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16. Abstract

Three squirrel monkeys did not respond to visual stimuli for at least one hour following combined administration of mevinphos (Phosdrin) and atropine. Therefore, aerial applicator personnel being treated for mevinphos (Phosdrin) poisoning with atropine may show potentially hazardous dysfunctions of visual perception. Some mechanisms for this effect were discussed.

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TRANSIENT BLINDNESS DUE TO THE COMBINED EFFECTS OF MEVINPHOS AND ATROPINE

I. Introduction.

Organophosphate pesticide (OP) toxicity is of continuing concern to aerial applicator personnel. The toxic effects of OPs which may be seen in the field are difficult to evaluate since most laboratory tests are done with a single OP in isolation while, in the "real world", aerial applicator personnel are exposed to a complex mix of agricultural chemicals including several different OPs and carbamates. Further, some aerial applicators may try to control effects of toxic doses of OPs by use of atropine, pralidoxime (Protopam, 2-PAM) and/or other drugs so that they can continue working. Evaluation of the effects of such drug mixtures is complex at best. At the doses required to produce overt signs and symptoms of poisoning, any given OP has a wide spectrum of actions, chiefly, but perhaps not entirely, related to its effects on cholinergic functions. The same is generally true of the OP antidotes such as atropine. Thus, combinations of agonists and antagonists could result in unexpected toxic effects. Experiments to investigate these possibilities were initiated under Task AM-B-73-TOX-15. Preliminary results were unexpected and disquieting; sufficiently so that early publication of this preliminary note was deemed essential.

II. Methods.

Three squirrel monkeys were used. The animals had been implanted with chronically placed intracerebral electrodes some months prior to these experiments. Data derived from these electrodes will be presented in another report. At this time it is only necessary to note that there were no signs of visual deficits in these animals, although two electrode tracks passed through the lateral geniculate nucleus, bilaterally. In these experiments, the animals were placed in a conventional 2-plate restraint chair. Mevinphos (Phosdrin), the specific OP under test, was injected intramuscularly in a dose of 0.4 mg/kg. This dose was an estimated LD_{10}—which implies a statistical probability that ten per cent of a large group of animals tested at this dose would die. This dose was deliberately chosen to increase the likelihood of producing readily detectable toxic signs. After development of initial signs of OP poisoning, atropine was injected intramuscularly in doses of 2 mg/kg, repeated every three minutes, until the parasympathomimetic signs of OP poisoning vanished. The behavior of the animals was followed for at least three hours after injection by three to five observers in the laboratory. We checked responses to touch and handling, to sound (tapping the side of the cage, key jingling, etc.) and to light (flashlight beams, sudden hand movements, threatening gestures, etc.). All observers participated in the testing and no result was recorded unless all observers agreed that a response was present or absent.

III. Results.

All animals developed typical parasympathomimetic signs within 2.5 min. of mevinphos injection. These signs included salivation, pupillary constriction, tremor and muscular weakness. Within 3–4 minutes of injection all animals developed seizures. One animal had prolonged, hard, tonic-clonic seizures which lasted for eight minutes. This animal required artificial respiration for about a minute during the peak of seizure activity. The parasympathomimetic signs were also difficult to control with atropine and this animal received a total dose of 30 mg/kg. The other animals were less severely affected by the insecticide and received less atropine; 15 mg/kg and 6 mg/kg respectively. In all animals the initial period of severe symptoms lasted 15–30 minutes. For the next 2.5–3.0 hours the animals in the observation cage appeared normal, though weak. They responded to handling with their

usual squealing and aggressive behavior directed toward the hand or hands holding them. If touched, they would jump away from the touch and, sometimes, bare their teeth and/or squeal. Responses to sound were clearly normal. A sudden noise, such as tapping the cage side or key jingling, caused a startle response followed immediately by orientation toward the sound. The animals also followed movements of "strange" noises, such as key jingling, in the space around them. All of these responses to auditory stimuli were quite normal for a squirrel monkey.

However, to our complete surprise, the animals which exhibited such normal responses to other stimuli appeared to be totally blind. There was no response of any kind to moving spots of light or sudden flashes which would normally elicit startle or orientation movements. There was also no response at all to "threatening" movements toward the animal which normally elicited startle, orientation, retreat and teeth-baring responses. Further, if a flashlight beam was directed into the animals' eyes, which were partly dilated from the atropine, there was no movement or *any* indication that the animal was being stimulated in any way. Normally, the responses to this stimulus include instant eyelid closure, head turning and escape movements. Varying ambient light from 50 ft.-candles to 0.1 ft.-candles (bright to dim room light) had no effect on this lack of response. However, at times the animals gave the observers the impression that they realized that *something* was happening when lights were flashing, etc., but they did not know specifically what it was. This period of blindness lasted for 1.5 ± 0.5 hours. Some vague signs of visual sensitivity were seen after this time followed within 5–10 minutes by complete visual normality—normality within the limits of these admittedly relatively crude observations. The animals remained slightly weak and "looked ill" for a further 2–3 hours, and all were completely normal the next morning—20 hours after injection.

IV. Discussion.

These results indicate a very serious potential hazard to aerial applicator personnel. In cases of exposure to both atropine and mevinphos some degree of centrally mediated impairment of visual function is probably to be expected. Blindness, seen here, is very dramatic and certainly has not been reported from the field.[4 5 6 9 10] However, it seems likely from these preliminary experiments that combinations of mevinphos and its nominal antagonist atropine could cause some degree of potentially dangerous visual dysfunction in aerial applicator personnel.

These effects are unique. There are no reports in the literature of blindness following OP or atropine poisoning in experimental animals or man. High doses of atropine alone, in excess of 10 mg/kg, will cause a complex variety of behavioral disorders and bizarre behavior patterns in cats, monkeys and man,[1 12 13] but the animals under study appeared reasonably normal, except for their blindness. OP poisoning can, of course lead to visual dysfunction of peripheral origin,[4 11] but centrally-mediated visual deficit has not been reported in any studies available to us. The animals did go into seizures after mevinphos and the blindness could possibly be a post-ictal phenomenon. However, the rapid recovery of normal tactile and auditory responses tends to argue against this.

Perhaps the most surprising symptom seen was the complete lack of response to a bright flash light beam shone directly into the animal's eye in a darkened room. This stimulus was painful to the human observers and normally elicited rapid escape behavior in the monkeys. Again other sensory responses seemed normal. Indeed the animals would respond to the "click" made by the switch on the flashlight some four feet away. The lack of any response to the bright light into the eyes argues that the blindness is real (not due, say, to inattention) and that the locus of action for this effect must be in the retina or the superior colliculus. In either case oculomotor reflexes would tend to be inhibited which would not be true for a block in the lateral geniculate nucleus or visual cortex. However the monkeys at times seemed to know that *something* was happening during periods of visual response testing and this is inconsistent with the notion of a complete retinal blockade. Thus, the primary localization of the blindness-producing OP+atropine effect seems most likely to be in superior colliculus. The blindness seen is, however, more severe than that produced by massive collicular lesions so the collicular effects cannot be the only factors.

Specific and high concentrations of acetylcholinesterase are seen in both retina and superior colliculus using histochemical staining technique.[7] Microiontophoretic and more conventional neuropharmacological experiments have established that cholinergic receptors do exist in these areas.[2 3 7 11] Furthermore, some of these experiments indicate that certain of the cholinergic receptors are nicotinic and are not blocked by atropine.[2 11] The duration of the apparent blindness extends to 1.0–2.0 hours after mevinphos injection. This is the approximate duration of the behavioral and electrophysiological changes seen after mevinphos but is rather less than the duration of atropine effects, judged by pupillary reactivity and diameter. This suggests that the blindness is related to the combined actions of atropine and mevinphos, and could result from the presence of high levels of acetylcholine at unblocked nicotinic receptors at a time when the atropine-sensitive muscarinic receptors are blocked.

V. Summary.

Three squirrel monkeys did not respond to visual stimuli for at least one hour following combined administration of mevinphos (Phosdrin) and atropine. Therefore, aerial applicator personnel being tested for mevinphos (Phosdrin) poisoning with atropine may show potentially hazardous dysfunctions of visual perception. Some mechanisms for this effect were discussed.

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of a causal relationship between the changes in hippocampal potentials seen here and their behavioral inhibition. As in the present study, no peripheral symptomatology was seen at doses of less than 0.250 mg/kg.

Perhaps the most noteworthy finding was that mevinphos could induce hippocampal biopotential and behavior[14] changes—including seizure activity—without any of the usual peripheral manifestations of OP poisoning. This is a bit surprising, and disquieting. Although mevinphos is said to penetrate the blood-brain barrier more readily than most other OP pesticides, it does not penetrate freely.[11,20] Thus, one would expect that peripheral effects would tend to develop before the CNS effects of the OP. That this order is reversed suggests that the effects of mevinphos on AChE in the CNS differ from those in the periphery and/or that mevinphos has actions in the CNS not directly related to its effects on AChE.

More importantly, the data suggest that aerial applicator personnel exposed to mevinphos—and, perhaps, the other OPs—can suffer significant CNS dysfunctions, even local hippocampal seizures, in the absence of the usual "peripheral" pathognomonic signs. Since hippocampus "plays a crucial role in the programming of acquired sensory-response patterns,"[6] the hazards to the aerial applicator may be substantial in absolute terms, the more so since patients seem generally unaware of hippocampal dysfunctions, even though substantial deficits in performance, consciousness or memory may be present.[1,9] As a practical matter these data reinforce previous emphasis on the need for extreme caution in handling the organophosphate pesticides.

V. Summary.

Mevinphos (Phosdrin) was found to inhibit the amplitude of hippocampal evoked potentials in unanesthetized squirrel monkeys with chronically indwelling electrodes. The threshold dose was 0.050 mg/kg and the maximal dose studied was 0.200 mg/kg. Doses above 0.200 mg/kg induced hippocampal seizures. Within the dose range of 0.050 mg/kg to 0.200 mg/kg the amplitude and duration of the inhibition were directly proportional to dose. No peripheral signs of poisoning, such as tremor or salivation, were seen at doses of 0.200 mg/kg or under. The discussion emphasizes that mevinphos produces changes in brain function in the absence of the peripheral symptomatology usually taken as indicators of poisoning by aerial applicator personnel. Therefore, it is concluded that exposure to mevinphos may be unexpectedly hazardous since the aerial applicators may be unaware that they have been poisoned.

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