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Elevated Quantitative Vibrotactile Threshold Among Workers Previously Poisoned With Methamidophos and Other Organophosphate Pesticides

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To evaluate chronic effects of acute organophosphate pesticide poisoning, quantitatively determined vibrotactile thresholds were measured as an index of peripheral neuropathy among agricultural workers in Nicaragua. Thirty-six male workers were evaluated between 10 and 34 months after hospitalization for acute organophosphate poisoning and compared to an age- and sex-matched community reference group. Vibrotactile thresholds were measured quantitatively in right and left index fingers and right and left great toes. Study subjects were stratified into three groups: 1) never poisoned; 2) poisoned with organophosphates other than methamidophos, agents which have not been reported to cause peripheral neuropathy; and 3) poisoned with methamidophos, a peripheral neurotoxin. For all digits, there was a statistically significant trend of increasing age- and height-adjusted thresholds across these three exposure categories. Over one fourth of patients previously poisoned with methamidophos we studied had abnormal vibrotactile thresholds. These results suggest that previously reported cases of organophosphate-induced delayed polyneuropathy may represent only the worst disease in a spectrum of impairment, a sequela of exposure that may be much more common than previously thought.

Key words: neuropathy, pesticide poisoning, index fingers, great toes, methamidophos, vibrotactile thresholds, organophosphate, Nicaragua

INTRODUCTION

Most organophosphate insecticides produce acute poisoning characterized by inhibition of neuronal acetylcholinesterase. Symptoms result from cholinergic overstimulation and include salivation, sweating, vomiting, miosis, headache, and lightheadedness [Morgan, 1989]. In addition, organophosphate-induced delayed polyneuropathy (OPIDP) is a well-recognized but uncommon sequela to acute, usually severe poisoning by certain organophosphate insecticides or to exposure to certain noninsecticidal organophosphate compounds. This disease, which generally occurs 10 days to 3 weeks after the initial exposure or poisoning is characterized pathologically by a

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distal "dying back" axonopathy and clinically, by mixed sensorimotor symptoms affecting primarily the lower extremities [Vasilescu et al., 1984; Jedrzejowska et al., 1980; Smith and Spalding, 1959; Bidstrup and Bonnell, 1953; Kidd and Langworthy, 1933; Susser and Stein, 1957; Smith and Elvove, 1930]. In more severe cases, the upper extremities and the central nervous system also are affected. Neurophysiologic studies in humans and animals have demonstrated relatively normal nerve conduction velocities with markedly decreased sensory amplitudes and muscle action potentials [Vasilescu et al., 1984; Hierons and Johnson, 1978; Hern, 1973]. Prognosis is variable, depending on severity of disease. The disease is thought to occur as a result of the inhibition (and "aging") of neuropathy target esterase (NTE) [Lotti et al., 1986; Johnson, 1974, 1975; Clothier and Johnson, 1979], a protein distinct from the acetylcholinesterase which is affected in acute poisoning.

Epidemics of OPIDP have occurred among populations consuming products contaminated with (noninsecticidal) triortho-cresyl phosphate [Smith and Spalding, 1959; Susser and Stein, 1957; Smith and Elvove, 1930]. Follow-up of affected individuals has demonstrated persistent effects, some life-long [Jedrzejowska et al., 1980; Morgan and Penovich, 1978; Susser and Stein, 1957]. There has been only one study, however, which demonstrated chronic peripheral neuropathic effects among a well-defined population of workers exposed to a specific organophosphate pesticide, in this case leptophos [Xintaras et al., 1979]. In contrast, one prospective study of workers occupationally exposed to neuropathic organophosphate insecticides (DEF and merphos), in whom NTE was monitored in peripheral lymphocytes, showed no demonstrable effects on electromyograms and nerve conduction velocities [Lotti et al., 1983].

To evaluate chronic neuropathic effects of organophosphate poisoning, we studied workers from Nicaragua's Northern Pacific coastal plain who were previously hospitalized for acute organophosphate poisoning. We have previously reported evidence of persistent central nervous system effects among this population [Rosenstock et al., 1991]. We report here our assessment of peripheral nervous system sequelae. Methamidophos, an organophosphate insecticide which has been reported to cause OPIDP in individuals who have been poisoned [Senanayake and Johnson, 1982], is a common cause of organophosphate poisoning here and elsewhere in Central America [Conroy et al., in press], and accounted for 25% of the 766 poisonings reported to the Nicaraguan Ministry of Health, Region II, in 1986. We are not aware of any prior studies of chronic peripheral neurologic effects among previously poisoned individuals who did not come to medical attention for treatment of clinical polyneuropathy in the convalescent phase of the acute poisoning.

MATERIALS AND METHODS

Study Population

Hospital inpatient discharge diagnoses were reviewed for all admissions between July 1, 1986 and July 31, 1988 at the University teaching hospital in the regional capital. Fifty-two male patients, age 15–44 years at the time of admission, were identified as having been treated for occupational organophosphate poisoning. Fourteen of 52 had inadequate addresses or had moved out of the region. Of the 38 located, 36 (95%) agreed to participate. Each person in the previously poisoned

group was matched by sex and age (within 5 years) to a sibling or friend in the same community who never had been treated medically for a pesticide poisoning. During May and June 1989, the matched pairs (previously and never poisoned) were brought to the regional capital for examination.

Data Collection

Vibrotactile threshold was measured using a Vibratron II (Sensortek, Inc: Clifton, NJ) for right and left index finger and right and left great toe, in that order. The apparatus consists of a box with a protruding vibrating post upon which the subject rests the digit being examined. A separate control box displays a digital reading of the vibration amplitude, which is varied by the examiner. A previously validated "trimmed 2-5 method of limits" procedure was used [Gerr and Letz, 1988; Gerr et al., 1990]. Briefly, the amplitude is alternately decreased until the subject cannot feel the stimulus (reading no. 1), then raised until the stimulus is felt. Five readings were made for each digit. The first reading was discarded, as were the lowest and highest remaining readings. The remaining two readings were averaged to obtain the vibrotactile threshold used for analysis. Callus thickness (none, mild, or moderate) was evaluated qualitatively by the examiner (who had no knowledge of subject exposure status), and height was measured. The vibrotactile thresholds were normalized for age and height, using regression formulae for an unexposed North American population [Gerr et al., 1990].

All subjects were administered a questionnaire asking about previous poisonings, demographic characteristics, and a variety of potentially confounding characteristics or exposures. Of the 36 participating workers, 21 were classified as previously poisoned with methamidophos. The hospital record had identified methamidophos as the cause of poisoning in 14 cases; in the questionnaire, an additional 7 reported having been treated for methamidophos poisoning on that or another occasion. Fifteen (of 36) previously poisoned cases reported never having been treated for methamidophos poisoning. Pesticides reported by these workers as being responsible for poisonings for which medical attention had been sought included other organophosphates (acephate, chlorpyrifos, dicrotophos, ethyl and methyl parathion, malathion, mephosfolan, monocrotophos, and profenfos), sometimes in mixtures with nonorganophosphates (bacillus thuringiensis, carbofuran, chlordimeform, DDT, deltamethrin, Jupiter, methomyl, and toxaphene).

Data Analysis

An unmatched analysis was conducted. Univariate and multivariate analyses were conducted using SPSS-PC+ [Norusis, 1988]. Trends for means for ordered categories (not poisoned, poisoned not with methamidophos, and poisoned with methamidophos) were evaluated using a Jonckheere test for ordered categories [Siegel and Castellan, 1988].

RESULTS

The 36 treated patients all had medical record documentation of symptoms consistent with severe organophosphate insecticide poisoning, and all received atropine, as described previously [Rosenstock et al., 1991]. The two groups were well matched by age (Table I). The previously poisoned subjects had a slightly higher

TABLE I. Characteristics of Previously Poisoned and Comparison Nicaraguan Agricultural Workers Assessed for Vibrotactile Thresholds in 1989

	Never poisoned (N = 36)	Previously poisoned (N = 36)
Mean age (SD)	27.8 (9.3)	27.6 (9.5)
Height in centimeters (SD)	168 (6.4)	166 (6.4)
Moderate or heavy callus (%)	13 (36)	20 (56)
Ever worked with pesticides (%)	25 (69)	36 (100)
Recent pesticide exposure (%)	4 (11)	5 (14)
Consume any alcohol in previous month (%)	16 (44)	13 (36)
History of solvent exposure (%)	6 (17)	13 (36)
History of work with vibrating machinery (%)	17 (47)	15 (42)

prevalence of moderate or heavy callus formation in one or both lower extremities than the never poisoned referents. The higher prevalence of reported history of exposure to solvents among the previously poisoned group is likely due to working with pesticides formulated with solvents.

The previously poisoned subjects had an increased (normalized) vibrotactile threshold in all four digits tested. The group poisoned with methamidophos (n = 21) had higher mean thresholds than the group (n = 15) poisoned with other organophosphates, who nevertheless also had moderate increases in mean thresholds compared with the unexposed cohort (Table II). These differences were larger in the lower extremities. Examination of the proportion with abnormal thresholds in each group demonstrated a similar trend.

The relation between potential confounders and threshold was evaluated by comparing mean normalized thresholds between individuals with and without each confounder. The means were similar for all confounders evaluated (recent pesticide exposure, history of solvent exposure, and history of work with vibrating machinery), except among those who consumed alcohol, who had, paradoxically, lower thresholds than those who did not, and for those with moderate or heavy callus formation (Table III). Mean threshold increased with extent of callus formation. After controlling by stratification for the potential confounding effect of callus formation, the mean normalized threshold was found to increase across exposure categories (Fig. 1). Because there were small numbers of individuals with mild or moderate callus formation in the upper extremities, only the lower extremity results are shown.

The time elapsed between poisoning and examination was not statistically significantly associated with vibrotactile threshold in a multivariate model adjusting for age, height, exposure, and callus formation.

DISCUSSION

We found marked differences in vibrotactile threshold between previously poisoned workers and not poisoned referents. These differences were more pronounced in the lower extremities and among methamidophos poisoned workers. Abnormal vibrotactile threshold was common, affecting over one fourth of the previously poisoned cohort. Although there have been epidemics of tens of thousands of cases of OPIDP related to ingestion of the organophosphate tri-ortho-cresyl phosphate, which

TABLE II. Mean Vibration Threshold* (SD) and Number (%) Abnormal Among the Community Comparison Group and Workers Previously Hospitalized for Poisoning With Methamidophos (MTD) and Other Organophosphates

	Not poisoned (N = 35[a])	Poisoned, not by MTD (N = 15)	Poisoned by MTD (N = 21)	
	Threshold (SD); No. (%)	Threshold (SD); No. (%)	Threshold (SD); No. (%)	Trend[b] (p value)
Right index finger	−0.20 (0.95); 0 (0%)	0.12 (1.1); 1 (6.7%)	0.50 (0.87); 2 (9.5%)	.007
Left index finger	−0.17 (0.88); 0 (0%)	0.09 (1.2); 1 (6.7%)	0.34 (0.76); 1 (4.8%)	.002
Right first toe	0.07 (1.1); 2 (5.9%)	0.70 (1.1); 2 (13%)	1.1 (0.96); 5 (24%)	.001
Left First toe	0.19 (0.97); 2 (5.9%)	0.57 (1.3); 4 (27%)	1.1 (0.96); 6 (29%)	.003

*In log microns normalized for age and height. (The proportion abnormal was determined using North American reference formulae; Gerr et al., 1990.)
[a]One worker had unusable data.
[b]Jonckheere test for ordered alternative tests trend for means.

TABLE III. Mean Vibration Threshold* (SD) Among All Workers (Poisoned and Never Poisoned) With Mild, Moderate, or Heavy Callus Formation

	Minimal callus	Moderate callus	Heavy callus
Right index finger	−0.01 (0.97)	1.01 (0.83)	—
Left index finger	−0.02 (0.94)	0.66 (0.46)	—
Right first toe	0.36 (0.96)	0.51 (1.6)	1.0 (0.98)
Left First toe	0.37 (0.93)	0.41 (1.2)	1.2 (1.2)

*In log microns normalized for age and height. (The proportion abnormal was determined using North American reference formulae; Gerr et al., 1990.)

is not an insecticide [Smith and Spalding, 1959; Kidd and Langworthy, 1933; Susser and Stein, 1957; Smith and Elvove, 1930], OPIDP from insecticides has generally been regarded as a rare disease. These results strongly suggest a chronic sensory impairment resulting from methamidophos poisoning. The florid OPIDP reported in the medical literature may represent only the worst cases of a spectrum of neuropathy which may be much more common than previously thought.

Quantitatively measured vibrotactile threshold has not been used to evaluate OPIDP. However, in a 4–7 year follow-up of cases of OPIDP, three of four cases presented had decreased vibrotactile sensation on neurologic examination [Morgan and Penovich, 1978]. In animals, sensory nerve damage has been demonstrated electrophysiologically as reduced amplitude of sensory nerve action potentials, an effect which is reported to be sensitive to the neuropathic effects of certain organophosphates [Hierons and Johnson, 1978]. In addition, our results were consistent with the predilection of OPIDP (especially mild cases) commonly to affect the lower extremities more than the upper extremities.

Increased quantitatively determined vibration threshold has been shown to correlate well both with physical examination of vibrotactile perception and with neurophysiologic parameters in neuropathies of varied etiologies [Gerr and Letz, 1993; Gerr et al., 1991; Dyck et al., 1987; Bertelsmann et al., 1986; Tegnér and Lindholm, 1985], including axonopathies (the pathology corresponding to descriptions in case reports of OPIDP). Of electrophysiologic measurements, quantitative vibrotactile threshold correlates best with the F-wave and H-reflex of lower extremity nerves [Gerr et al., 1991].

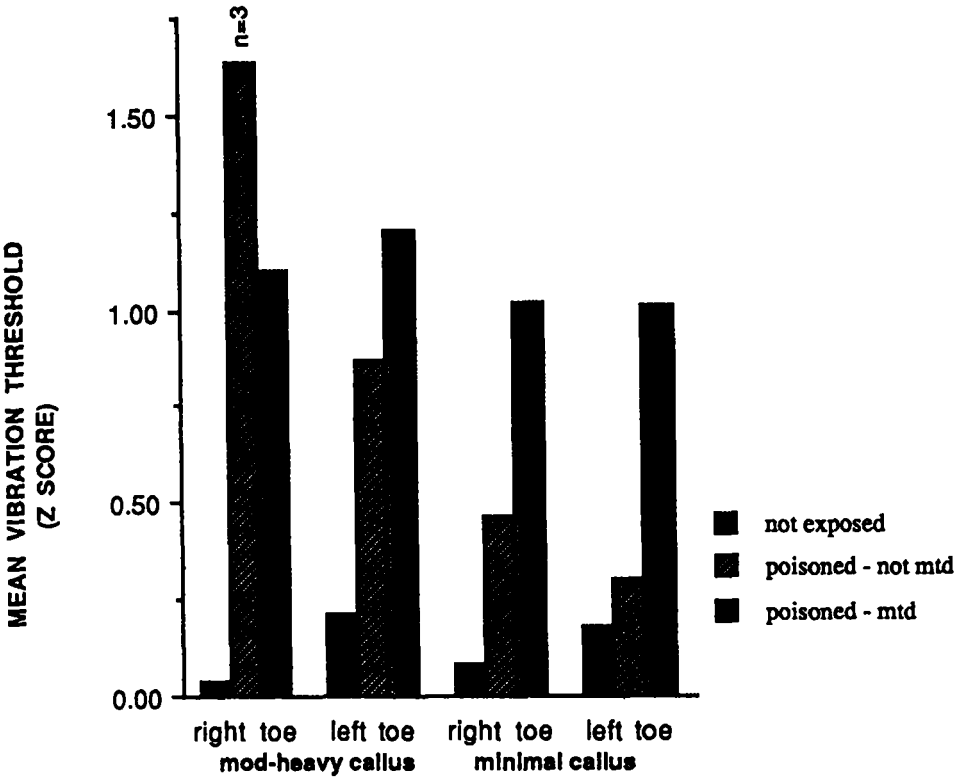

Fig. 1. Mean normalized vibrotactile threshold increases according to exposure category after stratifying by callus formation among a community comparison group and workers poisoned with methamidophos (MTD) and other organophosphates.

One limitation to the interpretation of these results is that impairment of vibrotactile threshold is not specific for peripheral neuropathy. Although peripheral neuropathy is the hallmark of OPIDP, damage anywhere in the afferent pathway might be expected to impair vibrotactile sensation. Cerebral damage, for example, especially if subcortical, may produce decreased vibrotactile threshold [Fox and Klemperer, 1942]. In addition, there is evidence that poisoning by a variety of organophosphate insecticides (not just by the inhibitors of NTE which characteristically produce OPIDP) results in diffuse central nervous system damage [Rosenstock et al., 1991; Savage et al., 1988; Eskenazi and Maizlish, 1988]. In a concurrent study of this same population, we have found deficits among the poisoned cohort in neurobehavioral tests of attention, memory, visuomotor, and motor performance [Rosenstock et al., 1991]. However, there were no differences or trends suggestive of differences between individuals previously poisoned with methamidophos and with other organophosphates on 14 neuropsychologic tests, with the exception of one test, block design, for which the difference was of borderline statistical significance in the unanticipated direction. These results suggest that inhibition in the brain of NTE, the putative target enzyme for methamidophos neuropathy, does not explain the central nervous system damage previously reported in this cohort, because the central im-

pairment was seen equally for organophosphates which do not inhibit NTE. Conversely, the observed neuropathic effects of methamidophos may be independent of damage to the cerebrum resulting from methamidophos poisoning, because the damage to vibrotactile threshold is so much more marked in the workers poisoned with the known peripheral neurotoxin.

There was no reliable index to distinguish severity of poisoning in this population. Therefore, it was not possible to evaluate a dose-response relationship between poisoning and vibrotactile threshold within the methamidophos poisoned group, nor was it possible to infer whether a threshold dose is necessary to produce neuropathy, as has been reported in the experimental literature [Lotti, 1992]. Although time elapsed since exposure was not associated with improved vibrotactile threshold, recovery may have occurred, but could have been obscured by differences in severity of initial impairment.

The effect of callus formation on vibrotactile threshold may demonstrate a potentially important and previously unappreciated confounder in the evaluation of peripheral neuropathy by measuring vibrotactile threshold. However, in this study, neuropathy may be causal to callus formation, in which case callus formation is not necessarily a confounder. There was no difference in vibrotactile threshold according to callus formation among the unexposed group (Fig. 1), and a larger proportion of workers with heavy callus were in the poisoned group (Table I). Therefore, the increased threshold among heavily callused workers may be a result of sensory loss in previously poisoned workers predisposed to injury and callus formation. Rural workers in Nicaragua often go barefoot and often do not have appropriate work shoes, which would make individuals with sensory impairment particularly susceptible to injury.

One unexpected finding was that decreased vibrotactile threshold was seen in workers poisoned with organophosphates other than methamidophos. This may have been due 1) to methamidophos-induced polyneuropathy among workers misclassified as never poisoned with methamidophos; 2) to an effect of methamidophos exposure not resulting in clinical poisoning (as exposure without poisoning was not reported in the questionnaire); or 3) to a neuropathic effect of organophosphates other than methamidophos. Among other organophosphates with which hospitalized workers were poisoned, chlorpyrifos has been reported to cause peripheral neuropathy [Kaplan et al., 1986; Lotti et al., 1986], and acephate is metabolized to methamidophos [U.S. E.P.A., 1988]. However, when the four cases poisoned with these two pesticides were excluded from the analysis, there was no decrease in the mean vibrotactile thresholds of the 11 other workers poisoned with non-methamidophos organophosphates, making it unlikely that either chlorpyrifos or acephate poisoning was responsible for the higher vibrotactile threshold among workers not reporting methamidophos poisoning.

The United States Environmental Protection Agency (EPA) requires that organophosphate insecticides be screened through animal testing for neuropathic effects before approval for marketing in the United States [Sette, 1991]. Unfortunately, there are marked interspecies differences in susceptibility to OPIDP, and results from test animals may not always be predictive of effects in humans [Johnson, 1975]. In addition, many organophosphates currently available have not been adequately tested for neurotoxicity, because they were on the market before the requirements for neurotoxicity testing were implemented [Cherniack, 1988].

Further work is needed to characterize more carefully the clinical and biochemical impairment of methamidophos poisoned workers, the natural history and dose-response relationship of methamidophos neuropathy, and the potential contribution of central nervous system disease to the measured sensory impairment. In addition, the clinical and subclinical impairment of workers previously poisoned with other organophosphates should be explored.

Nevertheless, the public health implications of this study are worrisome. It appears that poisoning with methamidophos results in chronic sensory impairment, and that this impairment is frequent among those poisoned. In the United States, methamidophos is marketed under the brand name Tamaron; in California alone there were 86 cases of methamidophos poisoning between 1982 and 1987 (Worker Health and Safety Unit, California Department of Food and Agriculture, unpublished data). In 1987, there were 390,000 pounds of methamidophos sold in California. Occupational methamidophos poisoning is a major public health problem in Nicaragua and in the rest of Central America, where methamidophos is reported to be among the top three causes of pesticide poisoning in every country (Pesticide Program, National University of Costa Rica: Second Regional Seminar on Pesticides, El Zamorano, Honduras, June 1991). In other parts of the developing world, methamidophos has been reported to be responsible for a large proportion of sporadic OPIDP. A series of 74 methamidophos associated cases was reported recently by investigators in China [Zheng, 1990]. Of 27 cases of sporadic OPIDP occurring in Sri Lanka, 25 were caused by methamidophos [Senanayake, 1985]. Given the current evidence, we would recommend substitution of methamidophos with other pest control methods without known potential to cause peripheral neuropathy.

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