Experience with the intensive care management of organophosphate insecticide poisoning

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Summary
During the 5-year period 1975-1979, 41 out of a total of 157 patients treated for 'organophosphate poisoning' (26%) were admitted to intensive care units. Treatment comprised atropine (0.02-0.04 mg/kg every 15-30 minutes or 0.02 - 0.08 mg/kg/h by continuous intravenous infusion), intermittent mandatory ventilation (IMV) with continuous positive airways pressure (CPAP) where indicated, and general supportive measures including adjustment of electrolyte, fluid and acid-base balance. Oxime-type cholinesterase reactivators were administered to 10 patients. Serum cholinesterase (S-ChE) and erythrocyte acetylcholinesterase (E-AChE) activities were monitored continuously. Despite intensive therapy, 5 patients (12%) died.

IMV and CPAP proved to be a near-ideal method of mechanical ventilation. Atropine administered by continuous infusion was found to be superior to intermittent administration during the acute phase, while oral administration of atropine proved adequate thereafter. Oxime-type reactivators were not found to be of any significant value. Clinical recovery (the point at which atropine could safely be discontinued) generally correlated with a recovery of E-AChE activity to 30% or more of normal. Sudden deterioration due to possible 'endogenous re-intoxication' was observed in some patients days after the initial exposure to an organophosphate insecticide.

Of the 50,000 known organophosphate compounds, approximately three dozen have come into use as pesticides. Organophosphate insecticides (OPI) are highly toxic to mammals and present a serious threat as far as human intoxication is concerned. The high mortality ascribed to OPI poisoning is due to delayed diagnosis and improper treatment. Death may occur in 86% of patients with acute OPI poisoning, and prompt diagnosis and specialized treatment are essential in these cases.

In this article we describe our experience with the management of the more serious cases in an intensive care environment.

Patients and methods
A retrospective study was conducted on patients with OPI poisoning admitted to the two multidisciplinary intensive care units in the Bloemfontein teaching hospitals during the 5-year period 1975-1979.

The diagnosis was based upon the history, clinical manifestations and measurement of erythrocyte acetylcholinesterase (E-AChE) and serum cholinesterase (S-ChE) activities by a modification of the method described by Ellman et al. E-AChE and S-ChE activities were determined on admission and daily thereafter until discharge. Normal values for the local laboratory are: S-ChE 2000-3000 mU/ml serum and E-AChE 2000-3000 mU/μmol haemoglobin. 'Normal', in this publication, always refers to the lower value.

Active treatment commenced as soon as the diagnosis of OPI poisoning was suspected. This consisted of elimination of the source of intoxication, oxygen therapy with or without endotracheal intubation and mechanical ventilation, repeated administration of atropine 0.02-0.04 mg/kg and gastric lavage.

Conventional doses of oxime-type cholinesterase reactivators (pralidoxime or obidoxime) were administered to the first 7 patients only. In addition, 3 patients had received reactivators before admission.

The patients in the series were selected for intensive treatment on the basis of severity of clinical signs. The indications for endotracheal intubation were: (i) excessive secretions; (ii) depressed level of consciousness of a degree which compromised the airway; and (iii) application of mechanical ventilation. Tracheostomy was performed when mechanical support was still necessary after a week.

Intermittent mandatory ventilation (IMV) with continuous positive airways pressure (CPAP) was applied when indicated. Indications for mechanical support included: (i) apnoea or obvious hypventilation; (ii) respiratory acidosis with inability to maintain the pH above 7.35 or a PaCO2 level below 50-55 torr; (iii) inspiratory force below -20 to 25 cm H2O; (iv) vital capacity below 15 ml/kg; and (v) inability to maintain stable vital signs, and acceptable blood gas and acid-base status on spontaneous breathing with CPAP. The IMV-CPAP technique permitted the patients to breathe spontaneously with additional mechanical support. Mechanical support was gradually withdrawn as ventilatory ability improved. Patients were extubated once they could maintain satisfactory vital signs and acceptable blood gas and acid-base values on minimal CPAP without mechanical support.

Atropine was administered intravenously in a dosage ranging from 0.02 to 0.04 mg/kg every 15-30 minutes until satisfactory clinical control of hypersecretions had been established. Later in the series a continuous infusion of undiluted atropine (0.02-0.08 mg/kg/h) was used.

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mg/kg/h), was employed. Since atropine is light-sensitive, the containers were protected from light. Subsequent atropine dosage was titrated to control tracheobronchial secretions and salivation while guarding against overt atropine toxicity. Little attention was paid to heart rate, intestinal motility and pupil size as indices for gauging atropine dosage.

Clinical recovery was taken as the point in time when atropine administration could be discontinued without recurrence of symptoms and signs of intoxication.

Blood gas, acid-base and electrolyte determinations were performed at least once daily and abnormalities corrected as necessary. Psychiatric consultation and rehabilitation, when indicated, commenced as soon as possible.

Results

During the study period 41 patients out of a total of 157 treated for ‘organophosphate poisoning’ (26%) were admitted for intensive care. Their ages ranged from 2 to 63 years. Suicide had been attempted in 18 cases (44%), while accidental ingestion occurred in 21 cases (51%). One patient suffered intoxication from smoking a home-made cigarette made from organophosphate-contaminated paper. Another patient (a nurse) had injected herself intravenously with OPI. Oxamylmon methyl (Metasystox) was the agent responsible in 28 cases (68%). Often the exact OPI could not be identified. No known cases of carbamate poisoning were identified.

There was no difference in the clinical course, time to clinical recovery, and normalization of cholinesterase activity in patients who received cholinesterase reactivators and those who did not. Five of the 41 patients (12%) in this series died.

Often the lowest E-AChE and S-ChE activities were reached only 24-48 hours after initial exposure to the OPI. S-ChE activity recovered earlier than E-AChE activity in the majority of cases. Plotted against time, the cholinesterase activity in a typical case is illustrated in Fig. 1. Generally, clinical recovery correlated with recovery of E-AChE activity, but no correlation with S-ChE could be demonstrated. When E-AChE activity had returned to 30% or more of normal, atropine could usually be discontinued.

Daily atropine dosage varied considerably between individuals. The minimum daily dosage was 168 mg and the maximum 1 124 mg. Atropine could safely be discontinued after 10,6 ± 7,6 days (mean ± SD). Ventilatory support was necessary in 17 patients (41%) and was continued for 6,6 ± 4,2 days. With 1 exception, patients who required ventilatory support all had E-AChE activities of < 30% of the normal. Several patients with E-AChE activities of < 5% of the normal exhibited satisfactory spontaneous ventilatory ability. Endotracheal intubation was adequate in 11 of the 17 patients, but tracheostomy was required in the remaining 6. The condition of patients with E-AChE activities < 30%, and especially < 5%, of the normal, who were in all respects satisfactorily controlled, sometimes deteriorated suddenly and unexpectedly, necessitating intubation and ventilatory assistance. Troublesome complications included prolonged ileus, aspiration pneumonitis, sudden deterioration in spontaneous breathing ability, and delirium. Two cases were of special interest.

Case 1. A 21-year-old female nurse, who had injected herself with 2 ml fenithion (Lebaycid) intravenously, presented with abdominal cramps and diarrhoea, but showed no serious clinical manifestations of toxicity. Cholinesterase activities in her case are depicted in Fig. 2. E-AChE activity only reached 30% of normal after 33 days. Atropine was initially administered intravenously, and later orally.

Fig. 1. A typical case — a 63-year-old woman had ingested about 50 ml Metasystox 4 hours before admission. Intubation and ventilation were required. Cholinesterase reactivator was not administered. The graph depicts E-AChE (S-ChE) activities plotted against time (A = atropine discontinued (i.e. clinical recovery)).

Case 2. An obese 33-year-old man suffering from alcoholism, had ingested Metasystox 75 ml together with ethanol (100 mg/100 ml blood) about 4 hours before admission. He presented with the typical clinical picture of OPI intoxication, but had normal muscle power. Three days after admission acute delirium tremens developed. Sedative dosage required to control the muscular manifestations of toxicity. Cholinesterase activities in her case are depicted in Fig. 3. E-AChE activity only reached 30% of normal after 33 days. Atropine was initially administered intravenously, and later orally.

Fig. 2. Case 1 (see text). E-AChE and S-ChE activities plotted against time.

Fig. 3. Case 2 (see text). E-AChE and S-ChE activities plotted against time (A = endotracheal intubation and mandatory ventilation; B = progressive skeletal muscle weakness and reappearance of ‘Metasystox odour’ in exhaled air; C = tracheostomy performed; D = mandatory ventilation discontinued; E = extubation; F = atropine discontinued (i.e. clinical recovery)).
delirium was so heavy that respiratory function became compromised, and endotracheal intubation with IMV had to be used. Fig. 3 shows that E-AChE activity remained relatively stable, between 30% and 40% of normal for the first week, but that it dropped progressively thereafter. This fall in E-AChE activity was accompanied by a decrease in muscle power and ventilatory ability. At the same time the typical smell associated with Metasystox ingestion could again be detected at the expiratory port of the ventilator. A secondary increase in E-AChE activity was accompanied by clinical recovery after 20 days.

**Discussion**

OPI intoxication has become a serious health hazard in the RSA, as it involves the widespread use of these insecticides in horticulture and agriculture and because they are freely available over the counter. Although OPI intoxication is a notifiable disease in the RSA, it can reasonably be asserted that the actual number of cases far exceeds the number of notifications.7 OPI or their metabolites inhibit cholinesterase activity through the formation of stable phosphorylated enzyme complexes. Unhydrolysed acetylcholine accumulates in the central nervous system, as well as autonomic symaphtics, exocrine glands and motor end-plates. The resulting clinical picture is due to excessive continued action of acetylcholine on muscarinic and nicotinic receptors. A mixture of muscarinic and nicotinic manifestations usually coexists. Nicotinic manifestations include increased or decreased muscle power and skeletal muscle fasciculations (motor end-plate involvement). Muscarinic manifestations include excessive salivation and tracheobronchial secretions (exocrine gland stimulation), miosis and diarrhea (smooth muscle involvement). Miosis and muscle fasciculations are valuable signs in the diagnosis, but are not always present.

The cardiovascular manifestations encountered included hypertension, sinus tachycardia (nicotinic effects on the adrenal medulla and sympathetic ganglia), as well as hypotension and sinus bradycardia (muscarinic effects).

The central nervous system effects encountered included stupor, coma and tonic-clonic convulsions. Delirium could be ascribed to the central effects of the OPI, atropine intoxication or delirium tremens. Local experience militates against the inclusion of oxime-type cholinesterase reactivators in the treatment of OPI poisoning.8 We could detect no beneficial effects resulting from the use of these compounds in our series. Also, oxime-type reactivators are contraindicated in carbamate poisoning.9

Endotracheal intubation via the nasal or oral route by means of a low-pressure, high-volume PVC endotracheal tube proved adequate in the majority of cases, thus obviating the known dangers of tracheostomy. Where nursing standards are suboptimal, early tracheostomy should be seriously considered owing to the dangers of prolonged endotracheal intubation under such circumstances. Meticulous attention to proper oxygenation and ventilation is vital as long as high doses of atropine are prescribed, because of the danger of ventilricular fibrillation.10 IMV with CPAP proved to be a near-ideal method of mechanical ventilation in these cases. Mechanical support could be titrated against the patient’s ventilatory ability. The CPAP level could be titrated against the degree of gas exchange failure present and adequate lung volumes maintained. Maintenance of the patient’s spontaneous ventilatory rhythm acted as an additional safety measure, made weaning simple and added to patient compliance with the ventilator.

E-AChE activity appears to be a reasonable index of the degree of clinical recovery in most instances.11 The return of E-AChE activity to 30% of the normal correlated with clinical recovery in this series. Measurement of E-AChE activity still does not necessarily give an absolute measure of the acetylcholinesterase activity at the motor end-plate receptors, as illustrated in case 1. This is also exemplified by the fact that patients with E-AChE levels below 5% of normal did not always need mechanical ventilatory support, and that unexpected clinical deterioration could occur despite a reasonable level of E-AChE activity.

S-ChE activity, on the other hand, appears to serve as a sensitive index of the degree of exposure to OPI and other cholinesterase inhibitors,12 but does not necessarily correlate with the degree of clinical involvement.4 Our experience and that of others is that massive doses of atropine can and must be employed as soon as poisoning by OPI is diagnosed and hypoxia has been relieved.

Atropine appears to have a relatively short pharmacodynamic half-life in cases of OPI poisoning and should therefore be administered every 30-60 minutes. A dosage interval in excess of 2 hours is undesirable and dangerous. Our impression is that smooth control of the clinical manifestations is best achieved by a steady, continuous infusion of atropine in a dosage of 0.02-0.08 mg/kg/h, depending on the degree and stage of intoxication. In many cases atropine administration has to be continued for long periods. Here continuous atropine infusion by means of an infusion controller saves time and allows close monitoring and control of the patient. Atropine is well absorbed after oral administration and may be used in this manner when intravenous administration becomes unnecessary or impractical. In our experience, atropine administration can be safely discontinued when E-AChE activities reach 700-750 mU/μmol Hb (normal local values 2000-3000 mU/μmol Hb).

Prolonged icterus sometimes resulted from the atropine dosage required for the control of secretions. In such cases intravenous nutrition became necessary.

Case 2 suggests that 'endogenous OPI re-intoxication' is possible. The OPI compounds are highly lipid-soluble. The patient lost a considerable amount of Iatr during the first week in the intensive care unit. Fat breakdown with release of dissolved OPI may explain the reappearance of the typical odour on his breath and the secondary drop in E-AChE activity. Hayes et al.,9 described 2 patients who were readmitted for relapses of OPI intoxication, one 3 weeks and the other 1 month after initial discharge. These relapses can possibly be ascribed to the same mechanism.

In conclusion, OPI intoxication is usually a serious condition which demands due respect from all concerned. A high index of suspicion of OPI intoxication should be maintained in clinical practice. The degree of intoxication may vary considerably between individuals. The clinical course and management present many pitfalls, and continuous and prolonged intensive care may be necessary.

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**REFERENCES**


