Clinical confirmation of organophosphate poisoning by serial cholinesterase analyses.

Clinical Confirmation of Organophosphate Poisoning by Serial Cholinesterase Analyses

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• **Three groups of agricultural workers with a history of exposure to organophosphate pesticides were followed up to evaluate the utility of sequential postexposure cholinesterase analyses to confirm organophosphate intoxication in the absence of baseline cholinesterase values. Three or more cholinergic symptoms were reported by 50 of the 72 patients. Initial plasma and red blood cell cholinesterase values of 45 of the workers were above the lower limit of the laboratory normal range. Follow-up examinations, including cholinesterase analyses, were conducted on 57 patients. When final postexposure cholinesterase determinations were taken as estimates of individual normal baseline values, the plasma and red blood cell activity of the three groups was shown to have been inhibited. The data support the use of sequential postexposure plasma cholinesterase analyses to confirm the diagnosis of organophosphate-induced illness in the absence of baseline values.**

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Severe poisoning by organophosphate pesticides may be confirmed by the observation of increased tolerance to atropine and of improvement following administration of pralidoxime (Protopam) chloride.[1] More moderate organophosphate poisoning may be confirmed by comparing plasma and red blood cell (RBC) cholinesterase activities to preexposure baseline values. Because cholinesterase-inhibited individuals are more susceptible to further exposure to organophosphate and carbamate pesticides, cholinesterase activity should be allowed to return to 75% or more of the baseline value before the patient is released for work involving potential exposure to these chemicals.[2]

When the patient has no baseline value, the interpretation of single postexposure values is made difficult by the wide variation in normal cholinesterase activity. Values at the upper limit of the normal range may be 200% greater than those at the lower limit. Thus, patients with high normal values may lose half of their cholinesterase activi and still have values above the lower limit. For this reaso the diagnosis of organophosphate poisoning cannot be rul out when a single postexposure cholinesterase value within the laboratory normal range. The nonspecific natu of symptoms associated with organophosphate poisonin such as headache, nausea, and malaise, makes it even mo difficult for the clinician to reach an unambiguous dia nosis.

Despite the evident utility of baseline cholinestera values, California is the only state that recommends th baseline values be established for pesticide applicator Baseline tests are rarely available in cases of occupation illness that do not involve applicators or in cases of nonocc pational illnesses. Such cases account for most organopho phate poisonings.

Using information from poison information centers, Cal fornia officials estimate that there are as many as 12 0(pesticide illnesses a year in that state alone.[3] Most of the illnesses occur in nonoccupational settings, with organ phosphates the category of pesticide most frequently i volved. The following are examples of nonagricultural se tings for organophosphate poisonings.

- Ingestion by young children at home[3-5]
- Home use of aerosol insecticide[6]
- Indoor area treated by professional exterminators[6]
- Suicide attempts[4]
- Emergency workers exposed to fires and spills[3]
- Outdoor workers exposed to pesticide drift[3]
- Warehouse and transportation workers[3]
- Gardens[3]

We herein evaluate the utility of sequential postexposur cholinesterase analyses in the diagnosis and management c organophosphate-exposed individuals who have no baselin values.

PATIENTS AND METHODS

In each of the three cases reported herein, a group of agricultura workers presented with cholinergic symptoms after exposure t organophosphates but without baseline cholinesterase value Although atropine might have confirmed organophosphate expo sure, most of these workers had moderate symptoms, which di not warrant such treatment. Most patients (51 of 72) were initiall examined in a local emergency room. Plasma cholinesterase value were found to be within the laboratory normal range for 38 of thes

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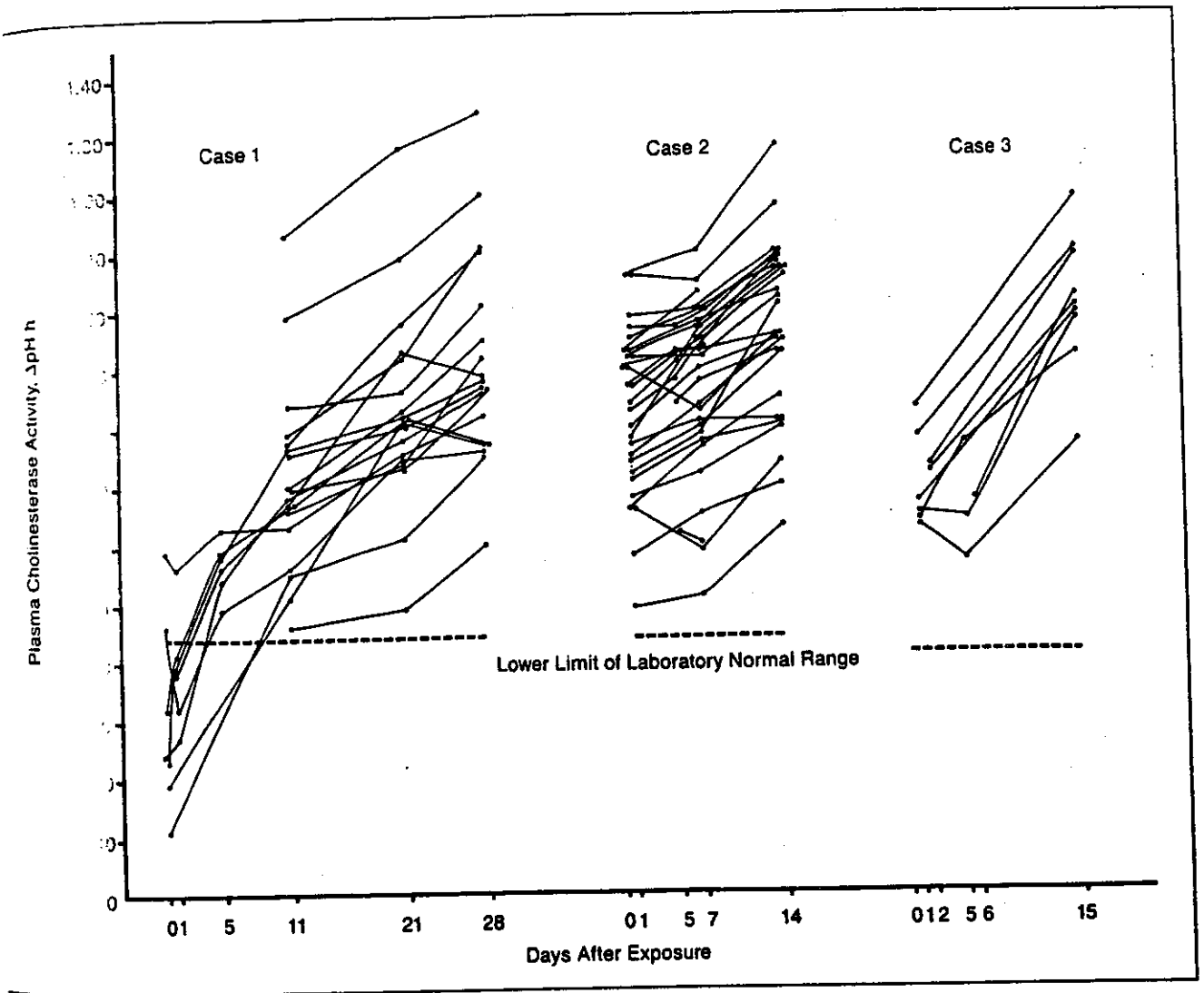

Plasma cholinesterase activity of 57 individuals in three groups of agricultural workers exposed to organophosphate insecticides. Although initial plasma and red blood cell cholinesterase values of 45 of these workers were above lower limit of laboratory normal range, subsequent plasma determinations demonstrated regeneration of cholinesterase activity consistent with moderate organophosphate exposure.

patients, resulting in their release for return to work. The remaining workers waited several days or more before seeking medical attention.

Of the 54 persons exposed to organophosphates in the first two cases, 44 first presented to the investigators with complaints of persistent cholinergic symptoms one to 11 days after exposure. These two groups were followed up with weekly examinations and cholinesterase analyses until symptoms abated and there was no further increase in cholinesterase activity. More limited data were gathered on the patients from the third group. All cholinesterase analyses were done by the Michel method, with a single laboratory performing the serial analyses for each group.

The plasma cholinesterase values observed in these cases are plotted in the Figure. The statistical significance of these changes was tested with repeated-measures analysis of variance and Scheffé comparisons.

REPORT OF CASES

Case 1.—A crew of 23 workers was exposed to the residues of the organophosphates mevinphos (Phosdrin) and phosphamidon (Dimecron) when they began tying leaves over the heads of cauliflower plants only six hours after the crop had been treated. California regulations require a 72-hour wait before workers enter a field treated with these insecticides. The workers experienced blurred vision, eye irritation, dizziness, weakness, disorientation, headache, nausea, and vomiting. Several workers had cramps in their arms, legs, and stomach, and two workers collapsed.

The workers sought medical care in separate groups. Three workers, including the two who had collapsed, were first seen by one of us (C.L.C.). They received atropine and were hospitalized for observation. Thirteen other workers presented at another facility, where each received 2 g of oral pralidoxime. Two of these workers were hospitalized; the others were released for return to work. Six additional workers sought treatment over the following week.

All 23 crew members were invited to attend a series of follow-up clinics, which began 11 days after exposure. Eighteen workers joined the study initially, and another joined ten weeks after exposure. These 19 patients were kept from work due to the persistence of symptoms and were seen weekly until symptoms abated and three successive RBC values showed that cholinesterase levels had stabilized. The seven female and 12 male patients ranged in age from 9 to 72 years.

Cholinergic symptoms initially reported, which abated within four weeks, included nausea, vomiting, abdominal pain, and ataxia. Headache, weakness, and anorexia were more persistent complaints. Reports of blurred vision persisted throughout the 18 weeks of the study.

These patients can be divided into two subgroups: nine patients

who had cholinesterase measurements within 24 hours of exposure and nine patients who did not have their initial analyses until 11 days later. One member of the first group and two from the second were unavailable for follow-up before their RBC cholinesterase levels stabilized.

The plasma cholinesterase levels of the nine patients in the first subgroup, those seen within 24 hours of exposure, increased by an average of 0.314 Michel units (change in pH per hour) between the initial examination and the second examination 11 days later, a significant difference ($P<.01$). These increases ranged from 0.04 to 0.54 units. After 21 days, their plasma cholinesterase activity had increased over initial values from 0.16 to 0.62 Michel units, an average increase of 0.461 units ($P<.01$).

Normal plasma and RBC cholinesterase activity was estimated for patients followed up to the end of the study, by averaging the last three values obtained. The initial plasma cholinesterase activity of the first subgroup was estimated to have been inhibited by an average of 66.3% and the RBC activity by an average of 32.5% (both significant, $P<.01$). Plasma activity of patients in the second subgroup was estimated to have been inhibited by an average of 34.3% at their first examination (11 days after exposure) and RBC activity by an average of 32.5% (both significant, $P<.01$).

There were 18 patients seen at examinations 11 and 21 days after the initial exposure. Plasma cholinesterase activity increased an average of 0.119 Michel units between these examinations, with increases ranging from 0.02 to 0.30 units ($P<.01$).

Of the 16 patients followed up until their cholinesterase activity stabilized, plasma activity reached 95% of the estimated normal within an average of 57 days. It took an average of 66 days for RBC activity to return to the level.

CASE 2.—A group of 31 workers was exposed to the organophosphate mevinphos when they packed and cut lettuce in a field two hours after the crop had been sprayed. California regulations require a 48-hour wait before workers enter an area treated with this insecticide.

Initial symptoms reported were eye irritation, headache, visual disturbances, dizziness, nausea, vomiting, weakness, chest pain or shortness of breath, skin irritation, pruritus, eyelid fasciculation, arm fasciculation, excessive sweating, and diarrhea. Twenty-two (76%) of the workers reported three or more of these symptoms. The members of the crew were taken to a local community hospital where they were decontaminated and examined. The plasma cholinesterase levels of two workers were below the lower limit of the laboratory normal range. Two other workers were hospitalized for observation and treatment of respiratory difficulties. No antidotes were administered, nor were any workers restricted from returning to work the next day.

On the day following their exposure, 29 workers presented to us (J.E.M., A.R.V., P.R., and C.L.C.) with concern about persistent symptoms. They were examined, and blood samples were taken for cholinesterase analysis. One worker with bradycardia was hospitalized for 24 hours' observation.

These 29 patients, men ranging in age from 22 to 46 years, were followed up weekly until eight weeks after exposure and were again examined at ten and 12 weeks. Each examination included a cholinesterase analysis. Almost all of the patients returned to field work within two weeks after the incident, in some cases against medical advice.

Headache, dizziness, visual disturbances, nausea, vomiting, and other symptoms were reported throughout the study. Six workers reported having recurring headaches more than ten weeks after their exposure.

The analyses done on the actual day of exposure are not comparable to the values obtained in this study, as they were performed in a different laboratory. The patients' plasma cholinesterase activity increased between the day after exposure and the examination one week later by an average of 0.051 Michel units, a significant difference ($P<.01$). After 14 days, the plasma activity of the group increased an average of 0.151 Michel units over the initial value ($P<.01$). Increases ranged from 0.04 to 0.35 Michel units, with 24 of 25 patients showing increases by at least 0.08 Michel units.

Plasma and RBC cholinesterase levels increased until 14 days after exposure. When the values obtained at day 14 were used as an estimate of baseline values, plasma cholinesterase activity was inhibited by an average of 15.6%, and RBC cholinesterase activity was inhibited by an average of 5.6%.

Final cholinesterase activity was estimated by averaging the last two cholinesterase values of the 26 patients who were seen at least twice five weeks or more after exposure. Plasma levels for these subjects declined between the 14th day after exposure and this end point. Despite the decline, initial plasma activity was an average of 9.7% below this end point ($P<.01$). There was no significant change in RBC cholinesterase activity after the 14th day.

CASE 3.—A crew of 18 workers was exposed to the organophosphate diazinon at a mushroom farm. The workers were cutting mushroom blight from beds in a darkened growing room when the only entrance to the room was sprayed with the insecticide. Within 15 minutes, all but one of the workers developed cholinergic symptoms, including headache, blurred vision, dizziness, fatigue, nausea, and vomiting.

Four workers were taken to a local hospital where atropine was administered, and they were decontaminated and admitted to the intensive care unit. Plasma and RBC cholinesterase activities of all four were above the lower limit of normal for that laboratory. Two of these workers felt nauseous and vomited shortly after returning to work two days later. Five of the remaining workers were seen within two days following their exposure, and one was seen six days after exposure.

Eight patients (five men and three women, aged 22 to 52 years) had a cholinesterase analysis performed within 48 hours of exposure as well as a follow-up analysis conducted 15 days after exposure. The determinations of the four workers on the day of exposure are not comparable, as they were performed at a different laboratory. Plasma activity significantly increased between the initial examination and the examination conducted 15 days after exposure ranged between 0.14 and 0.36 Michel units, for an average increase of 0.304 units ($P<.01$).

If the follow-up value is taken as an estimate of the patients' normal cholinesterase activity, their plasma cholinesterase level was inhibited by an average of 29.4%, while their RBC cholinesterase level was 27.2% inhibited. A ninth patient who had an initial cholinesterase measurement six days after exposure was estimated to have had plasma cholinesterase activity 34.3% inhibited and RBC cholinesterase activity 34.9% inhibited.

Three patients had cholinesterase determinations on both the day after exposure and four days later. Plasma activity between these two determinations declined for two workers, by 0.01 and 0.06 units. These were the patients who experienced nausea and vomiting shortly after returning to work. A sharp upturn in these patients' plasma activity was observed in later analyses after they had remained away from the workplace.

COMMENT

It has been stated that organophosphate poisoning may be diagnosed only when plasma or RBC cholinesterase activity falls below 50% of normal,[1,2] although authoritative texts state that patients suffering from mild poisoning may exhibit cholinesterase values within the laboratory normal range.[7]

The range of symptoms and degree of cholinesterase inhibition observed in these cases confirm the view that moderate poisoning may occur with less than 50% inhibition. These cases also support the findings of other studies that the velocity of decline in cholinesterase activity is a more critical determinant than the absolute amount of the decline in predicting whether symptoms will be manifest.[8]

A critical question for the clinician is the probability of error when depending on normal ranges to evaluate a single postexposure cholinesterase value. The probability of a false-negative diagnosis can be estimated by hypothesizing a depression of cholinesterase activity and calculating the portion of the population that would still be above the lower limit of the normal range. With RBC cholinesterase activity 25% inhibited, 46% to 90% of the population would still have activity above the lower limit of normal (Table 1). With plasma cholinesterase activity 25% inhibited, 92% to 99% would still have activity within the normal range.

Many of the patients in these three cases had initial

Table 1.—Probability of False-negative Diagnosis of Organophosphate Poisoning Using Cholinesterase Analysis*

Sample	Change in pH/h			% of Population Above Lower Limit of Normal When Inhibited	
	Mean	SD	Lower Limit of Normal	25% Inhibited†	50% Inhibited†
Red blood cell cholinesterase					
40 Men	0.766	0.081	0.58[9]	46.4	<0.1
Women	0.750	0.082	0.56[9]	51.6	<0.1
2 Men	0.861	0.091	0.554[10]	90.1	1.9
Plasma cholinesterase					
Men	0.953	0.187	0.52[9]	91.7	32.1
Women	0.817	0.187	0.38[9]	95.1	62.0
Men	0.912	0.112	0.408[10]	99.9	80.4

*Val... percent of sample that would be above the lower limit of the normal range when cholinesterase activity is inhibited by 25% and by 50%, based on ormal ...s found in studies[9,10] of large samples.
†Per... sample in the area under the normal curve and above the lower limit of laboratory normal when sample mean and SD have been multiplied by the ...antit... less the hypothetical inhibition.

Table 2.—Changes in Plasma Cholinesterase Values Initially Above Lower Limit of Laboratory Normal Range*

	Days From Exposure to Initial Exam				
	Case 1		Case 2	Case 3	
	0	11	1	1-2	6
No. patients seen at initial exam with plasma cholinesterase ... lower limit lab normal range	3/12	6/6	27/29	8/8	1/1
C... ...s in plasma cholinesterase from initial exam to first follow-up ... of days between exams	11	10	6	4	9
... of patients with analyses at both exams	3	6	25	3	1
...rage change between exams, Michel units	0.147	0.067	0.060	0.020	0.350†
...ge of changes between exams, Michel units	0.04-0.31	0.02-0.15	−0.07-0.17	−0.06-0.13	...†
...rage increase between exams, %	24.0	8.4	7.5	10.4	52.2
Ch... ge in plasma cholinesterase from initial exam to second follow-up ... of days between exams	21	18	13	13-14	...
No. of patients with analyses at both exams	3	6	24	8	0
Average change between exams, Michel units	0.287	0.175	0.163	0.299	...
Range of changes between exams, Michel units	0.16-0.41	0.11-0.25	0.04-0.35	0.14-0.36	...
Average increase between exams, % of initial value	50.1	24.0	20.4	42.1	...

*Lab indicates laboratory; exam, examination; and Michel unit, change in pH per hour.
†Only one value.

cholinesterase levels above the lower limit of normal. For this reason, most patients were released for return to work with no plans for follow-up. In all three cases, these patients continued to be symptomatic and sought additional care. The subsequent rise in cholinesterase activity demonstrated that plasma cholinesterase activity had been inhibited by 16% to 66% and that RBC activity was 6% to 32% inhibited.

The data in Table 2 report the increases in plasma activity on subsequent determinations for those patients whose initial values were above the lower limit of normal. Of these 15 patients, all but four had increases in plasma activity on retesting. Each of these four patients had returned to work before the subsequent samples were drawn and had reported that symptoms persisted or grew worse, suggesting that additional exposure may have led to this further decline in plasma cholinesterase activity. When these four patients were removed from work, they had substantial rises in plasma activity in their next subsequent examination.

Increases in plasma activity on subsequent analyses were seen even for those patients whose initial values were drawn several days after exposure, when substantial regeneration already would have occurred. These increases were smaller, however, than the increases observed in the patients whose initial values came immediately after exposure.

Sequential postexposure cholinesterase determinations may provide an alternative to use of the laboratory normal range in the confirmation of moderate cholinesterase inhibition. Such testing may improve the accuracy of diagnosis; provide evidence that the work was related to the illness, for purposes of worker's 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 level is retested in three to five days. The analysis must be performed at the same laboratory for results to be comparable. Our experience suggests that, on

retesting, plasma cholinesterase activity should increase if moderate inhibition has occurred. Plasma activity recovers more rapidly than RBC activity and thus is the more appropriate value to be used for confirmation of the diagnosis. Since individual plasma values vary up to 20% on retesting,[7] the increase observed on a second examination may not be large enough to be considered confirmatory; however, any increase in activity does indicate that a third determination is appropriate. If a third test three to five days later shows a further increase, this may be regarded as clinical confirmation of cholinesterase inhibition.

Sequential postexposure increases in RBC cholinesterase may confirm illness in patients without baseline values who do not present until many days after exposure, when plasma cholinesterase values may have already recovered. A further clinical trial at another center successfully applied this method to RBC activity, when initial values were not obtained until 17 days after exposure.[11]

Since cholinesterase-inhibited individuals are more susceptible to poisoning by exposure to organophosphate and/or carbamate pesticides, caution should dictate that patients should be kept from potential reexposure to these chemicals until they are asymptomatic and their RBC cholinesterase has stabilized.[12] Red blood cell cholinesterase values should be used to determine when recovery is complete, since RBC activity is more closely correlated with cholinesterase in nerve tissue.[13] Since RBC values may vary by 10% on retesting, an increase of less than 10% over the previous value may show that a plateau has been reached. Values at the lower limit of the normal range should be evaluated more strictly.

The cases reported herein indicate that caution is prudent even when the patient is not a pesticide applicator. As already indicated, patients from cases 2 and 3 became ill on return to work. Moreover, six of the patients from case 1 were again poisoned by organophosphate pesticide residues in a separate incident two years after the first, while 12 workers from case 2 became ill in yet another organophosphate poisoning of an entire crew in 1984.

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