposure were reported to the PCC-Taiwan from September 2004 to August 2009 (Table 1). All were males with age ranging between 22 and 61 years. Four patients were exposed to 25% TMAH; three of them presented with out-of-hospital cardiac arrest shortly after exposure and died despite the institution of advanced cardiac life support and intensive care (cases 11–13 in Table 1). Nine patients were exposed to 2.38% TMAH and all survived after receiving skin decontamination and/or symptomatic treatment. Atropine therapy was not given in any of the 13 patient because none of them manifested overt cholinergic features. Variable degree of chemical burns of exposed skin was the most common local manifestation, and concentrated TMAH seemed to result in more severe skin lesions. Moreover, patients exposed to 2.38% TMAH generally presented with milder toxicity except for case 1 who manifested severe effects after exposure.

Discussion

Within a 5-year period, 13 cases of TMAH exposure were reported to the PCC-Taiwan. Among them, 3 out of 4 workers who were exposed to 25% TMAH died. A worker with extensive exposure to 2.38% TMAH also developed life-threatening manifestations, which were similar to those of the fatal cases. These cases illustrated the lethal potential of both concentrated and diluted formulations of TMAH and the need for prompt ventilatory support in managing patients with severe TMAH toxicity.

Toxicity related to the alkalinity of TMAH is well known. However, the toxicity of TMAH is unlikely to be solely attributable to its corrosive effects. Chemical burn alone is not a sufficient explanation for the severity observed in our cases (Table 1) because the expected mortality rate in cases 12 and 13 was only 2% by calculating the abbreviated burn severity index.⁶ TMA⁺ cation might be another toxic principle

of TMAH and could play a major role in TMAH-related systemic toxicities. TMA ion is a well-known autonomic ganglionic agent. It is a simple quaternary ammonium compound, with a structure very similar to the cationic portion of acetylcholine, which can stimulate muscarinic and nicotinic receptors. Its action on these receptors induces an increased conductance in ganglion cells, contributing to depolarization blockade.⁷ In a recent study, TMAH was indeed found to be able to induce significant diaphragm contracture in isolated diaphragm of ICR mice, which supported the role of TMA in causing the dysfunction of respiratory muscles.⁸

TMA poisoning has been reported in cases of gastropod food poisoning through gastrointestinal tract absorption of TMA.⁹ The clinical features of TMA-exposed victims were largely similar and included nausea, vomiting, headache, vertigo, short periods of blindness, amblyopia, diplopia, and reeling gait. Toxic symptoms and signs appeared within 30 min post-exposure and complete recovery developed within a few hours. Only one lethal case had been reported, which was caused by *Courbonia virgata*.¹⁰ Injection of extract from the salivary gland of *Neptunea antique* can induce fasciculation, convulsion, motor paralysis, and respiratory failure.¹¹ In a recent study, Wu et al. injected 25, 50, 100, or 200 μmol/kg of TMA subcutaneously to four groups of male Wistar rats. Among those rats receiving 25 or 50 μmol/kg TMA, a significant decrease in heart rate and mean arterial blood pressure was found (as compared to rats without TMA exposure); whereas lethal dose (200 μmol/kg) of TMA resulted in respiratory failure manifesting hypoxemia and acute respiratory acidosis.¹² The above-mentioned effects were consistent with those of our cases who developed early muscle weakness followed by respiratory failure. Furthermore, although TMA could cause certain central nervous system toxicity, it has not been shown to cross the blood–brain barrier to any extent.⁹ Therefore, the development of respiratory failure after TMA poisoning is more likely to be related to the paralysis of respiratory muscles because of its ganglionic blocking effects.^{7,8,11–13}

Although TMA is a competitive inhibitor of acetylcholinesterase and can cause cholinergic symptoms by accumulation of acetylcholine, such an antagonistic action can be largely disregarded because it is several orders of magnitude weaker than its stimulating effects on the receptors.¹⁴ In case as well as the other cases reported to the PCC-Taiwan, all cholinesterase measurements were within normal limits.

Given its low lipid solubility and positive electrical charge,¹⁵ TMA ions are unlikely to easily penetrate normal skin to induce toxicity. Thus, corrosive injury from alkaline hydroxyl group of TMAH might be needed to facilitate the absorption of TMA ion through the exposed skin to induce toxicity. Strong alkaline can destroy the skin integrity by pathological liquefaction to hasten TMA absorption.^{16,17} Even 2.38% TMAH has the potential to result in significant corrosive injury and subsequent systemic toxicity. We speculated that this could be the reason why the latency between dermal exposure and the occurrence of systemic toxicity was relatively short in our cases.

Early decontamination by irrigation with copious water appears to be the most important procedure to prevent TMAH-related systemic toxicity given that TMAH is highly soluble in water. Seeking medical attention immediately after exposure is also needed, especially for those patients who develop systemic toxicity. Without prompt treatment, paralysis of respiratory muscles because of ganglionic toxicity may develop and may subsequently lead to apnea that is the usual cause of TMA poisoning.^{9,10,13} Severe TMA poisonings can also result in bradycardia, hypotension, and decreased cardiac output,^{4,12,13} which may be attributable to respiratory failure, muscarinic effect related to cardiac depression, and/or sodium channel blockade.^{12,13,18} Close cardiac and respiratory monitoring followed by adequate ventilatory support thus appear to be the mainstay in the management of severe TMAH poisoning. With a short elimination half-life of TMA ion,^{13,15} the prognosis of TMAH poisoning should be good if the patient can be stabilized in the life-threatening period.

No antidote for TMAH poisoning is currently available; however, atropine may be considered as a potential antidote. The binding of TMA ion to muscarinic receptor is largely reversible and antagonized by atropine in rat heart; therefore atropine therapy is indicated for the amelioration of bradycardia and other muscarinic cholinergic symptoms.¹⁵ In rats receiving 25–200 $\mu\text{mol/kg}$ TMA, pretreatment with 1 mg/kg atropine prolonged their survival time; however, the treatment did not prevent death in the experimental animals.¹²

The administration of acetylcholine during hyperpolarization evoked by TMA also partially antagonizes the late-occurring blockade of nerve transmission. Cholinesterase inhibitors, such as neostigmine, may be another therapeutic choice.¹⁹ The clinical usefulness of such agents nevertheless remains unknown.

Limitations

This study has several limitations and the study findings should be interpreted with caution. First, this was a descriptive only study and the number of cases included in this study was small. Second, most of the data were collected during telephone consultations; therefore, the detail of information might vary between cases. Given the retrospective nature of the study design, data incompleteness was probable. Third, not all TMAH exposures in Taiwan were reported to the PCC-Taiwan, which precluded an accurate assessment of the incidence and severity of TMAH poisoning.

Conclusions

In summary, dermal exposure to any concentrations of TMAH, especially the concentrated formulation, can result in severe poisoning. Vigorous skin decontamination followed by prompt ventilatory support should be given immediately to any patient with significant TMAH exposure. Clinicians

should also be on the alert for atypical presentations because of the possibility of inhalation/ingestion of mists or aerosols. Education, adherence to standard operation procedures, and the use of appropriate protective personal equipments are all important in the prevention of occupational exposures to TMAH and related toxicity.

This study highlighted the important role of PCC in serving as a useful tool for routine surveillance of emerging poisonings. Although the study findings should be interpreted with caution, they suggested that concentrated TMAH and larger area of exposure might be related to poor outcome following TMAH exposure. The significance of these as well as other prognostic predictors (e.g. age, gender, and elapsed time to presentation) needs further large-scale study. More evaluation of the toxic mechanisms and potential antidotes for TMAH poisoning are also warranted.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of this paper.

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