Toxic Exposure to Methyl bromide, a Case Study and a Review

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Abstract

Introduction
Methyl bromide (MeBr) is a soil fumigant that has been phased out by most countries by the early 2000s.

Case Presentation
A 37 years old male patient came to the emergency department (ED) to seek the medical advice for dysarthria and acute inability to walk. He gave a history of occupational exposure to methyl bromide due to a leak from fumigation tube 2 days before the onset of illness.

Electroencephalogram and other necessary investigations were done. Serum bromide was very high. The patient was admitted and given chelation therapy with monitoring of bromide levels until decreased to a minimum. The patient had mild psychosis and was referred to a psychiatrist.

Conclusion
Methyl bromide is a hazardous chemical that had been phased out by most countries. The developing countries, including Egypt, show lag in legislations controlling chemical hazards use with subsequent health effects due to human exposure.

Keywords: Methyl bromide; Neurologic Toxicity; Exposure; Health Consequences; Banning
Introduction

Methyl bromide, or bromomethane (CH3Br), is an organobromine compound which is a colorless, odorless and is a non-flammable gas. It is produced industrially and particularly biologically. It has a tetrahedral shape and a density of 1.73 g./cm³, a boiling point of 3.56°C, melting point of -93.66°C and molecular mass of 94.94 g./Mall [1].

Bromomethane is soluble in water and is three times heavier than air. It accumulates in poorly ventilated or low-lying areas. It can be obtained by reacting methanol with hydrogen bromide as follow: CH₃OH + HBr → CH₃Br + H₂O [1]

Methyl bromide is manufactured for agricultural and industrial uses. The gas is usually absorbed by inhalation and affects the lungs, gastrointestinal tract, skin, and brain. It is a well-recognized ozone-depleting chemical. It was used extensively as a pesticide until being phased out by most countries in the early 2000s [2].

However, developing countries are still late regarding taking legislations for restriction of this hazardous chemical. The Mediterranean area is an important source region for methyl bromide production and consumption. It shows a generally decreasing trend in use of the toxic gas. However, an emission pattern that is not consistent with the phase-out schedule of this compound exists, with a renewed increase in the recent years of pollution episodes [3].

Case presentation

A male patient, about 37 years old from a rural area who is working in a Fumigation Company since for 15 years and married with 2 offspring, had come to the Emergency Hospital in Mansoura University on 20th June, 2012. The patient complained of sudden-onset slurred speech, confusion and imbalance while walking which had developed over a period of 2 days ago. The patient gave a history of occurrence of a leak from fumigation tube in his work site 2 days before the onset of illness.

The patient and relatives gave no history of financial troubles, family troubles, previous suicidal attempts or drug abuse. The patient and the attendant relatives gave no history of gastrointestinal manifestations, seizures or abnormal movements.

On examination, the patient was confused (GCS score 11), pulse was 80/minute; regular and full. Blood pressure was 130/90 mmHg, respiratory rate was 16/minute, temperature 37°C, skin examination showed a presence of vesicles on the chest. Head and neck examination showed pupils to be rounded, regular, reactive, equal and central, gum showed a blue line on the margin. Chest examination showed mild basal lung crepitations on auscultation.

Neurological examination showed generalized hyporeflexia, normal muscle tone, and power. Sensation could not be assessed as the patient was confused. There were no signs of lateralization or meningeal irritation.

Bedside tests showed random blood sugar (RBS) to be 71 mg/L (Normal: < 200 mg/L) and nothing abnormally detected in Electrocardiogram (ECG).

Routine laboratory investigations showed nothing abnormal in urine analysis, Complete blood count showed WBCs of 10000/cc (Reference range: 4000-7000/cc), RBCs 4.8 million/cc (Reference range 5-6 million/cc), Hemoglobin 14 g./dl (normal 14.6-16 g./dl), Platelets 298×10³/ ml (normal 140-440 ×10³/cc).
Serum creatinine was 0.8 mg/dl, Liver function tests showed elevated serum ALT; 76.4 U/L (Reference range is 20-45 U/L), serum albumin was 4.4 g./dl (Reference range is 3.5-5.5 g./dl). Bleeding profile showed prothrombin time (PT) of 12.7 seconds, International Normalized Ratio (INR) 1.4, Activated Partial thromboplastin Time (APTT) 38 seconds (reference value range is 28-38 seconds).

Radiologic investigations showed mild lung opacity on both sides and free brain CT. Mild changes in EEG were found (figure 1). There was a mild alteration of the brain waves and the recorded brain electrical signals. Specific toxicological investigations showed serum bromide level of 200 mg/dl.

Figure 1: Mild changes in EEG after Methyl bromide exposure.

The patient was given supplemental oxygen and observed for 6-12 hours to detect the development of delayed symptoms including seizures and non-cardiogenic pulmonary edema. The patient was advised to remove contaminated clothes, wash affected skin with soap and water and irrigate exposed eyes with copious water or saline.

A chelator was administered to treat the elevated blood levels of bromide. Calcium disodium edetate was given in a dose of 0.5-1 g. twice daily for 5 days with monitoring of blood and urinary bromide level.

Bromide blood level was decreasing from 200 mg/dl on admission to 120 mg/dl on 22nd June, 2012 to 80 mg/dl on 25th June, 2012 then to 38 mg/dl on 30th June, 2012.

Symptomatic and supportive treatments were continued until the patient was discharged on 4th July, 2012. The patient was fully conscious (GCS 15). His pulse was 88/minute, full and regular. His blood pressure was 120/90 mmHg. Respiratory rate was 16/minute, full, regular and body temperature was 37°C.

Neurologic examination showed intact reflexes, normal muscle tone, and muscle power. Pupils were rounded, regular, equal, central and reactive to light. Dysarthria was improved but the patient was observed to have a mild degree of abnormal behavior. Liver function tests showed serum transaminases to return to normal (serum ALT; 40 U/L). Magnetic resonance imaging (MRI) showed mild parenchymal volume loss in cortex and cerebellum (previously referred to as cortical and cerebellar atrophy) (figure 2). However, the basal ganglia appeared normal. No evidence of altered signal was noted in the corpus callosum. No contrast was administered and MR spectroscopy was not done.

Figure 2: MRI of the brain revealed bilateral symmetrical volume loss in cortical and cerebellar areas on T2 sequences.
The history, clinical examination, laboratory and radiologic findings are characteristic of Methyl bromide toxic encephalopathy. Other differentials with similar MRI features were excluded which are non-alcoholic Wernicke’s encephalopathy, drug-induced toxic encephalopathy, entero-viral encephalitis. The main differential diagnoses of similar MRI findings were all excluded.

In non-alcoholic Wernicke’s encephalopathy, increased T2-weighted and FLAIR signal intensities in the regions of the peri-aqueduct, periventricle, and medial thalami are the main features. [4]

In drug-induced toxic encephalopathy (e.g., cancer chemotherapy), dentate nuclei are most commonly involved followed by tectum, red nucleus, periaqueductal gray matter, and dorsal pons. The dorsal medulla and the corpus callosus are less often affected. When corpus callosum is involved, splenium is affected in all cases.[5]

Entero-viral (EV71) encephalitis is another condition that shows bilateral symmetrical signal in the dorsal brainstem and cerebellar dentate nuclei.[6]

The patient was referred to a psychiatrist for his psychosis. The patient was advised to follow-up MRI after stopping exposure to Methyl bromide.

Repeat MRI brain was done after 4 months and showed complete resolution of the above-mentioned findings, confirming the diagnosis.

Discussion

Fumigants are volatile poisonous substances used to kill insects, nematodes, and other animals or plants that damage stored foods, seeds, and human dwellings. Soil fumigants are pesticides which are sprayed or spread over an area to be cultivated [7].

Fumigants share the common feature of being gases at room temperature. There are four categories of fumigants as follows:

I. The halogenated hydrocarbons include methyl bromide
II. Ethylene dibromide and DBCP (dibromochloropropane) are fumigants that were used in the past to sterilize soil prior to planting. Both these fumigants are banned in the USA since the late 1970s because they are male reproductive toxins.
III. Metal-phosphide compounds are toxic through the generation of phosphine. They are used for rodent control and on agricultural commodities.
IV. Sulfuryl fluoride is an example of an inorganic compound used as a structural fumigant [8].

Methyl bromide is one type of fumigants that is readily photolyzed in the atmosphere to release elemental bromine, which is far more destructive to stratospheric ozone than chlorine. So, it is subject to phase-out requirements of the 1987 Montreal Protocol on Ozone Depleting Substances [3].

The London Amendment in 1990 added methyl bromide to the list of Office of Dietary Supplements (ODS) to be phased out. In 2003, the Global Environment Facility approved funding a project for methyl bromide total sector phase out in seven countries in Central Europe and Central Asia, which was due for completion in 2007 [7].

The health effect of methyl bromide on humans and other mammals vary according to the intensity of exposure. Oral LD₅₀ in rat is <100 mg/kg and inhalation LC₅₀ (15 minutes) in rat is 21 000 mg/m³. It is cumulative upon repeated exposure. After absorption bromine is widely
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distributed in body tissues and is stored in lipoid tissue. Respiratory, kidney, and neurological effects are of the greatest concern after exposure [9].

At non-fatal concentrations, methyl bromide produces neurological symptoms. High concentrations may cause death through pulmonary injury and associated circulatory failure. The onset of toxic symptoms is delayed, and the latent period may vary between 0.5 to 48 hours, according to the intensity of the exposure and the personal reaction of the patient. Contact of the human skin with the liquid or strong concentrations of the gas may cause severe local blistering [10].

A single small exposure from which a person recovers quickly is not likely to cause delayed or long-term effects. After a serious exposure that causes lung or nervous system-related problems, permanent brain or nerve damage can result. Also, prolonged exposure to methyl bromide was found to cause cancer and birth defects in newborns [11].

Methyl bromide likely produces these health effects by methylation of intracellular lipids, protein and glutathione; production of toxic metabolites; defective neurotransmitter function; and abnormal oxidative phosphorylation [9].

As regards to the toxicity of methyl bromide, it may involve a latent period of several hours after exposure, followed by signs such as nausea, abdominal pain, weakness, confusion, pulmonary edema, and seizures. Individuals who survive the acute phase often require a prolonged convalescence. Persistent neurological deficits such as cognitive impairment, optical atrophy, asthenia and paresthesia are frequently present after moderate to severe poisoning [12].

Blood or urine concentrations of inorganic bromide, a bromomethane metabolite, are useful to confirm a diagnosis of poisoning in hospitalized patients or to assist in the forensic investigation of a case of fatal exposure [13].

Serum bromide levels can be used to document that exposure did occur only if it is done within 1 to 2 days following exposure. However, bromide levels in the blood do not accurately predict the clinical course as bromide also occurs naturally in the blood [9]. Radiological investigations as MRI of the brain are usually normal in cases of MeBr exposure [14].

The Workplace Exposure Standard for MeBr at 5 ppm over 8 hours is 30 times below any known effect over a 5-7 week inhalation study according to the EPA Methyl Bromide Risk Assessment conducted in 2005. The workplace exposure standards apply to long-term exposure to a substance over an eight-hour day, for a five-day working week [15].

An interesting comparison is with carbon monoxide (CO) that people are exposed to every day from vehicles and other sources. Fumigation gas is similar to car exhaust; both have no warning signs, being odorless and colorless. So, a fumigant should be diluted to safe levels and run in the open air not in closed spaces [1].

Treatment after methyl bromide exposure includes decontamination, symptomatic and supportive measures. There is also the treatment of complications, if occurred, as seizures, coma and pneumonia [16].

There is no proven antidote for methyl bromide poisoning. Chelation therapy and haemodialysis may be used in acutely-ill poisoned patients after MeBr exposure. Haemodialysis is successful in removing bromide from the blood but cannot reverse the neuropsychiatric sequelae of MeBr toxicity [17].
Dimercaprol (BAL) or N-acetylcysteine (NAC, Acetylcysteine) have been suggested as antidotes based on the postulated mechanism of methyl bromide’s toxicity. Both N-acetylcysteine and dimercaprol can offer a reactive sulfhydryl group to bind free methyl bromide. However, no adequate studies have tested the efficacy of these agents. There were strikingly different outcomes for two patients with the same exposure but different glutathione transferase activity, suggesting that NAC could possibly exacerbate toxicity. Neither agent can be recommended for routine use at this time [18].

Methyl bromide has been phased out from most countries of the world. Developing countries still use methyl bromide and other hazardous chemicals and require more strict regulations and policies to control and limit the use of such harmful chemicals 3. This adds to the burden of toxic exposures in developing countries [19], [20].

One-hundred ninety-six (196) countries had signed to the Montreal Protocol and agreed to specific reduction steps that lead to the phase-out of production and import of ozone-depleting substances, including methyl bromide [19].

All fumigators are required to have a controlled substance license, be an approved handler under the Hazardous Substances Act 1996 and be an MAF approved treatment supplier. Protective respirators should be worn for methyl bromide at any detectable concentration. It is advised to add a lacrimator (an agent that irritates the eyes and causes tearing), most commonly chloropicrin, to act as a warning agent for methyl bromide because methyl bromide is odorless and nonirritating [18].

Use of alternatives will help to decrease MeBr import and manufacture until it is phased out [21].

Many alternatives to methyl bromide in the agricultural field are currently in use and yet further alternatives are in development, not least of which include propylene oxide and furfural [22].

**Conclusion**

Methyl bromide is a potent neurotoxin and causes stratospheric ozone layer depletion. Despite that this fumigant had been phased out by most countries in the early 2000s; it is still used in developing countries, including Egypt, with subsequent exposure including occupational exposure leading to acute and long-term health effects and sequelae. Prompt steps in making regulatory policies and legislations controlling methyl bromide use become mandatory to save lives and prevent health and environmental complications.

**Abbreviations**

µg, microgram; ALT Alanine transaminase; APTT, Activated partial thromboplastin time; CT, Computerized Tomography; dl, deciliter; ECG, Electrocardiogram; EEG, Electroencephalogram; EPA, Environmental protection agency; g., gram; g/dL, grams per deciliter; GCS, Glasgow Coma Scale; INR, International normalized ratio; LC₅₀, Lethal concentration 50; LD₅₀, Lethal dose 50; m³, Cubic meter; mg, milligram; MRI Magnetic resonance imaging; oC, degree centigrade; OSHA, Occupational Safety and Health Administration; ppm, part per million; RBC, Red Blood Cell; RBS, Random Blood Sugar; USA, United States of America; WBCs, White Blood Cells.
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Declaration

Author, states that this research work is original and has not been published in whole or in part elsewhere.

Authorship (author(s) contribution or attribution)

The single author of this work is the one who collected information, wrote and revised the manuscript and had the concept to be published and submitting for publication.

References

PMID: 24243005 DOI: 10.1002/ajim.22269

PMID: 18575299

PMID: 24347845 PMCID: PMC3843323 DOI: 10.4103/0971-3026.120233

PMID: 20823625

PMID: 19360507 DOI: 10.1080/15563650902802544

PMID: 23473464 DOI: 10.3109/15563650.2013.772624

PMID: 15141858

DOI: 10.12691/ajmcr-2-10-4

DOI: 10.12691/ajmcr-2-11-2

PMID: 10332508

PMID: 15149099

PMID: 23732880 PMCID: PMC3672928 DOI: 10.1289/ehp.121-a198

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