Poisoning by organophosphorus insecticides and sensory neuropathy

Angelo Moretto, Marcello Lotti

Abstract

Objectives—Poisoning by organophosphorus insecticides causes cholinergic toxicity. Organophosphate induced delayed polyneuropathy (OPIDP) is a sensory-motor distal axonopathy which usually occurs after ingestion of large doses of certain organophosphate insecticides and has so far only been reported in patients with preceding cholinergic toxicity. Surprisingly, it was recently reported by other authors that an exclusively sensory neuropathy developed in eight patients after repeated unquantified exposures to chlorpyrifos, which did not cause clear-cut cholinergic toxicity. The objective was to assess whether an exclusively sensory neuropathy develops in patients severely poisoned by various OPs.

Methods—Toxicological studies and electrophysiological measurements were performed in peripheral motor and sensory nerves in 11 patients after acute organophosphate poisoning among which two subjects were poisoned with chlorpyrifos. Exclusively sensory neuropathy was never seen after either single or repeated acute organophosphate poisoning. A mild sensory component was associated with a severe motor component in two of the three cases of OPIDP, the other was an exclusively motor polyneuropathy.

Results—Three patients developed OPIDP, including one poisoned by chlorpyrifos. Exclusively sensory neuropathy was never seen after either single or repeated acute organophosphate poisoning. A mild sensory component was associated with a severe motor component in two of the three cases of OPIDP, the other was an exclusively motor polyneuropathy.

Conclusion—A sensory-motor polyneuropathy caused by organophosphate insecticides might occur after a severe poisoning and the sensory component, if present, is milder than the motor one. Bearing in mind the toxicological characteristics of these organophosphate insecticides, other causes should be sought for sensory peripheral neuropathies in patients who did not display severe cholinergic toxicity a few weeks before the onset of symptoms and signs.

Keywords: organophosphorus insecticide poisoning; sensory neuropathy; delayed polyneuropathy

Several organophosphorus esters are used as insecticides because they inhibit the acetylcholinesterase (AChE) of insects.1 The same mechanism accounts for acute toxicity in humans and is characterised by signs of cholinergic overstimulation.2 In addition, certain organophosphates may cause a distal, sensory-motor, central-peripheral axonopathy known as organophosphate induced delayed polyneuropathy (OPIDP).3 4

The toxicological characteristics of organophosphates currently in use as insecticides have been assessed in animals.1 These organophosphates are more potent inhibitors of AChE than of neuropathy target esterase (NTE), which is thought to be the target for OPIDP.4 57 Consequently, OPIDP was found both in hens (the animal of choice for OPIDP studies) and humans only at doses exceeding those which cause cholinergic toxicity.1 6 7 9 9 9

However, it has been reported that the development of an exclusively sensory neuropathy was associated in eight patients with repeated low level exposures to the organophosphate insecticide chlorpyrifos (O,O-diethyl O-3,5,6-trichloro-2-pyridylphosphorothioate).28 No or mild symptoms or signs compatible with cholinergic overstimulation were reported in these patients. Possible explanations for this unexpected finding might be that sensory neuropathies in humans exposed to organophosphate insecticides have been overlooked, that animal testing is not predictive, or that chlorpyrifos itself represents an exception. Therefore, we evaluated peripheral nerve sensory function in 11 patients after acute poisoning by various organophosphates, including two patients poisoned by chlorpyrifos. Three patients developed OPIDP and in two of them a sensory component was found.

Methods

Patients underwent extensive neurological examination on several occasions. The examination of the peripheral nervous system included assessment of gait, deep tendon reflexes, muscle strength, and vibration, pin, light touch, and thermal sensitivities. Plasma butyryl cholinesterase (BuChE) was measured with commercial kits. Red blood cell, AChE, and lymphocyte neuropathy target esterase (L-NTE) were determined according to Ellman et al11 and to Bertoncin et al,12 respectively. Blood concentrations of organophosphates were measured by gas chromatography-mass spectroscopy. Electrophysiological studies were performed at controlled temperature as described by Kimura,13 two to six weeks after poisoning on one or more occasions. To assess conduction velocities, surface electrodes were used to stimulate the nerves whereas bipolar concentric needle and surface electrodes were used to record muscle and sensory potentials respectively. The following nerves were assessed: ulnar (stimulation below the elbow and at the wrist, recording at the abductor digiti
minimi muscle), median (stimulation at the wrist and at the elbow, recording at the abductor pollicis brevis muscle; sensory: stimulation at the third finger, recording at the wrist), common peroneal (stimulation below the head of the fibula and at the ankle, recording at the extensor digitorum brevis muscle), sural (anterior tibial stimulation 14 cm proximally to the recording site below the lateral malleolus).

Standard concentric needles were used for the EMG examination. The abductor pollicis brevis and the extensor digitorum brevis muscles were assessed; when data were abnormal, more proximal muscles were studied.

Case presentation

Table 1 shows the enzyme inhibition and organophosphate concentrations in blood of poisoned patients. Table 2 shows a summary of the electrophysiological studies in patients with OPIDP.

**GROUP 1: POISONING BY ORGANOPHOSPHATES NOT KNOWN TO CAUSE OPIDP WHICH DID NOT RESULT IN CLINICAL OR ELECTROPHYSIOLOGICAL SIGNS OF NEUROPATHY**

**Case 1**

A 50 year old man attempted suicide by ingesting a commercial formulation of methidathion (S,3,3-dihydro-5-methoxy-2-oxo-1,3,4-thiadiazol-3-ylmethyl O,O-dimethyl phosphorothioate). The estimated dose was 6 g. He was comatose for four days and was treated with pralidoxime (up to 1 g/day intravenously for nine days), atropine (up to 12 mg/day intravenously for 15 days), and artificial ventilation (for 15 days). This case has been partly described previously.14

**Case 2**

An 82 year old man attempted suicide by ingesting an unknown amount of a commercial formulation of azinphos-methyl (S,3,3,4-dihydro-4-oxo-1,2,3-benzotrazin-3-ylmethyl O,O-dimethyl phosphorothioate). He was comatose for five days and was treated with pralidoxime (400 mg intravenously at admission), atropine (up to 30 mg/day intravenously for 15 days), and artificial ventilation (for nine days).

**GROUP 2: POISONING BY ORGANOPHOSPHATES KNOWN TO CAUSE OPIDP WHICH DID NOT RESULT IN CLINICAL OR ELECTROPHYSIOLOGICAL SIGNS OF NEUROPATHY**

**Case 3**

A 39 year old woman attempted suicide by ingesting a commercial formulation of coumaphos (O-3-chloro-4-methyl-2-oxo-2H-chromen-7-yl O,O-diethyl phosphorothioate). The estimated dose was 4 g. She was comatose for two days and was treated with pralidoxime (up to 2.5 g/day intravenously for seven days), atropine (up to 22 mg/day intravenously, for eight days), and artificial ventilation (for nine days).

**Case 4**

A 32 year old man was repeatedly administered unknown amounts of organophosphate(s) over a five month period for homicidal purposes, presumably always coumaphos because this chemical was found in his meals (and in his blood) at the time of the last episode. The first poisoning was mild and short lasting (few hours). A second, more severe episode occurred some days later. He was comatose for two days and was treated with pralidoxime (up to 2.5 g/day intravenously for seven days), atropine (up to 22 mg/day intravenously, for eight days), and artificial ventilation (for nine days). Eventually, coumaphos was detected in the parmesan cheese brought to him from outside the hospital.

**Table 1  Toxological data from patients poisoned with organophosphates**

<table>
<thead>
<tr>
<th>Case No (compound)</th>
<th>Time after poisoning</th>
<th>Red blood cell AChE (mU/l) (normal 4.9-11.7)</th>
<th>Plasma BuChE (mU/l) (normal 2.4-8.3)</th>
<th>Lymphocyte-NTE (mU/g protein) (normal 6.5-16.5)</th>
<th>Blood concentration (µmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Methidathion)</td>
<td>12 h</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>10.7†</td>
<td>5.6*</td>
</tr>
<tr>
<td></td>
<td>3 days</td>
<td>0</td>
<td>0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>2 (Azinphos-methyl)</td>
<td>12 h</td>
<td>0</td>
<td>0</td>
<td>8.2‡</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td>2 days</td>
<td>0</td>
<td>0</td>
<td>8.6‡</td>
<td>ND</td>
</tr>
<tr>
<td>3 (Coumaphos)</td>
<td>10 h</td>
<td>0</td>
<td>0</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>4 (Coumaphos)</td>
<td>3 h‡</td>
<td>&lt;0.5</td>
<td>0</td>
<td>0.06</td>
<td></td>
</tr>
<tr>
<td>5 (Coumaphos)</td>
<td>2 h</td>
<td>2.0</td>
<td>&lt;0.5</td>
<td>12.5</td>
<td>ND</td>
</tr>
<tr>
<td>6 (Chlorpyrifos)</td>
<td>15 h</td>
<td>0</td>
<td>&lt;0.5</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>7 (Isofenphos)</td>
<td>10 h</td>
<td>0</td>
<td>0</td>
<td>9.5</td>
<td>ND</td>
</tr>
<tr>
<td>8 (Trichlorfon)</td>
<td>4 h</td>
<td>ND</td>
<td>0</td>
<td>5.9§</td>
<td>ND</td>
</tr>
<tr>
<td>9 (Chlorpyrifos)</td>
<td>24 h</td>
<td>3.6</td>
<td>&lt;0.5</td>
<td>5.9**</td>
<td>0.7†</td>
</tr>
<tr>
<td>10 (Methamidophos)</td>
<td>8 h</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>1.0††</td>
<td>27.0*</td>
</tr>
<tr>
<td>11 (Isofenphos + phoxim)</td>
<td>3 h</td>
<td>&lt;0.5</td>
<td>&lt;0.5</td>
<td>ND</td>
<td>10.1‡‡</td>
</tr>
</tbody>
</table>

* Half life of about 10 hours. † Within normal range also at later measurements. ‡ Refers to the last episode. § Within normal values on day 3 (10.0 mU/g protein). ¶ Half life of about 2 days, but the chemical was detected up to 10 days after poisoning. ** Within normal values on day 45 (8.2 mU/g protein). †† Within normal values on day 9 (12.5 mU/g protein). ‡‡ ISOfenphos. §§ Phoxim. ND = not done. AChE = acetyl cholinesterase; BuChE = butyryl cholinesterase; NTE = neuropathy target esterase.
Organophosphates and sensory neuropathy

Table 2

<table>
<thead>
<tr>
<th>Case No</th>
<th>Compound</th>
<th>Day after poisoning</th>
<th>Nerve*</th>
<th>CV (m/s)</th>
<th>Motor*</th>
<th>CMAP (mV)</th>
<th>Sensory*</th>
<th>Nerve*</th>
<th>CV (m/s)</th>
<th>SAP (µV)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Chlorpyrifos</td>
<td>24</td>
<td>Common peroneal</td>
<td>50</td>
<td></td>
<td>15</td>
<td>Ulnar</td>
<td>55-60</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ulnar</td>
<td>41-44</td>
<td></td>
<td>8†</td>
<td>Ulnar</td>
<td>48-52</td>
<td>12†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Methamidophos</td>
<td>10</td>
<td>Common peroneal</td>
<td>47</td>
<td></td>
<td>8</td>
<td>Ulnar</td>
<td>44</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median</td>
<td>40</td>
<td></td>
<td>0.1</td>
<td>Sural</td>
<td>54</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median</td>
<td>54</td>
<td></td>
<td>15</td>
<td>Ulnar</td>
<td>53</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Isophos (poxim)</td>
<td>26</td>
<td>Common peroneal</td>
<td>47</td>
<td></td>
<td>8</td>
<td>Ulnar</td>
<td>44</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Median</td>
<td>54</td>
<td></td>
<td>0.3</td>
<td>Ulnar</td>
<td>55</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Reference values were: motor conduction velocity (CV): common peroneal > 45, ulnar > 50, median > 48; sensory conduction velocity: sural > 48, ulnar > 53, median > 48; compound motor action potential (CMAP): common peroneal > 5, ulnar > 6, median > 7; sensory action potentials (SAP): sural > 6, ulnar > 4, median > 7.
† An increased frequency of polyphasic potentials was found. ‡ Fibrillation potentials were present in distal leg muscles, but not in arm muscles. § Fibrillation potentials were present in both leg and arm distal muscles. ¶ In subsequent electrophysiological studies motor and sensory CVs were not measurable and severe signs of denervation (fibrillation potentials) were found in arm, and especially, leg muscles. ** Signs of denervation (fibrillation potentials) were still present and much less evident in both arm (only distally) and leg muscles. Partial reinnervation took place (scarce interference pattern with high frequency potentials) in arm muscles and to a lesser extent in proximal leg muscles.

Case 5
A 23 year old woman attempted suicide by ingesting an unknown amount of a commercial formulation of a carbamate. She was comatose for 12 hours and was treated with pralidoxime (4 g/day intravenously for two days), atropine (12 mg/day intravenously for three days), and artificial ventilation (for four days).

Case 6
A 78 year old man attempted suicide by ingesting an unknown amount of a commercial formulation of chlorpyrifos. He was comatose for five days and was treated with pralidoxime (up to 12 g/day intravenously for five days) and atropine (up to 2.5 mg/day intravenously for six days). Artificial ventilation was continued for 21 days because of pneumonia for which he was treated with antibiotics for about six weeks.

Case 7
A 80 year old man attempted suicide with self injection (subcutaneously and intramuscularly) of a commercial formulation of isophos (isopropyl O-(ethoxy-N-isopropylamino phosphoryl) salicylate). The estimated dose was 1.5 g. He was comatose for six days and was treated with pralidoxime (up to 1.6 g/day intravenously for 10 days), atropine (up to 12 mg/day intravenously for 10 days), and artificial ventilation (for 10 days). Electrophysiological studies performed on day 16 were normal. He developed severe pneumonia and died on day 32.

Case 8
A 53 year old woman attempted suicide by ingesting a commercial formulation of trichlorfon (dimethyl 2,2,2-trichloro-1-hydroxyethylphosphonate). The estimated dose was 1.6 g. She was treated with pralidoxime (800 mg intravenously on admission) and atropine (up to 2.5 mg/day intravenously for seven days). Assisted ventilation was not necessary.
Electrophysiological data were indicative of a purely motor neuropathy of the lower limbs (table 2). About two months later the clinical and electrophysiological conditions were unchanged (data not shown). The patient died a few weeks later in a car accident.

**Case 11**
A 26 year old man voluntarily ingested a commercial formulation of isofenphos and phoxim (diethoxyphosphinothioiclyximino (phenyl) acetonitrile). Estimated doses were 35 and 9 g respectively. He was treated with atropine (7 mg/day intravenously) and pralidoxime (8 g/day intravenously). Treatment lasted five days with tapering off over the next seven days. Cholinergic signs were detectable only for about one day and artificial ventilation was not needed. The patient was discharged asymptomatic on day 17. A few days later, he complained of lower limb paraesthesia and weakness. Within four days, he developed flaccid tetraplegia. On day 26, electrophysiological data were consistent with severe motor neuropathy (table 2). No sensory alterations were recorded at physical examination. Subsequently, severe motor denervation was evident in his arms and legs lasting for several months along with signs of sural and sensory median nerve damage (data not shown). After 22 months the clinical condition of his arms greatly improved. Partial recovery was also evident in his legs although he developed spastic paraparesis. Electrophysiological studies performed at this time were indicative of some axonal regeneration of peripheral nerves.

**Discussion**
Neuropathy was not expected in patients of group 1, despite severe cholinergic toxicity, because neither methadion nor azinphos-methyl cause OPIDP in hens when tested at or above the LD<sub>50</sub>, and in humans there have been reported. Moreover L-NTE was not inhibited in these cases. High L-NTE inhibition measured soon after exposure is thought to herald the development of OPIDP.

Neuropathy may have been expected in patients of group 2 because the involved organophosphates cause OPIDP in hens and cases were also reported in humans. OPIDP did not develop, likely because of insufficient doses, although the doses were high enough to cause severe cholinergic toxicity. Coumaphos causes OPIDP in hens, but neuropathy was not reported in humans after acute poisoning. Moreover, L-NTE was not inhibited in two of our three patients poisoned with coumaphos (cases 3–5). Chlorpyrifos causes OPIDP both in humans (case 9) and hens, but did not in case 6. The patient poisoned with isophenfos (case 7) showed about 50% L-NTE inhibition soon after dosing but he died on day 32, and OPIDP might have developed after this time. Isophenfos causes OPIDP both in humans and hens as does trichlorfon but patient 8 had a relatively mild poisoning and her L-NTE was not inhibited.

Patients of group 3 (cases 9–11, table 2) developed OPIDP and the inhibition of L-NTE was predictive (cases 9 and 10). Other causes of neuropathy such as diabetes, alcoholism, uraemia, porphyrias, and trauma have been excluded. The sensory component of polyneuropathy in the patient poisoned by chlorpyrifos was mild both when symptoms and signs first appeared and when they fully developed. The patient poisoned with methamidophos displayed a purely motor neuropathy. When electrophysiology was performed during the silent period between poisoning and onset of polyneuropathy, the motor-sensory function was normal. In previously reported cases of OPIDP by methamidophos, some sensory symptoms, but no objective signs, have been recorded. Methamidophos causes OPIDP in hens. In the patient poisoned by isofenphos and phoxim, sensory impairment was not detected at the onset of polyneuropathy and it recovered at later stages, when motor neuropathy was still evident. Phoxim does not cause OPIDP in hens and no cases of human poisoning have been reported.

Quantitative sensory examination was performed in some of the patients reported on by Kaplan et al, although it was not apparently used as a diagnostic criterion. We did not perform a quantitative sensory examination either because there were no sensory symptoms or clinical and electrophysiological signs or because sensitive and complex electrophysiological tests to assess sensory functions in subjects exposed but not poisoned by organophosphates, as suggested recently, does not seem justified in the absence of signs or symptoms.

In summary, the features of the cases reported here and in the medical literature indicate that:

1. OPIDP caused by insecticides is preceded by severe cholinergic toxicity.
2. An exclusively sensory neuropathy does not occur after severe cholinergic poisoning by organophosphates.
3. Mild sensory neuropathy is inconsistently associated with the motor component of OPIDP and is unlikely to be a more sensitive indicator of OPIDP (by comparing cases 6 and 9).

These findings accord with the known toxicological characteristics of chlorpyrifos but contrast with those described in patients exposed to low concentrations of chlorpyrifos.

Toxicological studies showed that commercial organophosphate insecticides have a very low in vitro AChE<sub>L</sub><sup>N</sup> NTE<sub>L</sub> ratio with both human and hen enzymes which correlates well with the corresponding in vivo ratio (acute unprotected LD<sub>50</sub>, single neurotoxic dose) in the hen. (L<sub>50</sub> is the concentration of inhibitor which inhibits 50% of the enzymatic activity in given experimental conditions.) In particular,
the active metabolite of chlorpyrifos, chlorpyrifos-oxon, has an AChE \textgreater \textless\textless\textless NTE \textgreater \textless\textless\textless ratio of 0.07 with human enzymes, which correlates with the corresponding in vitro and in vivo (with chlorpyrifos) ratios in hens.\textsuperscript{21, 30, 37}

Therefore, given the sensitivities of target enzymes, it is unlikely that the threshold of NTE inhibition (about 70\%) can be reached in the absence of severe cholinergic toxicity (which requires 80\%-90\% AChE inhibition), after either single or repeated doses of chlorpyrifos to humans. Moreover, it was shown that hens given repeated small doses of neuropathic organophosphates (not AChE inhibitors) tolerate very high cumulative doses without signs of OPIDP when the dosing schedule is such that rate of NTE reexpression is higher than that of NTE inhibition.\textsuperscript{38}

All but one of the patients of Kaplan et al\textsuperscript{39} developed sensory neuropathy within four weeks from the beginning of a reported low level repeated exposure to chlorpyrifos. Most toxic neuropathies including OPIDP are somewhat delayed. Therefore, to allow time for the development of clinical signs, a critical biochemical/pathophysiological effect in the nervous system of these patients should have been reached after about two weeks of exposure. The pharmacokinetics of chlorpyrifos is long,\textsuperscript{21, 30, 37} as indicated by the lengthy cholinergic symptomatology of our patients (about one and three weeks) associated with long lasting blood concentrations of chlorpyrifos and enzyme inhibition (case 9 and table 1). Therefore it might be assumed that the chemical was present in the nervous system of our patients for at least two and four weeks, respectively. This is consistent with a reported half life of urinary elimination of chlorpyrifos metabolites reported in poisoned subjects corresponding to about 80 hours.\textsuperscript{39} We argue that our patients also had a prolonged (at least two weeks) although declining exposure to chlorpyrifos, which was similar in time to that of the patients of Kaplan et al.\textsuperscript{10} Moreover, our patients' single dose was certainly much higher than the cumulative dose of the patients of Kaplan et al.\textsuperscript{10} If sensory neuropathy was the result of continuous additive toxicity of chlorpyrifos, then a sensory neuropathy in patient 6 and a more severe sensory component of OPIDP in patient 9 should have been found. On the contrary, the first patient did not develop neuropathy and the second had a mainly motor neuropathy with a degree of sensory impairment similar to that detected in the patients of Kaplan et al,\textsuperscript{10} who did not display motor deficits.

We conclude that polyneuropathy may follow a severe poisoning by certain organophosphorus insecticides. In our patients, the sensory component of the polyneuropathy was never an isolated finding and, if present, was mild when compared with the motor deficit. Although sensory neuropathies have been consistently associated in a series of patients with low level repeated exposures to chlorpyrifos, there is little evidence for a causal relation, because the assessment of those exposures was limited and based almost exclusively on medical history.\textsuperscript{10}

Bearing in mind the toxicological characteristics of organophosphate insecticides, other causes should be sought for peripheral neuropathies in patients who did not display severe cholinergic toxicity a few weeks before the onset of the neuropathy.

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