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Acute intoxication due to exposure to maneb and zineb

A case with behavioral and central nervous system changes

by Raphael Israeli, MD, DIH,¹ Mario Sculsky, MD,¹ Pascal Tiberin, MD²

ISRAELI R, SCULSKY M, TIBERIN P. Acute intoxication due to exposure to maneb and zineb: A case with behavioral and central nervous system changes. *Scand j work environ health* 9 (1983) 47-51. The dithiocarbamates are considered chemicals of low toxicity. They are known to cause dermatitis, conjunctivitis, rhinitis, pharyngitis, and bronchitis in humans. Central nervous system effects in humans have not been found, but some cases have been reported in experimental animals. This case report concerns a 42-year-old man previously in good health, who sprayed a combined dithiocarbamate of maneb and zineb on a cucumber plantation twice during a week, the second time with a more concentrated solution than the first. Behavioral changes appeared after he walked through the sprayed area following the first application, and loss of consciousness, convulsions, and right hemiparesis with diffuse slow rhythm in the electroencephalogram occurred after the second exposure. Both the behavioral and central nervous system symptomatology disappeared spontaneously after a few days. An electroencephalogram was normal two weeks later. The absence of a positive previous history of the patient, the sudden appearance and spontaneous disappearance of the symptoms, and the apparent dose-response relationship strongly suggested that maneb and zineb were the cause of the illness.

Key terms: behavioral changes, central nervous system symptoms, dose-response relationship, manganese-ethylenebis (dithiocarbamate), slow rhythm in electroencephalogram, zinc-ethylenebis (dithiocarbamate).

The carbamates are salts of carbamic acid (H_2NCOOH), a chemical that does not exist in nature. Their mode of action and clinical symptomatology resemble those of the organophosphorus insecticides (11). Contrary to the carbamates, the dithiocarbamates have been known to cause mild symptoms in humans, ie, dermatitis, conjunctivitis, rhinitis, pharyngitis, and bronchitis (1). The dithiocarbamates are derivatives (metal salts or organic esters) of dithiocarbamic acid [$\text{H}_2\text{NC(S)SH}$], with the general structure $(\text{CH}_3)_2\text{NC(S)S-Me}$, -S-alkyl or -S-aryl, where Me equals metal, such as Na^+ , Fe^{3+} , MN^{2+} or Zn^{2+} (18).

Depending on the methyl radical or ethylene, and on the metal included in the

molecule, different kinds of dithiocarbamates can be obtained, with different properties and uses. The three main groups of dithiocarbamates (12) are (i) the dimethyl derivatives [bis (dimethylthiocarbamoyl) disulfide (thiram), zinc dimethyldithiocarbamate (ziram), ferric dimethyldithiocarbamate (ferbam), sodium methyldithiocarbamate (vapam), disodium ethylenebis(dithiocarbamate) (nabam)], (ii) the diethyl derivatives [selenium-diethyldithiocarbamate (ethyl selenac), zinc-diethyldithiocarbamate (ethyl zimate), tellurium-diethyldithiocarbamate (ethyl tellurac), cadmium-diethyldithiocarbamate (ethyl cadmate)], and (iii) the ethylenebis-dithiocarbamates [manganese-ethylenebis-dithiocarbamate (maneb), zinc-ethylene bis-dithiocarbamate (zineb)].

Maneb, zineb, ziram, nabam, and ferbam are being used in agriculture as fungicides. Maneb and zineb are also used for the protection of stored wheat because of their growth inhibition properties and in the plastics and rubber industries as accelerators and catalysts. Ferbam, thiram and zineb, which inhibit cholinesterase,

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are used as insecticides. Dithiocarbamates find application in therapeutics as a chelating agent for copper and thallium and in the treatment of Wilson's disease (2).

Compared to the carbamates, a group of highly toxic pesticides similar with respect to molecular structure, the dithiocarbamates are considered chemicals of low toxicity. These agents may be absorbed through the dermal route (13). Their metabolism produces carbon disulfide and ethylene diamine (12).

Renal failure (5) and impotence (3) have been reported in man as a result of dermal absorption, but the doses in these cases were not defined. In animals hepatic and renal damage (6), teratogenicity, mutagenicity, and carcinogenicity have been reported (7, 10, 14). Central nervous system (CNS) effects in animals include behavioral and neurotoxic changes (8) and convulsions (9). We report a case of intoxication, with behavioral and CNS changes, caused by a combined maneb and zineb compound.

On 20 January 1981 a 42-year-old man was admitted to the emergency ward of the "Soroka" Medical Center. He was unconscious with occasional tonic and clonic convulsions and signs of right hemiparesis. He had been spraying a maneb-zineb compound before his admission.

Past history

The patient denied drinking alcoholic beverages, smoked three cigarettes a day from the age of 18, drank three to four cups of coffee a day, and did not use drugs. He had not been admitted to a hospital earlier nor had any surgical interventions or accidents. He denied any illnesses in the past and was not getting any medical treatment. There were no known cases of epilepsy or mental illnesses in his family.

Present illness

First exposure. On the morning of 13 January 1981 the patient took 250 g of the compound and dissolved it in a barrel containing 100 l of water. He sprayed the solution on a cucumber plantation, using a mechanical device attached to his tractor. He wore protective clothing including a

mask and gloves. A day later, 14 January, he took a walk in the field without taking any protective measures. On the same day his wife noted a change in his behavior. He was not as communicative as usual, refused to talk, was very nervous, and did not play with his children, as he usually did. He complained of tiredness, dizziness, and weakness. The same symptoms were present on the following day, on which he did not go to work. Despite this, he did not visit his physician. During the next two days his symptoms subsided.

Second exposure. On 19 January the patient used a ten times stronger solution of the compound and sprayed it again. He took the same preventive measures and felt well. On the morning of 20 January he again took a walk through his field without any protective clothing. Returning home, he complained of weakness, headache, nausea, and fatigue. He went to bed, and, when undressing, he had difficulty taking off his shirt and trousers, started to take off and put on his shoes and socks, and then tried to put his shirt and gown on his legs. His speech was unclear, and he lost consciousness and began to have tonic and clonic convulsions.

Findings on admission

On admission to the emergency ward the patient was unconscious with occasional tonic and clonic convulsions, his pupils were symmetric and reacted to light. He showed right hypertonic hemiparesis. His reflexes were augmented on the same side, and the Kernig sign was positive. His heart rate was 64 beats/min, regular, without evidence of any heart disease, and his blood pressure was 130/70 mm Hg. [17,332/9,325 Pa] His body temperature was 36.7°C, and his electrocardiogram normal. The optic disks showed no sign of increased intracranial pressure. A lumbar puncture revealed a normal pressure of the cerebrospinal fluid, the Pandy reaction was negative, the proteins were 48 mg%, the glucose was 75 mg% (with a glycemia of 122 mg%), the chlorine 122, and the cells 7/3. All the other clinical biochemical examinations made produced normal results. The electroencephalogram showed a diffuse slow rhythm

without evidence of focal irritation or epilepsy (fig 1a).

The patient received symptomatic treatment with diazepam (5 mg, intra-

venous) three times a day, dexacort (6 mg, intramuscular) four times a day, tagamet (200 mg, intramuscular) four times a day, and ritalin (20 mg, intramuscular).

Fig 1. (a) 20 January 1981: "Disorganized irregular, high voltage, 1–2 c/s waves; patient disoriented with gross mental confusion." (b) 22 January 1981: "Marked reduction in delta activity with short runs of bilateral synchronous, high voltage, 3 c/s waves, emerging on a dominant low voltage fast rhythm." (c) "Further improvements; no delta activity; emergence of normal occipital alpha rhythm at 9 c/s; sensorium cleared."

Fig 2. (a) Rest record: "Slow alpha activity, 6–8 c/s waves." (b) Hyperventilation record: "Short runs of theta waves, 4–5 c/s, after 3 min of hyperventilation." (c) Intermittent light stimulation: "Similar activity, with 6 c/s waves."

Clinical course

On 21 January the patient began to respond to external stimuli. Computer tomography was performed without abnormal findings. No convulsions were present, and by the late evening he recovered consciousness, though he continued to be mildly confused and did not talk. The same treatment was continued.

On 22 January the patient began to talk, answered questions without problems, and was fully aware of place and time. A new electroencephalogram was performed which showed a diffuse slow rhythm, especially in the left hemisphere, but with improvement in comparison to the previous one (fig 1b).

On 25 January the patient was fully conscious without any abnormality in his behavior and clinical examinations. The electroencephalogram revealed a diffuse and very slightly slow rhythm (fig 1c). The patient was discharged in apparently good health.

On 6 February a follow-up electroencephalogram was performed, this time including hyperventilation and intermittent light stimulations. The examination was normal (fig 2).

Comments

The patient had been exposed to a high concentration of maneb-zineb twice during a week. A number of facts justify the presumption that the patient's symptoms were due to exposure to the fungicide: (i) the history of the patient, no previous illnesses, not an alcoholic, a nondrug taker, a minimal smoker, low exposure to caffeine, and no precedents for epilepsy or mental illnesses; (ii) the clinical course of the illness, with a sudden onset after exposure to the compound, while "taking a walk" in the vegetable field, and the rapid and progressive improvement of the patient after cessation of exposure; and (iii) the difference in the of dilution of the substance, related with the severity of the symptoms and strongly suggesting a dose-response relationship.

Skin penetration and inhalation are known routes of entry for dithiocarbamates (13). Our patient was probably exposed mostly by skin absorption, but

both skin and respiratory uptake were probable.

In 1974 a revised temporary acceptable daily intake of 0–0.005 mg/kg was established for man for all dithiocarbamate fungicides (16). The suggested hygienic standard for dithiocarbamates is 0.5 mg/m³ (15). The oral median lethal dose for maneb in mice is 4.1 g/kg, and for rats it is 6.7 g/kg (4). For zineb, the oral median lethal dose for rats is 1–8 g/kg (16).

To our knowledge no cases of behavioral and CNS changes due to maneb and zineb have been reported for humans, and the evidence from animal experimentation is fragmentary and incomplete.

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