CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.2629487

Available online at: http://www.iajps.com *Research Article*

NEUROPSYCHIATRICAL EVALUATION IN SUBJECTS CHRONICALLY EXPOSED TO ORGANOPHOSPHORUS POISONING

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Article Received: February 2019 **Accepted:** March 2019 **Published:** April 2019

Abstract:

Following acute organophosphorus (OP) poisoning patients complain of numbness without objective sensory abnormalities or other features of OP induced delayed polyneuropathy. The aim of this study was to measure peripheral nerve function after acute exposure to OP.

A cohort study was conducted with age, gender and occupation matched controls. Motor nerve conduction velocity (MNCV), amplitude and area of compound muscle action potential (CMAP), sensory nerve conduction velocity (SNCV), F- waves and electromyography (EMG) on the deltoid and the first dorsal interosseous muscles on the dominant side were performed, following acute OP poisoning. All neurophysiological assessments except EMG were performed on the controls.

Assessments were performed on the day of discharge from the hospital (the first assessment) and six weeks (the second assessment) after the exposure. The controls were assessed only once. There were 70 patients (50 males) and 70 controls. Fifty-three patients attended for the second assessment.

In the first assessment MNCV of all the motor nerves examined, CMAP amplitude and SNCV of ulnar nerve, median and ulnar F-wave occurrence in the patients were significantly reduced compared to the controls.

In the second assessment significant reduction was found in SNCV of both sensory nerves examined, MNCV of ulnar nerve, CMAP amplitude of common peroneal nerve, F-wave occurrence of median and ulnar nerves. No abnormalities were detected in the patients when compared to the standard cut-off values of nerve conduction studies except F-wave occurrence. EMG studies did not show any abnormality.

There was no strong evidence of irreversible peripheral nerve damage following acute OP poisoning, however further studies are required.

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Please cite this article in press Muneeb Anwar et al., ***Neuropsychiatrical Evaluation In Subjects Chronically Exposed To Organophosphorus Poisoning.,*** *Indo Am. J. P. Sci, 2019; 06(04).*

INTRODUCTION:

Organophosphate (OP) compounds have become the most widely used pesticides for agricultural-pests throughout the world from the 1980s and the risk of acute and sub-acute toxicity is high in humans. Acute pesticide poisoning is a major health problem especially in developing countries. It was estimated that one million serious, unintentional poisonings occurred and an additional two million people were hospitalized for attempted suicide with pesticides annually. The majority of poisoning cases are self-inflicted and 77% of the cases are in the age range of 11–30 years. OP and carbamate compounds were involved in 74% of pesticide poisoning.

OP poisoning leads to four well defined neurological syndromes, namely acute cholinergic crisis, intermediate syndrome, organophosphate induced delayed polyneuropathy (OPIDN) and chronic organophosphate induced neuropsychiatric disorders (COPIND).

Animal studies have shown axonal degeneration and demyelination following acute OP poisoning. Chronic neuropsychological dysfunction with a single episode of acute unintentional OP intoxication has also been reported. Human studies of nerve function in farm workers who had chronic, probably low level exposure to pesticides show sensory and motor neuropathy. Systematic studies which focus on peripheral nerve function with acute OP ingestion are scant. The aim of the study was to find out whether there is any evidence of sub-clinical axonal damage and demyelination following acute OP poisoning in humans.

METOHDS:

A cohort study was conducted with matched controls with the approval of the Ethical Review Committee of the concerned area. The patients with self-ingestion of OP were recruited from a tertiary care hospital and a secondary care hospital. At the time of recruitment to the study, subjects either had features of the cholinergic syndrome or had been given atropine to counteract cholinergic syndrome in the peripheral units and then transferred to the collaborating hospitals. OP poisoning was confirmed by the history from the patient and/or accompanying person, the cholinergic features and plasma cholinesterase activity (ChE).

The controls were recruited from the persons accompanying the patients to the tertiary care hospital. Age, gender and occupation matched healthy volunteers who did not have a history of acute pesticide exposure were recruited within one month of the recruitment of the respective case. Age of the controls was matched to ±3 years of the patients. Subjects with features of peripheral neuropathy, diabetes mellitus or those who were on long term medications, were excluded.

Motor nerve conduction studies (MNCS), sensory nerve conduction studies (SNCS), F-wave studies and electromyography (EMG) were performed at the time of discharge from the ward (the first assessment) and at six weeks (the second assessment) following acute exposure to OP. All neurophysiological investigations done on the patients were carried out on the controls except EMG. The room temperature of the neurophysiology laboratory was maintained at 25°C.

The patients were assessed twice to explore the acute and subsequent effects on peripheral nerves. The earliest possible time to assess the cases was at the time of discharge. Immediately after the development of an acute neuropathic lesion, EMG does not show any abnormalities. The subsequent changes depend on the occurrence of denervation. The appearance of denervation on EMG may be delayed for up to five weeks. Therefore the earliest possible time for the second assessment with the least drop outs was at the sixth week.

F-wave studies

F wave studies were performed on median, ulnar and tibial nerves. Electrodes were placed as for MNCS on median and ulnar nerves. For the tibial F-wave studies, the recording, the reference and the ground electrodes were placed over the abductor hallucis muscle between the great toe and between the recording electrode and the stimulating probe respectively. The nerve was stimulated at a point slightly posterior and proximal to the medial malleolus. Sixteen stimulations were analyzed, percentage of F-wave occurrence and minimum reproducible F-wave latency were recorded.

EMG studies

EMG studies were performed on the deltoid and the first dorsal interosseous muscle on the dominant side. The ground electrode was placed on the same side of the upper limb. A concentric needle electrode was inserted into each of the selected muscles at rest and during contraction. Spontaneous activity at rest, amplitude of the motor units, presence or absence of polyphasia and the interference pattern during muscle contraction were noted.

Estimation of plasma ChE activity

Generally the term acetylcholinesterase activity is referred to red blood cell acetylcholinesterase or acetylcholinesterase at the nerve tissue. However we analyzed ChE (ChE=acetylcholinesterase (AChE) plus butyrylcholinesterase (BChE)) activity in plasma. The modified Ellman method developed by Worek F et al. (1999) was used to estimate ChE activity in plasma. Plasma samples were obtained from EDTA blood after centrifugation (10 min, 500g) and stored in 1 ml aliquots at −80°C until analysis.

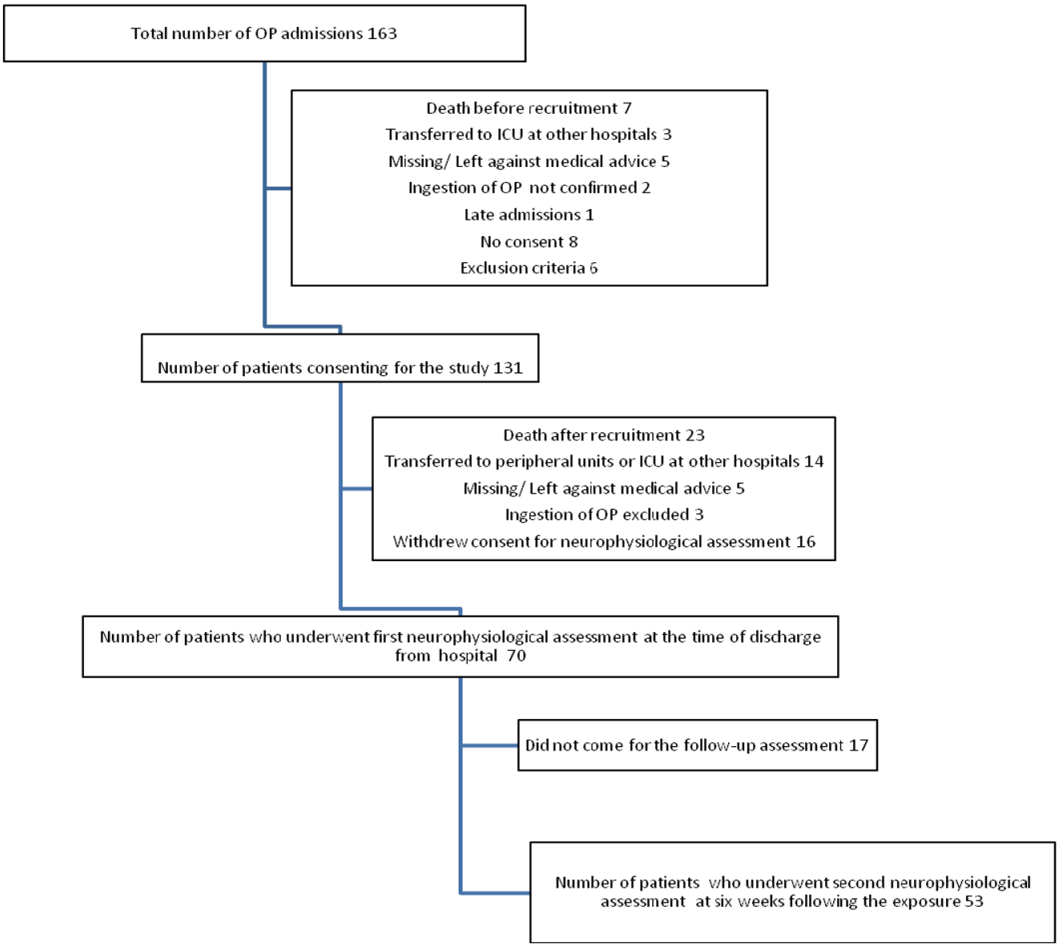
Prior to analysis the thawed samples were kept on ice until analysis. Preparation of inhibited cholinesterase were made by incubating plasma samples with PX-ethyl, PX-methyl and obidoxime for 15 min at 37°C followed by immediate dilution of the samples (1:100 in diluting reagent) and freezing.

Statistical Analysis

Data which had no normal distribution were analysed with non-parametric tests. The paired T-test was used to compare the results of the first and the second assessment and the unpaired T-test was used to compare the results of the patients and the controls. Correlation of neurophysiological parameters with potential confounders (alcohol consumption; regular, occasional or none, smoking habits; regular, occasional, none, type of OP ingested, minimum plasma ChE activity, pralidoxime (PAM) therapy and Glasgow Coma Scale (GCS) on admission) were evaluated using multiple linear regression model.

RESULTS:

From a total of 163 acute OP poisoning admissions to the collaborating hospitals, 70 (50 males) patients underwent the first electrophysiological assessment in median (inter quartile range) of 6 (4–7) days following the exposure. Fifty three came for the second assessment at six weeks following the exposure, as mentioned in below Figure 1. Mean (SD) GCS on admission was 14. All patients received atropine; 54 patients received pralidoxime.



Plasma ChE activity at four and/or twelve hours after the exposure was available in 33 patients. The

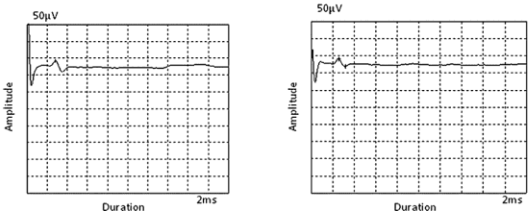
median (inter quartile range) of plasma ChE activity at four and twelve hours was 790 (146–2598) µmol/l/min and 431 (136–3068) µmol/l/min respectively. None of the patients or the controls had diabetis mellitus. The mean HbA_1C of patients and the controls were 5.4±0.5% and 5.7±0.6%. Descriptive data of the patients and the controls are shown in the below mentioned Table 1.

Descriptive data	Number of patients (n = 70)	Number of controls (n = 70)
Age (years)[Φ]	31.8 (12.2)	32.7 (11.9)
Height (cm)[Φ]	158.7 (7.5)	158.7 (10.6)
Weight (kg)[Φ]	54.9 (10.8)	54.7 (9.4)
Alcohol consumption		
No	36	41
Yes - occasional	18	5
Yes - regular	16	24
Smoking		
No	40	43
Yes - occasional	5	2
Yes - regular	25	25

Accordingly, below mentioned Table 2 discloses the numbers of subjects exposed to individual specific OPs.

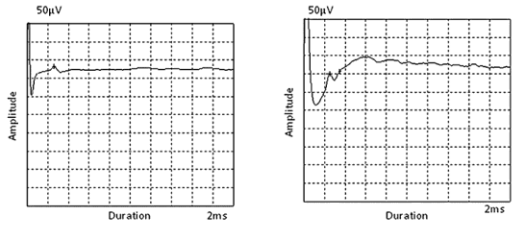
Type of OP	Number of poisoned cases
Chlorpyrifos	26
Dimethoate	12
Profenofos	5
Diazinon	4
Malathion	2
Fenthion	1
Others	3
Type of OP was not identified	17

The number of participants who underwent individual neurophysiological assessment; in Table 3 and the results of SNCS, MNCS and F-wave studies are shown in the Table 4. The wave forms of nerve conduction studies are shown in the Figure 2. Impairment of peripheral nerve function was observed at both occasions in the cases compared to the controls. In the first assessment these were significant for MNCV of median, ulnar and common peroneal nerves, SNCV and CMAP amplitude of ulnar nerve and F wave occurrence of median, ulnar and tibial nerves. However no abnormality was detected when compared to the standard cut-off values for normal MNCS and SNCS except F-wave occurrence. In the second assessment significant worsening of peripheral nerve function was seen in common peroneal CMAP-area and reduction of tibial F-wave latency compared to the first assessment.



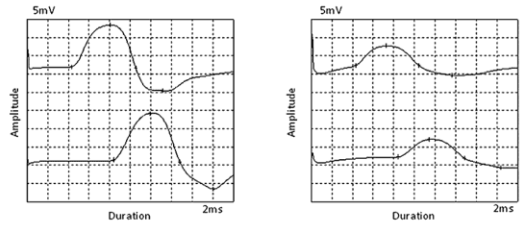
(A) SNCV = 62.1 m/s (B) SNCV = 58.6 m/s

Figure 2.1: Median nerve sensory action potential, (A) control, (B) patient



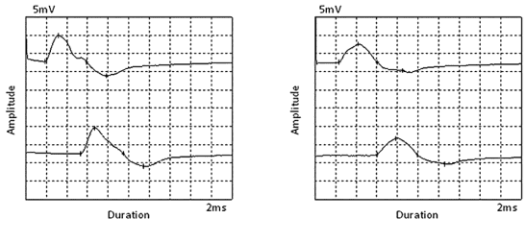
(A) SNCV = 64.4 m/s (B) SNCV = 53.8 m/s

Figure 2.2: Ulnar nerve sensory action potential, (A) control, (B) patient



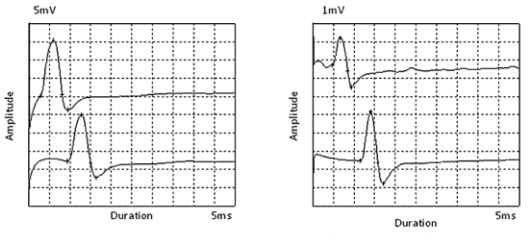
(A) MNCV = 58.0 m/s (B) MNCV = 54.5 m/s

Figure 2.3: Median nerve CMAP, (A) control, (B) patient



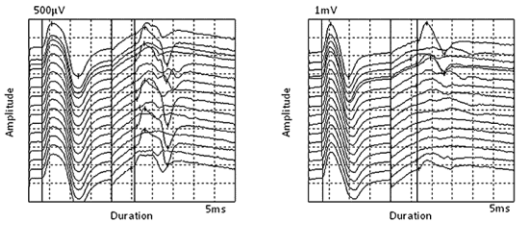
(A) MNCV = 57.2 m/s (B) MNCV = 47.1 m/s

Figure 2.4: Ulnar nerve CMAP, (A) control, (B) patient



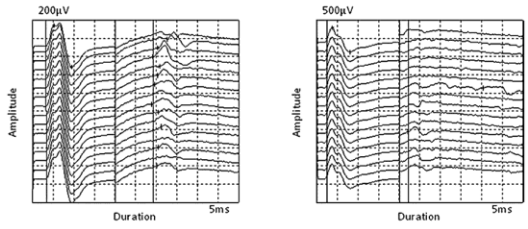
(A) MNCV = 53.4 m/s (B) MNCV = 48.5 m/s

Figure 2.5: Common peroneal nerve CMAP, (A) control, (B) patient



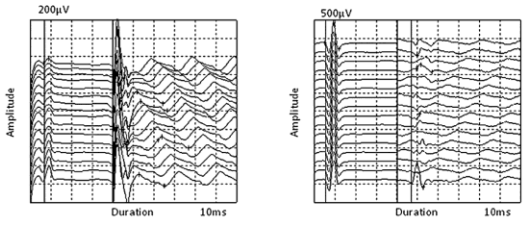
(A) F wave occurrence = 100% (B)) F wave occurrence = 44%

Figure 2.6: Median nerve F-waves, (A) control, (B) patient



(A)) F wave occurrence = 100% (B)) F wave occurrence = 19%

Figure 2.7: Ulnar nerve F-waves, (A) control, (B) patient



(A)) F wave occurrence = 100% (B)) F wave occurrence = 25%

Figure 2.8: Tibial nerve F-waves, (A) control, (B) patient

Neurophysiological assessment	First assessment of the patients (n = 70)	Second assessment of 2the patients (n = 53)	Controls (n = 70)
Median sensory nerve conduction studies	61	48	68
Ulnar sensory nerve conduction studies	58	45	70
Median motor nerve conduction studies	70	53	69
Ulnar motor nerve conduction studies	70	53	70
Common peroneal motor nerve conduction studies	66	48	68
Median F-wave studies	70	53	69
Ulnar F-wave studies	69	53	69
Tibial F-wave studies	65	50	65

Neurophysiological assessment	First assessment of the patients	Second assessment of the patients	Controls	Difference (Controls - 1st assessment)	95% CI/P value (Controls - 1st assessment)	Difference (Controls - 2nd assessment)	95% CI/P value (Controls - 2nd assessment)	Difference (1st assessment - 2nd assessment)	95% CI/P value (1st assessment - 2nd assessment)
SNCV (m/s)									
Median	53.6 (1.0)	52.8 (1.2)	56.0 (0.7)	2.3	−0.2 to 4.7	3.2¥	0.6 to 5.8	1.2	−0.6 to 3
Ulnar	55.3 (0.9)	55.9 (1.0)	59.7 (0.6)	4.4¥	2.3 to 6.5	3.7¥	1.5 to 5.9	0.01	−2.5 to 2.5
Amplitude of sensory complex (μV)									
Median	14.3 (10.4)	12.9 (10.6)	13.4 (7.1)	−0.9	−4 to 2	0.5	−3 to 4	0.5	−5 to 4
Ulnar	7.4 (6.3)	7.2 (7.4)	7.7 (4.3)	0.3	−2 to 2	0.4	−2 to 3	0.8	−4 to 3
MNCV (m/s)									
Median	55.2 (0.5)	55.6 (0.6)	56.6 (0.4)	1.4¥	0.1 to 2.7	1.05	−0.4 to 2.5	−0.8	−1.7 to 0.06
Ulnar	53.9 (0.6)	54.4 (0.7)	56.2 (0.5)	2.3¥	0.7 to 3.8	1.8¥	0.1 to 3.5	−0.4	−1.4 to 0.7
Common peroneal	46.6 (0.6)	48.2 (0.7)	49.4 (0.6)	2.8¥	1.1 to 4.5	1.2	−0.7 to 3.1	−1.2	−2.3 to 0.1
Amplitude of CMAP on distal stimulation (mV)									
Median	13.4 (0.4)	14.2 (0.6)	14.4 (0.5)	0.9	−0.4 to 2.3	0.1	−1.5 to 1.7	−0.7	−1.5 to 0.08
Ulnar	9.5 (0.3)	10.0 (0.3)	10.5 (0.3)	1.0¥	0.2 to 1.8	0.5	−0.4 to 1.3	−0.3	−0.8 to 0.3
Common peroneal	7.7 (0.4)	7.2 (0.4)	8.7 (0.4)	0.9	−0.2 to 2.1	1.4¥	0.3 to 2.6	0.6	−0.2 to 1.3
Area of CMAP on distal stimulation (mVms)									
Median	32.3 (1.2)	30.9 (1.4)	33.6 (1.2)	1.4	−2.0 to 4.8	2.7	−0.9 to 6.3	0.9	−0.7 to 2.7
Ulnar	18.7 (0.8)	17.1 (0.7)	19.5 (0.5)	0.8	−1.0 to 2.6	2.3¥	0.6 to 4	1.3	−0.02 to 2.6
Common peroneal	15.3 (0.8)	13.1 (0.7)	16.2 (0.8)	0.9	−1.4 to 3.2	3¥	0.8 to 5.2	2.7¥	1.2 to 4.2
F-wave latency (ms)									
Median	27.2 (0.4)	26.8 (0.3)	26.7 (0.3)	−0.4	−1.3 to 0.4	−0.1	−0.9 to 0.7	0.3	−0.4 to 0.9
Ulnar	27.0 (0.3)	27.3 (0.4)	26.7 (0.3)	−0.3	−1.2 to 0.5	−0.6	−1.6 to 0.3	−0.3	−0.9 to 0.3
Tibial	50.9 (0.6)	49.4 (0.8)	49.6 (0.6)	−1.3	−3.1 to 0.4	0.2	−1.7 to 2.1	1.9¥	0.2 to 3.6
F-wave occurrence (%)									
Median	82 (2)	78 (3)	90(1)	9¥	0.005†	12¥	0.002†	3	0.4‡
Ulnar	83(3)	84(2)	93 (1)	10¥	0.001†	9¥	0.002†	−2	0.6‡
Tibial	89(2)	92 (2)	93 (2)	4	0.059†	1	0.6†	−0.3	0.8‡

DISCUSSION:

We observed small magnitude adverse difference of SNCV, MNCV, amplitude and area of CMAP on distal stimulation and F-wave occurrence in acute OP poisoned patients compared to the controls.

ChE activity in patients poisoned with dimethoate may be high. In contrast the active metabolite of chlorpyrifos (chlorpyrifos-oxon) is more potent and inhibits BChE more than AChE. In chlorpyrifos poisoning, all patients with sufficient AChE inhibition to provide clinical symptoms will have markedly decreased BChE activity. Among 26 patients identified as chlorpyrifos ingestion from the label of the containers brought to the hospital, six patients showed high levels of ChE. All six patients had cholinergic features on admission and treated with atropine and pralidoxime. High levels of ChE activity may be due to incorrect identification of poison or mixed ingestion with dimethoate. It was unlikely to be due to mild ingestion since patients had full blown cholinergic syndrome at the time of admission. Over all high levels of ChE of our patients may be due to mild toxic patients and dimethoate poisoned patients.

Reduced amplitude and/or area of CMAP on distal stimulation were observed in several comparisons as per Table 4. These indicate that there may be an axonal damage since amplitude and area under negative curve of CMAP are directly proportional to the number of functioning axons. If the whole length

of the nerve is affected, F-wave latency should be prolonged. Reduced nerve conduction velocity only in the distal segment may be an evidence of distal demyelination with sparing of proximal segment. Since we did not perform segmental nerve conduction studies focal damage cannot be excluded.

CONCLUSION:

Our study suggests that there may be sub-clinical sensory and motor neuropathies following single acute exposure to OP. Reduced nerve conduction velocity with normal F-wave latency might reflect a distal demyelination process. However the reduced of amplitude of CMAP on distal stimulation may indicates axonal damage. The motor neuron excitability was reduced as reflected by the reduced F-wave occurrence. Although there was a small magnitude of adverse difference, no strong background to prove irreversible peripheral nerve damage. Further studies with long term follow up are required to address these issues.

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