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Richard G. Ames Ph.D. , Kyle Steenland , Barbara Jenkins , David Chrislip & John Russo

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Chronic Neurologic Sequelae to Cholinesterase Inhibition among Agricultural Pesticide Applicators

RICHARD G. AMES
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
Berkeley, California

KYLE STEENLAND
BARBARA JENKINS
DAVID CHRISLIP
JOHN RUSSO
National Institute for Occupational Safety and Health
Cincinnati, Ohio

ABSTRACT. To test the hypothesis that chronic neurologic sequelae are associated with cholinesterase depression short of frank organophosphate poisoning, we compared 45 male subjects who had a history of moderate cholinesterase inhibition with 90 male subjects who had neither past cholinesterase inhibition nor current pesticide exposure. Cholinesterase-inhibited subjects were defined as having had a history of (a) red blood cell cholinesterase at 70% or less of baseline or (b) plasma cholinesterase at 60% or less of baseline absent symptoms of frank poisoning. In the subject comparison evaluation, only 1 of 27 neurologic tests (i.e., serial digit performance) was significant statistically, but it was opposite of the direction hypothesized. In a companion study for which the same battery of neurologic tests and the same subjects were used, neurologic sequelae were related to high exposures among subjects who sought treatment for organophosphate poisoning. The data in the current study, in which the subjects experienced lower exposures short of frank poisoning, provide some evidence that preventing acute organophosphate poisoning also prevents neurologic sequelae.

THIS STUDY was designed to test the hypothesis that chronic neurologic sequelae are associated with pesticide exposure when there is cholinesterase inhibition without frank poisoning.

Background

Blood-sample cholinesterase inhibition is a general marker for organophosphate pesticide exposure; cholinesterase inhibition usually precedes acute illness.[1] Organophosphate-induced neurochemical changes, other than cholinesterase inhibition, include increases in blood adrenaline, decreases in monoamine oxidase,[2] and inhibition of neurotoxic esterase (NTE) associated with organophosphate-induced delayed neurotoxicity (OPIDN). Although case reports are often equivocal because of multiple pesticide exposures and interactions with other chemicals, neurotoxic effects in humans have been reported to result with use of the pesticides methamidophos (Monitor), chlorpyrifos (Dursban), and possible merphos (Folex)/DEF,[3] among others. Both chronic psychological and neurologic effects have resulted from organophosphate exposures[2–4]; however, the role of acute poisoning in the causality sequence has not been clarified.[4] Organophosphate and carbamate pesticides have been used widely in California agriculture.

Because California has a mechanism (i.e., medical supervision) to protect agricultural pesticide applicators from accumulative-inhibition poisoning, we feel it is reasonable to ask if prevention of acute poisoning also protects against chronic neurologic sequelae.

Cholinesterase monitoring in California. The goal of

the California medical-supervision program is to limit overexposure of agricultural pesticide applicators to potent cholinesterase-inhibiting pesticides by identifying at-risk individuals and practices. Workers who have red blood cell (RBC) cholinesterase values at 70% or less of baseline or workers who have plasma cholinesterase values at 60% or less of baseline are currently defined as cholinesterase-inhibited and are removed from exposure to organophosphate and *n*-methyl carbamate pesticides until their cholinesterase levels return to 80% or greater of baseline. This program is described elsewhere[5] and has been evaluated previously.[6]

The National Institute of Occupational Safety and Health (NIOSH)-California study. A large-scale, joint NIOSH-California study of the chronic effects of organophosphate poisoning and cholinesterase inhibition short of poisoning was planned and implemented. Poisoned subjects, identified from pesticide illness reports, and subjects who had a prior history of cholinesterase inhibition short of poisoning, based upon medical supervision records for 1985, 1988, and 1989, were used in the study. In this larger joint study, poisoned subjects, prior cholinesterase-inhibited subjects, and comparison subjects were brought to a central location during 1990 for medical and neurologic evaluation. All subjects were asked to bring a friend of comparable age ("comparison subject") who was not currently exposed to pesticides and who did not have a history of pesticide poisoning; however, not all subjects did so. An analysis of the poisoned subjects is presented elsewhere.[7]

Method

Description of sample. A subset from the larger, joint NIOSH-California study, comprising 45 male subjects with prior history of documented cholinesterase inhibition below worker removal thresholds (but with no evidence of frank poisoning) was analyzed and compared with 90 subjects. None of the subjects was expected to have current cholinesterase inhibition.

Cholinesterase activity. Reports of RBC and plasma cholinesterase activity for 1985, 1988, and 1989—gleaned from records of the California medical-supervision program and from assays by clinical chemistry laboratories certified for medical monitoring purposes—were used to define subjects with prior cholinesterase inhibition for this study.

Pesticide exposure. In this study, we assumed that workers who were being monitored medically and who had been removed from exposure because of a below-threshold cholinesterase test had, in fact, been exposed to one or more cholinesterase-inhibiting pesticides. Work history could not be used to identify the organophosphate or carbamate exposures responsible for the inhibition episode. It was, therefore, impossible to study either individual pesticides or pesticide interactions.

Neurologic factors. Neurologic factors were measured with neurobehavioral tests, nerve-conduction tests, vibrotactile sensitivity tests, a test of postural sway, and a clinical exam. Individual tests are described below.

Nerve-conduction amplitude (i.e., number of nerve fibers affected) and nerve-conduction velocity (i.e., time to response divided by distance) were tested on three arm nerves: (1) median motor, (2) median sensory, and (3) ulnar sensory. Both the peroneal motor and sural sensory leg nerves were also tested. The nerve-conduction test protocol is described by Sweeney et al.[8] Vibrotactile thresholds for fingers and toes were established by the method of limits described by Gerr et al.[9]

Eight computerized neurobehavioral tests from the Neurobehavioral Evaluation System[10] were used: (1) mood scales, (2) finger tapping, (3) sustained attention, (4) hand-eye coordination, (5) simple reaction time, (6) symbol digit, (7) pattern memory, and (8) serial digit learning.

The noncomputerized Santa Ana dexterity test and a pursuit aiming test were adopted from the World Health Organization test battery.[11] A computerized test of postural sway was used to measure central nervous system function. Additional details about these neurological tests and testing procedures may be found in the companion paper prepared by Steenland et al.[7] or may be obtained from the authors.

Other measures. Other measures included age, ethnicity, language chosen for the test, weight, grade level, smoking status, immediate before-exam use of alcohol and coffee or tea, and hours of sleep. Body-mass index (BMI) was calculated as weight divided by height, quantity squared.

Functional category scales. Neurologic measures were grouped into functional categories, and, when

Table 1.—Description of Subjects Included in the Study

Characteristic	Cholinesterase inhibited (n = 45)	Comparisons (n = 90)
Age (y) ($\bar{x} \pm SD$)	38.2 ± 11.7	29.5 ± 10.9
Grade level ($\bar{x} \pm SD$)	9.9 ± 4.1	10.6 ± 3.6
BMI* ($\bar{x} \pm SD$)	27.5 ± 4.0	26.8 ± 4.7
Ethnicity†		
Hispanic	29 (64%)	50 (56%)
White, non-Hispanic	13 (29%)	35 (39%)
Other	3 (7%)	5 (5%)
Preferred language‡		
English	29 (67%)	56 (66%)
Spanish	14 (33%)	29 (34%)
Current smokers	12 (27%)	30 (33%)
Current drinkers	28 (62%)	65 (72%)
Hours of sleep§ ($\bar{x} \pm SD$)	7.3 ± 1.5	7.2 ± 1.5
Cups of coffee# ($\bar{x} \pm SD$)	1.0 ± 1.2	0.9 ± 1.0
Alcoholic drinks// ($\bar{x} \pm SD$)	1.3 ± 1.8	1.8 ± 2.4

*BMI = body mass index: weight in lb./2.2/(height in in./39.37)^2.
†Self-identified ethnicity.
‡Language requested for testing.
§Hours of sleep the night before the test.
#Cups of coffee or tea the morning of the test.
//Alcoholic drinks the night before the test.

Table 2.—Test of Cholinesterase Inhibition Effect on Neurologic Outcomes: Subjects Versus Comparisons, by Adjusted Regression Models*

Neurologic outcome	Cholinesterase inhibition		Regression model	R^{2}‡	p§
	b value†	Significance			
Nerve conduction					
Median sensory NCV	0.04	NS	A	.11	.0056
Median motor NCV	–0.37	NS	A	.04	.27
Ulnar sensory NCV	1.28	NS	A	.14	.0007
Peroneal motor NCV	0.25	NS	A	.12	.002
Sural sensory NCV	0.73	NS	A	.10	.01
Median sensory amp	–1.46	NS	A	.35	.0001
Median motor amp	0.75	NS	A	.15	.0005
Ulnar sensory amp	–4.12	NS	A	.20	.0001
Peroneal motor amp	0.75	NS	A	.05	.20
Sural sensory amp	–2.32	NS	A	.32	.0001
Vibration					
Finger	0.06	NS	B	.06	.20
Toe	–0.12	NS	B	.37	.0001
Neurobehavioral					
Tapping	5.59	NS	C	.12	.0026
Hand-eye	0.07	NS	C	.20	.0001
Simple reaction time	4.12	NS	C	.02	NS
Sustained attention	4.93	NS	C	.03	.3680
Symbol digit	0.07	NS	C	.47	.0001
Pattern memory	1.15	NS	C	.07	.0788
Serial digit	–0.80	$p < .05$	C	.32	.0001
Mood scales					
Tension	0.01	NS	C	.02	NS
Depression	–0.15	NS	C	.02	NS
Anger	–.21	NS	C	.03	NS
Fatigue	0.07	NS	C	.06	NS
Confusion	0.14	NS	C	.15	.0007
Motor coordination					
Pursuit aiming	–4.62	NS	D	.10	.0071
Santa Ana dexterity	0.36	NS	D	.26	.0001
Postural sway	0.03	NS	E	.05	.4242

Notes: NCV = nerve-conduction velocity, amp = amplitude, and NS = not significant.
*The full models used in this Table ($Y = a + b_i + e$) include the neurologic outcome dependent variable (Y), the inhibited/noninhibited predictor variable (X_1), and one of the following adjustment models: A = age, ethnicity (Hispanic/non-Hispanic), and BMI; B = age, weight, ethnicity (Hispanic/non-Hispanic), and height; C = age, grade level, and test language (Spanish-English); D = ethnicity (Hispanic/non-Hispanic), age, and grade level; and E = ethnicity (Hispanic/non-Hispanic), age, grade level, height, and weight.
†The adjusted b values are the regression coefficients associated with being a "subject" (i.e., having documented prior cholinesterase inhibition in the absence of frank poisoning), rather than being a never-cholinesterase-inhibited comparison. A positive coefficient would mean that prior cholinesterase inhibition was related to impairment of neurologic outcome.
‡R^2 = the percentage prediction of the entire model.
§p = Statistical significance of the entire model.

necessary, multiple-item simple scales were created. These functional categories were nerve-conduction velocity, nerve-conduction amplitude, vibration, neurobehavioral battery, mood, motor coordination, and postural sway. The aggregation of tests is shown, by test category, in Table 2.

Consistency of scales. The following functional categories of neurologic effects were found to be correlated: (a) nerve-conduction amplitude and velocity, $r = .28$; (b) nerve-conduction velocity and vibration, $r = .29$; (c) mood and the neurobehavioral battery, $r = .24$; and (d) mood and motor coordination, $r = .14$.

Analysis methods. We used multiple linear regression analysis to test the hypothesis that subjects with prior cholinesterase inhibition differed from comparison subjects with respect to the various neurologic measures. Regression models were adjusted by factors appropriate for any specific neurologic test. Five adjustment models, A through E, were defined: A = age, ethnicity (Hispanic–non-Hispanic), and BMI; B = age, weight, and ethnicity; C = age, grade level, and language of test (Spanish or English); D = ethnicity; and E = ethnicity, age, grade level, height, and weight. Nerve conduction tests were adjusted by model A, vibration tests by model B, neurobehavioral and mood test by model C, and motor coordination tests by models D and E (Tables 2 and 3).

Table 3.—Test of Cholinesterase Inhibition Effect on Scales of Neurologic Outcomes: Subjects Versus Comparisons, by Adjusted Regression Models

Neurologic outcome scales	Cholinesterase inhibition		Regression model	R^{2*}	p
	b values	Significance			
NC velocity	0.14	NS	A	.09	.017
NC amplitude	0.18	NS	A	.34	.0001
Vibration	0.002	NS	B	.09	.027
Neurobehavioral	−.21	NS	C	.19	.0001
Mood	−.17	NS	C	.06	.0826
Motor coordination	−.06	NS	D	.20	.0001
Postural sway	0.15	NS	E	.07	.1599

Note: NS = not significant.
*R^2 = the percentage prediction of the entire model.
†p = statistical significance of the entire model.

Subjects versus comparison status was binary coded (i.e., 1 for cholinesterase-inhibited subjects, 0 for noninhibited comparison). The adjusted b values are the regression coefficients associated with being a subject (i.e., having documented prior cholinesterase depression in the absence of frank poisoning, rather than being a noninhibited comparison), after removal of the effects of the adjustment model. The percentage prediction of the entire model, R^2, and its statistical significance level are presented in Tables 2 and 3.

Results

Description of sample. All subjects were male. Prior cholinesterase-inhibited subjects were older than comparison subjects, had completed a lower grade level, had slightly more body mass, were less likely to be current smokers or current drinkers, and drank alcohol less often the night before the test (Table 1).

Subjects versus comparisons. Only 1 of the 27 neurologic measures that were considered separately (i.e., serial digit performance in the neurobehavioral battery) was significant statistically ($b = -.80$, $p < .05$ [Table 2]). The negative coefficient indicates that having prior cholinesterase inhibition was associated with enhanced neurologic performance (i.e., in the opposite direction than hypothesized). Subject-comparison status was not a predictor of neurologic outcome for any of the function group scales (Table 3).

Discussion

We found no evidence that moderate organophosphate or *n*-methyl carbamate pesticide exposure, as indexed by prior blood cholinesterase inhibition absent frank poisoning, is associated with chronic or long-term neurologic sequelae. In the companion study, in which subjects with higher exposure and frank poisoning were compared with these same comparison subjects, the authors reported some evidence of chronic neurologic sequelae for some of the tests reported in our study.[7] Rosenstock et al.,[13] McConnell,[14] and Savage et al.[15] also reported chronic neurologic sequelae to organophosphate poisoning. Tabershaw and Cooper[16] also reported similar effects, but their study lacked controls. The data in our study, therefore, provide some assurance that preventing acute organophosphate poisoning may also prevent chronic neurologic sequelae.

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Requests for reprints should be sent to Richard G. Ames, Ph.D., California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, 2151 Berkeley Way, Annex 11, Berkeley, California 94704.

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