CLINICAL AND TOXICOLOGICAL DATA IN FENTHION AND OMETHOATE ACUTE POISONING

Key Words: Fenthion, omethoate, bromazepam, poisoning, toxicology

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ABSTRACT

This study paper reports on two cases of poisoning with the organophosphorus insecticides, fenthion and omethoate. The two victims were admitted in the Intensive Care Unit (ICU) a few hours after ingestion of the two insecticides. They received appropriate treatment for organophosphorous poisoning (gastric lavage,
activated charcoal, atropine and pralidoxime) and supportive care. Both patients survived. Organophosphate blood levels were determined on admission (fenthion 2.9 μg/ml, omethoate 1.6 μg/ml) and during the hospitalisation and proved to be considerably high. Slow elimination rate of the poison already distributed in the body was indicated for both pesticides. The patient with omethoate poisoning remained clinically well (Glasgow Coma Scale : 15) and was discharged three days later. The patient with fenthion poisoning, who had also ingested 30 mg of bromazepam and 720 mg of oxetoron, developed cholinergic crisis six hours after admission and was intubated for 24 days, with concomitant complications.

INTRODUCTION

In Crete, different organophosphorous (OP) agents currently on the market, are increasingly used in land cultivation to increase production and raise crop quality. Intoxication with OP tend to be the commonest way of deliberate self-harm or homicide, accounting for more than 50% of all poisoning cases and almost 45% of fatalities resulting from poisoning in a two year period in Crete (Tsatsakis, Aguridakis, et al., 1996). Other poisons causing fatalities are carbamates and paraquat (Tsatsakis, Tsakalof, et al., 1996; Tsatsakis, Perakis, et al., 1996).
Evaluation of poisoned patients in the emergency department apart from supportive care and treatment includes routine body fluid (blood, gastric contents and urine) sampling for toxicological analysis (Troulakis et al., 1996; Michalodimitrakis et al., 1997).

This report presents the clinical and laboratory data of two cases of acute poisoning by the OP compounds fenthion and omethoate, which are selected on the basis of clinical and toxicological interest and not by any chance representing the very recent poisoning trends in Crete (Michalodimitrakis et al, 1997).

**CASE REPORTS**

**Case 1**

A 63-year old woman was referred to the intensive care unit of the University Hospital of Iraklion from another hospital of Crete, after having ingested approximately 150ml solution of Lebaycid 50EC® containing the extremely toxic organophosphorous compound fenthion as the active ingredient, 12 tablets of Nocetrone (720mg) (containing oxetoron, a drug against migraine) and 20 tablets of Lexotanil (30mg) (containing the benzodiazepine bromazepam), in an attempt to commit suicide. The initial treatment at the referring hospital included gastric lavage, administration of activated charcoal and bolus atropine, as required. Following her admission in the ICU the patient presented...
skeletal muscle weakness, somnolence, confusion and miosis. She was haemodynamically stable, with blood pressure 140/70 mmHg, heart rate 70 beats/min and normal heart rhythm, a small degree of hypoxaemia (Po₂ : 75 on air, Pco₂ : 40) and a normal chest-X-ray. Her temperature was normal. An arterial and a central venous line were introduced and dopamine infusion in diuretic dose was started. A blood sample was drawn for toxicological analysis, which showed a great decrease in the cholinesterase levels (90% inhibition from reference values) (Tsatsakis, Aguridakis, et al., 1996).

Six hours later the patient developed abdominal pain, diarrhoea, vomiting and attacks of bradycardia and lacrimation, whereas the nicotinic receptors were clearly affected, according to the electromyogram findings. Atropine infusion (0.5 mg/h) and pralidoxime treatment (Contrathion®, 500 mg x 4) was started. On the second day the patient was intubated due to respiratory failure. Tracheotomy was performed on day 9. The patient remained on mechanical ventilation for a total of 24 days.

Complications during the hospitalisation of the above patient in the ICU included: 1) A lower respiratory tract infection caused by Pseudomonas aeruginosa and Acinetobacter spp > 10⁷ colonies/ml in bronchoalveolar lavage (BAL), which was complicated by septicaemia and septic shock. This was successfully treated with antibiotics
(imipenem and netilmicin), 2) Right pneumothorax during mechanical ventilation, 3) Hepatic dysfunction, with increased levels of ALT and AST, attributed to the parenteral nutrition and the drugs given, which was overcome without further problems. 4) Cholelithiasis without signs of cholecystitis was also diagnosed, 5) Depression, treated with psychological support and medication.

The weaning from the mechanical ventilator began on day 16 and 8 days later the patient regained a satisfactory spontaneous respiratory function. She was discharged from the ICU 26 days after admission, in good general condition.

Case 2

A 30-year old patient was admitted to the ICU because of accidental ingestion of a solution of the organophosphorous pesticide Folimate® which contained 51% omethoate as the active ingredient and penconazole. The patient had prepared coffee using 100 ml of liquid taken from a container containing 25 ml Folimate diluted in 16 L of water. The other substance, penconazole (Topaz*) is relatively non-toxic. The patient was transported to the ICU 6 hours after ingestion.

On admission, the patient was fully alert (GCS 15) but slightly bradycardic (heart rate : 55 bpm). Following administration of 0.5 mg atropine, the blood pressure was 120/70 mmHg and his breathing rate 15 breaths /min. His muscle strength was normal. The patient didn't
present bronchorrhea or sielorrhea and declared that he was feeling well.

The treatment included the following measures: 1) Gastric lavage with activated charcoal, 2) atropine (1 mg/h for 72 h) 3) Pralidoxime (1 gr bolus slowly and 300mg every hour for 24 hours).

The first result of the toxicological analysis showed that the concentration of omethoate in the blood was 1.6 μg/ml, a value that was considered very high and life threatening, taking into account the time elapsed from ingestion. Twelve hours post ingestion the omethoate blood concentration fell to 0.68 μg/ml. The initial value of cholinesterase was 900 U/l and after 6 hours it rose to 1400 U/l (reference values 3500-8500 U/l). The patient was discharged from the ICU 3 days later in a good general condition. He was never intubated during his stay in the ICU.

MATERIALS AND METHODS

Instrumentation

Equipment used for toxicological analysis included a gas-chromatographic system (GC), Carlo Erba 6000 Vega with nitrogen-phosphorous detector (NPD) and a Spectra Physics integrator (SP4276). The GC analysis conditions for fenthion were as follows: capillary column DB-5, 30 m x 0.53 mm, film thickness 1.5 μm (J&W), He flow rate...
at 6 ml/min, temperature program from 180°C/3 min to 240 °C at a rate of 5°C/min.

The HPLC system used was a Spectra-Physics Model SP8810 solvent delivery system equipped with a Model 7125 Syringe Loading Sample Injector supplied with a 10 μl sample loop and a Model SP 8450 Variable UV-VIS Detector set at 254 nm. A reverse phase HPLC procedure for omethoate was carried out on a Silica 5u S/N, 25 cm, i.d. 4.6 mm column with acetonitrile : water (7.5% v/v) as the mobile phase, eluted at a flow rate of 0.5 ml/min (or a S10 ODS2, 25 cm, i.d. 4.6 mm (Spherisorb) with acetonitrile : water (70:30 v/v) as the mobile phase). The chromatograms were recorded and integrated using a Hewlett-Packard 3390A integrating recorder.

Toxicological analysis

The blood samples were collected from the poisoned patients in the ICU. General toxicological screening included head space GC for volatiles, immunoassay techniques (Abbott TDx and ADx) for acidic, basic and amphoteric drugs and colour tests for chemicals. Cholinesterase levels in blood were also monitored. Liquid-liquid extraction was used to clean up the samples. A 10 ml aliquot of the blood samples was extracted twice with 15 ml of dichloromethane. The organic phase was evaporated to dryness under a stream of nitrogen at
40°C and the residue was reconstituted in 0.2 ml of methanol. Diazinon was used as an internal standard.

RESULTS AND DISCUSSION

The recovery was determined using blood spiked with fenthion (2.5 μg/ml) and a standard curve was obtained using six standard solutions of fenthion at concentrations of 0, 1, 2, 3, 5, 7 μg/ml with diazinon as the internal standard. The recovery was determined to be about 85%. The retention time for fenthion was 17.2 min and for diazinon was 12.9 min. Recovery for omethoate was determined using spiked blood (3 μg/ml) and the standard curve was obtained using five standard solutions of omethoate at concentrations of 0, 0.5, 1, 3, 5 μg/ml. The retention time (Rt) of omethoate was 7.4 min in HPLC, under the aforementioned conditions.

Despite the poison high blood-levels both patients survived. Both patients remained in the intensive care unit and were treated with general detoxification measures such as gastric lavage and activated charcoal, received non-specific (atropine) and specific (pralidoxime) antidotes and general supportive care.

From the kinetics of the two poisons, depicted in the Figures 1 and 2, it is apparent that fenthion which is more lipophilic than omethoate
FENTHION AND OMETHOATE ACUTE POISONING

**FIGURE 1**
Fenthion levels in blood of the patient versus time

**FIGURE 2**
Omethoate levels in the blood of the patient versus time
exhibits two peaks in its blood levels during the ICU hospitalisation of the patient. This phenomenon is also known as redistribution and is attributed to the poisons re-entry in the blood stream from its reservoir in fat tissue.

Omethoate has a relatively high LD₅₀ of 30 mg/kg (p.o. ingestion, rats). Yet, in vitro research has indicated minimal toxicity when the pesticide is distributed solely, despite its irreversible binding and subsequent permanent inactivation of Ach-E, whilst in mixture with other pesticides omethoate enhances their lethal action (Dolara et al, 1992).

Even though our patient had ingested a total dose exceeding omethoate LD₅₀ he remained clinically and subjectively in a good, healthy state. His Ach-E levels dropped to 30% of the lowest reference value, but returned to near reference levels in two days.

Rapid elimination of omethoate compared to fenthion was observed which is believed to be due to the different quantities ingested and the different characteristics and biochemical behaviour of the two poisons. Similar was the clinical course of the two patients with complete recovery of the omethoate poisoned patient in three days.

The observations regarding the omethoate poisoning case tend to be attributed to omethoate’s relative hydrophilic character which facilitates its absorption from gastrointestinal tract. Furthermore it is
TABLE 1
Clinical Picture of the Presented Patients

<table>
<thead>
<tr>
<th>Case No</th>
<th>Sex/ Age</th>
<th>Poison</th>
<th>Clinical condition on admission</th>
<th>Poison blood levels On admission</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/63</td>
<td>fethion</td>
<td>GCS:12. Pupils: 3mm-reactive to light. BP:120/70 mmHg HR:70 bpm. ABGs: moderate hypoxia.</td>
<td>2.9 µg/ml</td>
<td>Survival</td>
</tr>
<tr>
<td>2</td>
<td>M/30</td>
<td>omethoate</td>
<td>GCS:15. HR:55-62 bpm. BP:120/70 mmHg No cholinergic signs.</td>
<td>1.6 µg/ml</td>
<td>Survival</td>
</tr>
</tbody>
</table>

possible that other endogenous mechanisms, such as rapid metabolism and excretion minimised the toxic effect and contributed to such a rapid positive outcome.

Neither patient developed the intermediate syndrome of organophosphate poisoning, which is quite common in fenthion poisoning cases (Tsatsakis, Aguridakis et al., 1996; De Bleecker et al., 1993; De Bleecker et al., 1992). Furthermore neither patient has developed delayed neurotoxicity so far (Stamboulis et al., 1991; Lott, 1987). Ach-E of the fenthion poisoned patient remained in levels < 30 % of the lowest reference value for a long period of time and only after her eleventh hospitalisation day did it show any tendency to return to normal
values. During ICU hospitalisation, the patient was supported with mechanical ventilation for more than thirteen days and successfully came over various complications: 1) Infection of the lower respiratory track (pneumonia) 2) Septicaemia from *Pseudomonas Aeruginosa* and *Acinetobacter* (isolated both in sputum and blood cultures) 3) Pneumothorax 4) Hepatic dysfunction 6) depressive disorder (ICU-Related Psychosis), which needed specialist care.

She developed the anticipated cholinergic crisis over a period of several hours after ingestion and not shortly after it. This phenomenon was attributed to bromazepam simultaneous ingestion and its well recognised sedative effect on the CNS, thus protecting the patient from the poison's cerebral toxic effects. Bromazepam is a benzodiazepine of intermediate duration of action, widely used in the symptomatic treatment of anxiety disorders and stress. Currently several workers have studied diazepam (as a representative of the benzodiazepine family) for a potential protective effect in poisoning cases with warfare OP chemical agents (Bokonjic et al., 1991; Shih, 1991, Shih, Koviak, et al., 1991). They demonstrated that benzodiazepines administered before exposure to OP agents had a protective effect both in the periphery and centrally, mainly against convulsions caused by OP action on the CNS. This protective effect is antagonised by flumazenil (Anexate®) (a competitive antagonist of the benzodiazepines in the
CNS) thus confirming the role of the GABA-ergic system in the pathogenesis of the early toxic effects of OP poisoning. It is suggested that the benzodiazepine protective effect is mediated via a cholinergic transmission mechanism, and more specifically by means of Ach release inhibition in the pre-synaptic neurone.

REFERENCES


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