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Acute Fatal Poisoning by Methomyl Caused by Inhalation and Transdermal Absorption

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In Crete, various pesticides are increasingly used in land cultivation to increase production and raise crop quality. Methomyl, S-methyl-N-[(methylcarbomoyl)-oxy]thioacetimidate, is a carbamate insecticide marketed as an aqueous solution but also in solid form, under the trade names Lannate® and Nudrin®. The main characteristics of the carbamate pesticides are the broad spectrum of activity, mainly attributed to the suppression of cholinesterase activity, and the high effectiveness.

The overwhelming majority of the poisonings caused by methomyl are due to ingestion of the compound, either accidentally (Tsatsakis et al. 1996; Liddle et al. 1979; Lifshitz et al. 1997; Lifshitz et al. 1999; Martinez-Chuecos et al. 1990; Lifshitz et al. 1994) or on purpose in order to commit suicide (Tsatsakis 1998; Miyazaki et al. 1989). Case reports of methomyl poisoning caused by inhalation or transdermal absorption are rare. Two of the reported cases were related to aircraft accidents and accidental exposure of the pilot to insecticides (Driskell et al. 1991; Cable and Doherty 1999). Until now, no death due to inhalation and transdermal absorption of methomyl has been reported. This report presents the clinical and laboratory data of one case of acute poisoning by methomyl caused by inhalation and transdermal absorption, with no signs of ingestion of the agent. The development of poisoning and the fatal outcome are discussed in relation to the use of Lexotanil® (bromazepam), a mild anxiolytic drug.

MATERIALS AND METHODS

A 60-year-old male farmer, was found comatose in his greenhouse and was admitted to the local Health Center. Cardiopulmonary resuscitation was immediately initiated and the patient was intubated in the ambulance on the way to the hospital. The patient was unresponsive, with Glasqow Coma Scale (GCS) of 3. His blood pressure (BP) was 80/50 mmHg and his heart rate (HR) 100 min^{-1}. On admission to the intensive care unit, almost 3½ hours after he was found in his

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greenhouse, the patient was unresponsive (GCS = 3, BP = 80/50 mmHg, HR = 80 min^{-1}, PaO_2 = 86 mmHg, $PaCO_2$ = 38 mmHg, $[HCO_3^-]$ = 15 mEq/l, F_IO_2 = 0.6 and pH = 7.21). The patient's body temperature was 36°C. The physical examination revealed pinpointed pupils, sialorrhea (with a typical garlic odor), reduced muscle tone and tendon reflexes. Samples of gastric contents, blood, urine and saliva were sent for toxicological analysis. The troponine test and the urine color test for paraquat were negative.

The patient was placed on mechanical ventilation (Dräger IPPV-PC). Based on the clinical signs and the relatives' statement, great suspicion of methomyl poisoning was established. Consequently, therapy included: 1) gastric lavage with H_2O and activated charcoal (for the first 24 hours after admission), 2) enemas with lactulose and 3) skin washing. Moreover, 15 mg of atropine were administered within 15 minutes and subsequently continued as infusion of 1 mg/h. Due to the hemodynamic instability of the patient no brain computerized tomography (CT) was carried out. The patient was sedated with propofol and fentanyl and his intracranial pressure (ICP) was regulated to levels of 10-13 mmHg. The rest of the therapy consisted of diuretics, bicarbonates, sympathomimetics, anaesthetics and antibiotics. The laboratory results on admission were: serum glucose 419 mg/dL, blood urea nitrogen (BUN) 43 mg/dL, serum creatinine 1.5 mg/dL, aspartate aminotransferase (AST) 113 U/L, alanine aminotransferase (ALT) 103 U/L, γ-glutamate transferase (γ-GT) 80 U/L, creatinine kinase (CK) 156 U/L, serum lactate dehydrogenase (LDH) 275 U/L, total bilirubin 0.65 mg/dL, serum sodium (Na^+) 136 mEq/L, serum potassium (K^+) 3.0 mg/dL, serum chloride (Cl^-) 100 mEq/L, serum calcium (Ca^{+2}), while blood cell count (WBC) 24500 mm^{-3}, hematocrit (Ht) 36.6%, hemoglobin (Hb) 11.6 g/dL, prothrombin time (PT) 15 s and activated partial thromboplastin time (aPTT) 38.9 s.

The patient was evaluated twice daily for the severity of his condition (APACHE II score) and the central nervous system function (GCS score) and biological samples were sent for toxicological analysis. Quantitative estimation of serum cholinesterase activity was determined spectrophotometrically, using Boehringer Mannheim Kit No 124125 (reference values 3500 – 8500 U/L), whereas the extracts (fluids and tissues) were analyzed using HPLC and GC-MS techniques (Tsatsakis 1996). Methomyl was detected in blood (1.6 mg/dL on admission) and urine, but not in stomach content. The inhibition of cholinesterase activity (89% on admission) and the methomyl blood concentration during the hospitalization of the patient are presented in table 1. His general condition gradually deteriorated leading to systemic inflammatory response syndrome (SIRS) and death, three days after his admission, because of multiple organ failure syndrome (liver and renal failure, haemodynamic instability, coagulation disorders and coma).

A careful interview with the patient's relatives revealed that the victim was a farmer, owning a greenhouse. He had been using large quantities of pesticides and

Table 1. Inhibition of cholinesterase activity (from the lowest reference value) and blood methomyl concentration.

	On admission	1st day	2nd day	3rd day
Cholinesterase activity (U/L)	380	860	2400	3200
Percentage of inhibition	89 %	75 %	31 %	9 %
Blood methomyl concentration (mg/L)	1.6	0.8	0.6	0.1

fertilizers for many years without any precaution, such as mask, special clothing or ventilation of his greenhouse. According to his son, the patient used to wear the same clothes every time he had to make use of pesticides without washing them afterwards. During the last week, the patient had been spraying in the greenhouse. He complained of tiredness and weakness and visited a general practitioner who attributed his symptoms to anxiety and subscribed bromazepam (Lexotanil®), a mild anxiolytic. Four days before the incident the patient sprayed again with methomyl. The patient continued to have the same symptoms and in the morning of the incident he was feeling very weak and reported bradycardia. He took a tablet of bromazepam (1.5mg) and visited his greenhouse at midday to spray with Lannate® (methomyl), where he was found comatose about three hours later.

The autopsy findings included congestion of viscera and pulmonary edema. The stomach cavity contained quantities of activated charcoal but the gastric contents had no special odor of ingested pesticide. There were excessive degenerative phenomena detected in the liver, the spleen, the pancreas, the adrenal glands and the urogenital tract. Autopsy samples of the stomach contents, heart blood, liver and hair were extracted and analyzed according to procedures previously published (Tsatsakis et al. 1996). Methomyl was detected in liver tissue but not in heart blood or gastric contents. The pesticide deposition in hair was also measured using ELISA and GC-MS (Tsatsakis et al. 1998a) and was found to be 4 ppb (4 ng/mg hair) in proximal hair.

RESULTS AND DISCUSSION

Methomyl is considered to be an extremely toxic pesticide widely used in agriculture. It is characterized by low chronic but high acute oral toxicity and the minimum lethal dose (LD_{50}) for male rats was found to be 17 mg/Kg body weight (Kaplan and Sherman 1977). The toxicology of methomyl poisoning in humans has not been extensively studied. In a report of three fatalities from accidental ingestion of methomyl the lethal dose was estimated to be 12 – 15 mg/Kg body weight (Liddle et al. 1979). Apart from the poisoning due to gastrointestinal absorption, the high potential of methomyl poisoning through inhalation or transdermal absorption should also be pointed out. However, the literature contains

no data on fatal cases of carbamate intoxication caused by inhalation or transdermal absorption.

This study presents the case of a farmer who was exposed to quantities of methomyl while spraying in his greenhouse for a time period of one week. His poisoning cannot be attributed to ingestion, since no methomyl was found in the stomach contents on admission. Consequently, the poisoning was caused by inhalation and transdermal absorption. According to the interview with the relatives, the patient used to wear the same clothes each time he had to spray. He would not take precaution such as mask, respirator, special gloves or ventilation of the greenhouse, regardless of the warnings mentioned on the label of the pesticide container. Moreover, when he was found comatose, his clothes were completely wet and had a garlic odor of pesticide. The concentration of methomyl found in a proximal hair sample (4 ppb) additionally supports the fact that poisoning was due to inhalation and transdermal absorption during the last few days prior to the incident (Tsatsakis et al. 1998a; Kintz 1996).

Evidence exists that short-term exposure to methomyl during spraying may have cardiovascular toxicity, as demonstrated by electocardiographic changes (ECG) and a rise in lactate dehydrogenase (LDH) activity (Saiyed et al. 1992). However, no ECG abnormalities were detected during the hospitalization of the patient and the serum LDH level was not elevated.

The patient's symptoms of hypotonia and bradycardia first appeared nearly six days before the accident and while the patient had started spraying in the greenhouse. The practitioner who examined him attributed these symptoms to anxiety and prescribed bromazepam. As a result, every time the patient was exposed to amounts of a cholinesterase inhibitor agent his muscarinic effects were becoming more intent and were "treated" with bromazepam. This would relieve his symptoms due to the sedative effect of bromazepam on the C.N.S., thus protecting the patient from the cerebral toxic effects of the poison. Recently, a similar case of combined fenthion and bromazepam ingestion was reported (Tsatsakis et al. 1998b). The patient developed the anticipated cholinergic crisis over a period of several hours after ingestion and not shortly after it. It is suggested that the benzodiazepine protective effect is mediated via a cholinergic transmission mechanism and therefore could be used as a potential therapeutic agent in cases of poisoning with organophosphates and carbamate agents (Tsatsakis et al. 1998b).

The concentration of methomyl in blood on admission to the intensive care unit was 1.6 mg/L, followed by a blood cholinesterase activity of 380 U/L (89% inhibition). The inhibition of cholinesterase is attributed to methomyl, since the effect of bromazepam on serum and red cell cholinesterase is considered to be minor (Holmes et al. 1978). Previous reports on fatal cases of ingested methomyl

poisoning present blood methomyl concentrations ranging between 4.8 and 57.0 mg/L (Tsatsakis 1996; Tsatsakis 1998). However, in previously reported similar cases the blood methomyl concentration was at a much lower level (0.57 – 1.4 mg/L) and it is generally implied that a fatal blood level of methomyl would be more than 1 mg/L (Tsatsakis 1996). Taking into consideration these reports, as well as the probable cardiac toxicity of methomyl, one could support the idea that even a blood methomyl concentration of 0.57 mg/L may be lethal (Driskell et al. 1991). Nevertheless, carbamate pesticides are rapidly metabolized and that is mainly because of their easy degradation and thermal instability. In order to estimate the average lethal blood level of methomyl from a fatal case, prompt poison measurements in blood before any detoxification procedure is initiated should be conducted. The methomyl blood levels remained toxic even during the second day after the admission (0.6 mg/dL). This is probably due to the slow reabsorption of methomyl from the tissues back into the blood (Miyazaki et al. 1989). It might also be possible that the skin had not been completely decontaminated and methomyl was still absorbed from the skin, although proper skin washing with the use of detergents was carried out.

Apart from skin washing, the basic treatment also included gastric lavage, activated charcoal and administration of atropine as it is suggested in similar cases (Martinez-Chuecos et al. 1990). No hemoperfusion was initiated although prompt intensive care including a direct hemoperfusion is necessary to affect the recovery of patients with lethal blood levels of methomyl (Miyazaki et al. 1989). No pralidoxime was administered, since it is not clear yet whether it should be used for the treatment of carbamate poisoning or not. It has been reported that in cases of methomyl poisoning, oxime therapy neither contributes to the recovery of the poisoned patients nor leads to exacerbation of the cholinergic symptoms and thus can prove beneficial in cases of unknown or mixed pesticide poisoning (Lifshitz et al. 1994). The same result was noticed in another study, where five of thirteen patients with carbamate poisoning were treated with pralidoxime and showed no adverse outcome (Tsao et al. 1990). In cases of methomyl toxicoses in fowl atropine alone was largely successful, whereas 2-PAM was mostly unsuccessful. The combination at high dosage was less effective than atropine alone and only at low dosage the combination proved to be the most successful (Sholsberg et al. 1997). However, in vitro studies with carbaryl, another carbamate pesticide, showed that the carbamate toxic effects were amplified by oximes (Claire et al. 1992). These findings enhance the necessity to investigate further the results of oxime therapy for severely methomyl-intoxicated patients.

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