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Clinical Confirmation of Organophosphate Poisoning of Agricultural Workers

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A group of 31 lettuce harvesters exposed to the organophosphate pesticide mevinphos presented to a local emergency room with moderate cholinergic symptoms and eye and skin irritation, with 22 of the subjects (76%) reporting three or more symptoms. None had baseline cholinesterase values, and plasma cholinesterase activity for all but two workers was above the lower limit of the laboratory normal range. None of the workers received antidotes and all were released for return to work. Twenty-nine workers sought additional care when symptoms persisted, and were followed by the investigators until 12 weeks after exposure. Plasma and red blood cell (RBC) cholinesterase increased until 14 days after exposure. Plasma cholinesterase was estimated to have been inhibited by an average of 15.6% ($p < 0.01$), and RBC cholinesterase by 5.6% ($p < 0.01$). These findings support the utility of sequential postexposure plasma cholinesterase analyses in confirmation of suspect organophosphate-induced illness when baseline values are not available.

Key words: organophosphate poisoning, mevinphos, cholinesterase

INTRODUCTION

The clinical diagnosis of severe or moderate organophosphate poisoning is confirmed when an initial dose of atropine fails to result in symptoms of atropinization. In cases of mild organophosphate poisoning, however, atropinization may occur [Namba et al, 1971]. In such cases, confirmation of organophosphate-induced illness depends primarily on a determination of cholinesterase inhibition. The individual's plasma and red blood cell (RBC) cholinesterase activity is compared to pre-exposure baseline values in order to confirm the diagnosis, and to determine when the patient may be released for work involving potential re-exposure to cholinesterase inhibitors [Milby, 1971; Namba et al, 1971].

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Because of the variability of normal cholinesterase activity, the interpretation of single postexposure values in the absence of baseline data is difficult. California is the only state where medical surveillance of workers who handle or apply organophosphates pesticides is required by law; that state's regulations recommend the establishment of baseline cholinesterase values as part of this medical monitoring.

Baseline cholinesterase values are not required and are frequently unavailable for pesticide applicators in other states. Moreover, baseline tests are not obtained for field workers, who account for the vast majority of the agricultural labor force. There have been numerous cases of illness among field worker crews that were induced by foliar borne organophosphate residues [Spear et al, 1977; Kahn, 1976]. In 1984, California physicians reported 466 illnesses induced by residues of all types of pesticides [California Department of Food and Agriculture, 1985]. Federal and state regulations now require mandatory waiting periods (re-entry intervals), between pesticide application and return to work in the treated field.

In the Salinas Valley of California, four incidents occurred between 1980 and 1983 in which 135 workers became ill after exposure to organophosphate residues on the foliage of lettuce and cauliflower plants [Midtling et al, 1985]. Since 1983, three incidents involving the exposure of field workers to the drift of organophosphate pesticides resulted in another 172 workers seeking emergency medical treatment from area hospitals. In each of these cases, workers presented without pre-exposure baseline cholinesterase values. Most of these workers had postexposure cholinesterase values above the lower limit of normal.

The range of normal cholinesterase activity is very wide. Values at the upper limit of the normal range may be 200% of those at the lower limit. Patients with high normal levels lose 50% of their cholinesterase activity and still have values above the lower limit of normal for the testing laboratory. For this reason, when a single postexposure value is within the range of laboratory normal, the diagnosis of mild organophosphate poisoning cannot be ruled out. The nonspecific nature of the symptoms associated with moderate cholinesterase inhibition, including headache, nausea, and malaise, make it even more difficult for the clinician to reach an unambiguous diagnosis of pesticide posioning in such cases.

To evaluate the use of sequential postexposure cholinesterase analyses for the confirmation of organophosphate poisoning in the absence of baseline values, cholinesterase activity was followed in a group of 29 field workers exposed to an organophosphate pesticide. To assess the correlation of results obtained from the local laboratory with a laboratory used for field research by the National Institute for Occupational Safety and Health (NIOSH), samples were divided for comparative analysis. The distribution of cholinesterase values of the exposed crew was also compared to controls of the same ethnic group, occupation, and socioeconomic class.

CASE REPORT

A group of 31 workers began harvesting iceberg lettuce in the Salinas Valley, California, on April 23, 1981, only 2 hours after the field had been sprayed with the organophosphate insecticide mevinphos (Phosdrin). The material was applied at a rate of 1 quart per acre, along with a surfactant (Glyco-Buffer). Mevinphos is a compound of high toxicity, with an oral LD_{50} of 6.1 mg/kg and a dermal LD_{50} of 4.7 mg/kg

body weight [Gaines, 1960]. California regulations require a 48-hour interval between application of the insecticide and the re-entry of workers into the treated area.

The workers began to harvest the crop at 7 A.M. By 9 A.M., many of them began to experience cholinergic symptoms and eye irritation. Some of the workers complained to the foreman and several were unable to continue working because of their symptoms. A field supervisor arrived at 11 A.M., and informed the foreman that the field had been sprayed in error earlier that same morning.

The members of the crew, together with three agricultural officials who had been inspecting the harvested lettuce, were taken to a local community hospital for evalutation and treatment. None of the workers had previous baseline cholinesterase determinations. Plasma cholinesterase determinations were done, and two workers exhibited levels below the lower limit of the laboratory normal range. Most of the workers complained of eye irritation and visual disturbances, and one worker presented with nystagmus. The eyes of 11 workers were irrigated. Two workers presented with respiratory difficulties, and were hospitalized.

No antidotes were administered to any of the workers. They were decontaminated and told to wash their clothes when they got home. None was restricted from returning to work the next day.

Fourteen additional workers, the truck drivers, crew foremen, and the carton folder and stitcher, were taken to two other hospitals, where they were examined and released.

The following day, a number of workers from the crew were unable to return to work because of symptoms. Twenty-nine workers presented to the investigators, where they were examined and blood samples were drawn for analysis of plasma and red blood cell (RBC) cholinesterase activity. One subject presented with fasciculations of the tongue. Another worker who presented with bradycardia was hospitalized for 24 hours for observation.

Later in the week, agricultural officials ordered the destruction of some 1,300 cartons of lettuce packed by the crew because the harvest interval had not been observed. Harvest intervals, the legally mandated waiting periods between pesticide treatment and harvest, are longer than the worker safety intervals, the time in which work is prohibited in the treated area. In this case, both the 96-hour harvest interval and the 48-hour worker safety interval had been violated.

The crop was found to contain 0.2 ppm mevinphos residues. While this is well within the amount permitted by law, the lettuce sample that was analyzed was not taken until 4 days after worker exposure, when much of the residue may have already decomposed.

MATERIALS AND METHODS

All 31 members of the crew were invited to attend a series of follow-up clinics, which were held weekly until 8 weeks after exposure, and then at 10 and 12 weeks. The 29 subjects who were seen were all Hispanic males, from 22 to 46 years of age. Almost all of them returned to field work within 2 weeks after the incident, in some cases against medical advice.

At each clinic, beginning on the day after exposure, the subjects were examined, the symptoms that they reported were recorded, and blood samples were drawn for analysis of plasma and red blood cell cholinesterase activity using the method of

Michel [1949]. All samples were analyzed at the same laboratory (normal range for this laboratory was 0.58–1.05 Δ pH units per hour for RBC and 0.44–1.25 for plasma). The plasma analyses done on the actual day of exposure were performed in a different laboratory, and are therefore not comparable to the values obtained in this study.

The number of crew members attending each clinic varied. We saw 22 workers at the final examination, 12 weeks after exposure. We saw 27 crew members at least twice in clinics held 5 weeks or more after exposure. Subjects' cholinesterase values were analyzed by repeated measures analyses of variance. Missing values were estimated using the method of Yates [1933], and the differences between mean values on different examination dates were analyzed by Scheffé post hoc comparisons.

At seven of the follow-up clinics, blood samples were divided for cholinesterase analysis by the Michel method at the NIOSH contract laboratory (normal range for this laboratory was 0.44–1.09 Δ pH units per hour for RBC and 0.38–1.54 for plasma). The values for these divided samples were compared to those obtained by the local laboratory by computation of the Pearson correlation coefficient.

A field crew with no known recent exposure to organophosphate pesticides was invited to serve as a control for the study. This group consisted of 49 male Hispanic field workers, aged 18 to 53 years, who contributed blood samples analyzed for cholinesterase activity at the NIOSH contract laboratory. The cholinesterase values of the exposed subjects were compared to the controls with analyses of variance and Scheffé post hoc comparisons of means.

Additional subjects who attended the follow-up clinics were three female family members, aged 13, 34, and 35, who handled and washed the workers clothes, and one male worker who helped disrobe the affected workers immediately after they were exposed. Results reported, including symptoms and cholinesterase levels, are for the 29 crew members only unless otherwise specified.

RESULTS

Symptoms

The crew members reported initial symptoms of eye irritation, headache, visual disturbances, dizziness, nausea, vomiting, weakness, chest pain or shortness of breath, skin irritation, pruritis, eyelid fasciculation, arm fasciculation, excessive sweating, and diarrhea. Twenty-two (76%) of the workers reported three or more of these symptoms.

Additional symptoms developed in the first 24 hours after exposure. Figure 1 presents the course of symptoms as reported by the crew members over the follow-up period. Episodes of headache, dizziness, visual disturbances, nausea, vomiting, and other symptoms were reported throughout the study. Six workers reported recurring headaches more than 10 weeks after their exposure.

The subject who had helped the workers disrobe complained of headache, burning eyes, and blurred vision, and presented with injected conjunctiva. These problems resolved within 1 week. Two of the female family members exposed to contaminated clothing in the laundry presented with symptoms. One complained of headache, eye irritation, and pruritis of the arms and legs. The complaints of headache and eye irritation persisted for 4 weeks. The second complained of transient headache, abdominal pain, and diarrhea. The third of these subjects was asymptomatic.

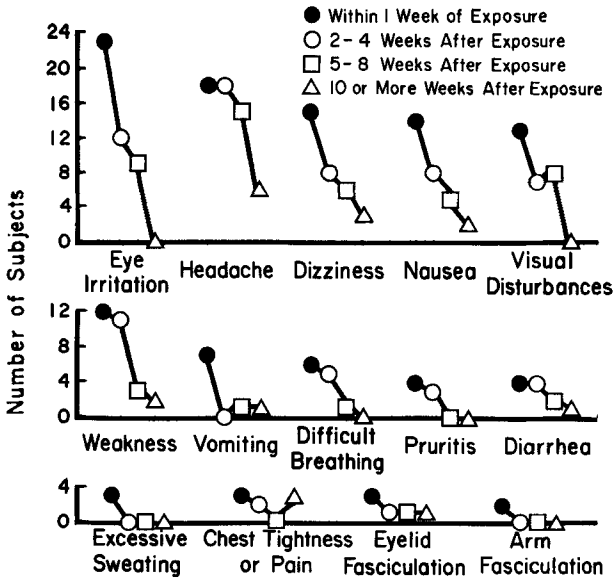

Fig. 1. The course of symptoms reported by crew members over the follow-up period.

Cholinesterase Activity

Because samples for the first 2 weeks were analyzed solely at the local laboratory, values for this laboratory are used to describe the changes in cholinesterase activity among the exposed subjects. Plasma cholinesterase activity for the individual crew members is plotted in Figure 2. Plasma activity increased between the day after exposure and the follow-up exam 1 week later by an average of 0.051 Michel units (Δ pH units per hour); this represents a significant difference ($p < 0.01$). When the plasma activity of the crew members the day after exposure is compared to the activity 14 days later, the difference is even more striking. The subjects' plasma cholinesterase increased an average of 0.151 Michel units ($p < 0.01$). Differences ranged from 0.04 to 0.35 Michel units. Of the 25 subjects seen at this exam, 24 had differences of 0.08 Michel units or greater. When the values obtained during this exam are taken as an endpoint (estimated baseline), the subjects' plasma cholinesterase is estimated to have been inhibited by an average of 15.6%.

We saw 25 subjects at least twice in clinics 5 weeks or more after exposure. An estimate of the final cholinesterase activity was prepared for each of these subjects by averaging their last two cholinesterase values. Plasma cholinesterase for these subjects declined by an average of 0.063 Michel units between the 14th day after exposure and this endpoint. Despite this decline, the subjects' cholinesterase had increased by an average of 0.088 Michel units between the day after exposure and the estimated final activity, a difference that is still significant ($p < 0.01$). If this final activity is regarded as each individual's normal cholinesterase value, the subjects' plasma cholinesterase was inhibited by an average of 9.7%.

Increases in crew members' RBC cholinesterase were not as great (see Table I). RBC cholinesterase increased by an average of 0.046 Michel units between the first follow-up exam and the exam 14 days after exposure (significant with $p < 0.01$). Final activity was estimated with the same method used for plasma cholinesterase,

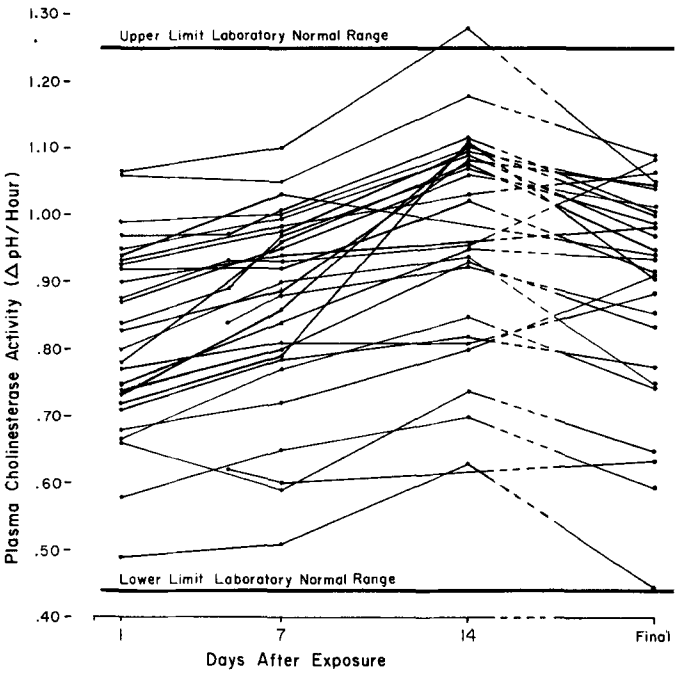

Fig. 2. Plasma cholinesterase activity for individual crew members.

and no further regeneration of RBC cholinesterase was observed. Using either endpoint as an estimate of baseline activity, the subjects' RBC cholinesterase is estimated to have been inhibited by an average of 5.6%. As indicated in Table I, the subjects with three or more symptoms had greater increases of RBC activity than subjects with fewer symptoms; however, the difference was not statistically significant.

The rate of regeneration of cholinesterase activity was calculated for the initial recovery period (from the day after exposure until 14 days after exposure) and expressed as a percentage of the value at 14 days. On the average, subjects' plasma activity regenerated at a rate of 1.20% per day, while RBC cholinesterase activity regenerated at a rate of 0.43% per day.

There was no detectable cholinesterase inhibition in the subjects exposed to contaminated clothing.

The cholinesterase activity of the exposed crew members was compared to that for the control group of lettuce harvest workers. The contrast used the earliest analyses of the subjects' cholinesterase at the same laboratory used for the controls, which occurred 14 days after exposure. The exposed crew members' RBC cholinesterase activity was an average of 0.485 Michel units, significantly less than the activity of the control group, which averaged 0.583 ($p = 0.01$). The situation was reversed for plasma cholinesterase activity. The exposed crew's mean plasma cholinesterase activity (0.854) was greater than that of the control group (0.746), a difference which was significant ($p = 0.01$). Since the samples from the cases were analyzed in one batch, and the controls in a later batch, part of these differences between groups might be attributed to the day-to-day variation in laboratory results. Interindividual and intraindividual variations are a much greater source of variation

TABLE I. Red Blood Cell Cholinesterase Activity (Change in pH per Hour)

Subject No.	RBC cholinesterase activity: Days after exposure 1	7	14	Final[a]	Change in activity: Between day 1–14	Between day 1–final
Subjects with three or more symptoms						
1	.72	.77	.82	.855	.10	.135
2	.60	.61	.62	.63	.02	.03
4	.86	.86	.94	.90	.08	.04
5	.66	.65	.71	.73	.05	.07
8	.83	.85	.89	.895	.06	.065
9	.90	.85	.97	.955	.07	.055
10	.63	.61	.72	.695	.09	.065
11	.79	.81	.85	.875	.06	.085
12	.83	.82	.84	.855	.01	.025
13	.80	.82	.86	.85	.06	.05
14	.74	.74	.76	.795	.02	.055
15	.67	.67	.72	.755	.05	.085
17	.67	.62	.77	.75	.10	.08
19	M[b]	.81	.83	.825	M	M
20	.85	.89	.86	.855	.01	.055
21	.73	.69	.82	M	.03	M
22	.70	.72	.73	.73	.03	.03
23	.82	.80	.85	.845	.03	.025
24	.82	.81	.88	.885	.06	.065
25	.82	.81	.89	.815	.07	−.005
26	.81	M	.84	.875	.03	.065
29	.78	.79	M	.785	M	.005
Mean change in activity					.054	.051
Subjects with fewer than three symptoms						
3	.79	.79	.81	M	.02	M
6	.73	.74	.73	.77	.00	.04
7	1.02	.99	.95	.94	−.07	−.08
16	.82	.84	.88	.865	.06	.045
18	.78	.76	.82	.865	.04	.085
27	M	.65	M	.72	M	M
28	.85	.84	M	.855	M	.055
Mean change in activity					.010	.019
Mean change in activity, all subjects					.046	.045

[a]Final values are an average of the last two analyses if the subject was seen at least twice 5 weeks or more after exposure.
[b]M = Missing values.

than the batch effect in Michel method cholinesterase analysis, however. Rider et al. [1957] found that 97% of the variation in the values of 800 subjects was explained by sources other than the day-to-day variation in analysis.

Duplicate analysis of blood samples allowed comparison of the values obtained by the local laboratory with those obtained by another commerical laboratory under contract to NIOSH. There was a more significant correlation between the values obtained by these laboratories for plasma activity ($r = 0.71$) than there was for RBC activity ($r = 0.32$).

DISCUSSION

The range of symptoms and degree of cholinesterase inhibition demonstrate that the members of this crew suffered moderate poisoning by mevinphos residues. Most of the pesticide residue illnesses previously reported have involved workers in orchard and vineyard crops, where these is substantial dermal contact with foliage [Quinby and Lemmon 1958; Maddy and Lowe, 1981]. Our previous paper on mevinphos poisoning among cauliflower workers is one of the first reports of residue-induced illness among workers in low-lying row crops [Midtling et al., 1985]. The cauliflower workers, and the lettuce workers described in this case, had substantial upper extremity dermal contact with foliage contaminated with residues which were only a few hours old. We have observed two subsequent cases of organophosphate-residue-induced illness of field crews working in these crops.

A remarkable finding was the persistence of complaints, including visual disturbances, headache, and dizziness. These reports continued even after cholinesterase values had stabilized. Other studies have also found such sequelae. A follow-up study of individuals with a history of organophosphate-induced illness found that 43 of 114 individuals had symptoms that persisted for 6 months or longer [Tabershaw and Cooper, 1966]. There has been little follow-up of field workers suffering from organophosphate-residue-induced illness, however. The majority of the group of cauliflower workers we followed reported symptoms 70 days or more after exposure [Midtling et al, 1985]. Headache, gastrointestinal upset, and visual disturbances were persistent complaints in both studies.

The anxiety associated with return to work was very intense in some cases. Initial complaints of eye irritation were followed by concern on the part of subjects that pterygia might be caused by the chemical irritation. One worker complained of palpitations and chest pains. He was given a stress test, and then a Holter monitor while at work. Both tests showed normal cardiac activity.

The return of complete cholinesterase activity appears to have occurred within 14 days after exposure. It is probable that the regeneration rates and degree of cholinesterase inhibition reported here are underestimates, because the first comparable cholinesterase values were not drawn on the day of exposure, but on the following day.

There are two possible explanations for the decline in plasma cholinesterase activity that occurred after the maximum values observed at 14 days after exposure. The workers may have been exposed to low levels of organophosphate residues upon their return to work, depressing subsequent cholinesterase values. Moderate plasma cholinesterase inhibition in the absence of disabling symptoms has been reported among workers handling pesticide-treated produce [Wicker et al, 1979; Brown et al,

1978]. An alternative explanation is the rebound effect, a transient elevation of plasma cholinesterase activity, that has been observed in human subjects exposed experimentally to organophosphate [Rider et al, 1958]. The latter interpretation is supported by the fact that the mean of the subjects' plasma cholinesterase activity 14 days after exposure was found to be greater than that of the control group of field workers, at a point when the RBC cholinesterase activity for the exposed crew was still depressed in comparison to the control group.

Although authoritative texts state that patients suffering from mild organophosphate poisoning may exhibit cholinesterase values within the laboratory normal range [Hayes, 1982], it is also commonly stated that organophosphate-poisoned individuals must have plasma or RBC cholinesterase activity that is 30–50% of normal before symptoms are manifest [Namba, 1971]. In this incident, a group of workers suffered moderately severe symptoms yet manifested plasma cholinesterase inhibition of approximately 16%, and RBC cholinesterase inhibition of approximately 6%, supporting the former viewpoint.

Two separate studies of subjects who ingested small daily doses of mevinphos over a month-long period found that the pesticide inhibited RBC cholinesterase to a greater degree than plasma cholinesterase [Rider et al, 1975; Verbek, 1977]. This contrasts with our previous experience when cauliflower workers poisoned by residues of both mevinphos and phosphamidon (a less toxic organophosphate) had plasma cholinesterase initially inhibited by 66.3%, while RBC was only 32.5% inhibited [Midtling et al, 1985]. The current case provides further evidence that plasma cholinesterase may be more susceptible to inhibition by a single exposure to mevinphos.

The problems inherent in the use of single postexposure cholinesterase values to diagnose organophosphate pesticide poisoning in the absence of baseline data are also illustrated by this case report. The laboratory normal range is too broad to provide a useful standard for the estimation of moderate cholinesterase inhibition. All but two of the subjects had initial plasma cholinesterase levels above the lower limit of the laboratory normal range for the hospital emergency room where they were originally examined, and were released for return to work; yet symptoms prevented a large number of these subjects from returning to work the next day. The subsequent rise in cholinesterase activity over the following 2 weeks demonstrated that the activity of both plasma and RBC cholinesterase had in fact been inhibited.

Sequential postexposure cholinesterase determinations may provide an alternative to use of the laboratory normal range in the confirmation of mild organophosphate-induced illness [Wolfsie and Winters, 1952]. Such testing may improve the accuracy of diagnosis, provide evidence of the work-relatedness of the illness for purposes of compensation, and guide the physician in determining when the patient should return to work.

Patients who present with a history of exposure, cholinergic symptoms, no baseline cholinesterase test, and values at the lower limits of normal should be kept from work involving any additional exposure until their cholinesterase is retested in 3–5 days. Our experience in this incident, and in a previous case [Midtling et al, 1985], suggests that plasma cholinesterase should increase upon retesting if moderate inhibition has occurred. Regeneration of plasma activity is more likely to be observed over this short period, because it recovers more rapidly than RBC cholinesterase activity. If a third test, 3–5 days later, shows a further increase, this may be regarded as clinical confirmation of cholinesterase inhibition.

Cholinesterase-inhibited individuals are at increased risk upon re-exposure to organophosphate or carbamate pesticides because of the cumulative effect of these agents. Although plasma cholinesterase is the more useful enzyme for initial confirmation of an organophosphate-induced inhibition, RBC cholinesterase activity is the appropriate means of determining when recovery has been completed because it is more closely correlated with the toxicologic effect of the nervous system [Durham and Hayes, 1962]. When the patient is employed in a job involving potential re-exposure to these chemicals, caution should dictate that they be kept from work until they are asymptomatic and their RBC cholinesterase has stabilized [Midtling et al, 1985].

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