Ital. J. Neurol. Sci. 9:437-446, 1988

CNS involvement in acute organophosphate poisoning: specific pattern of toxicity, clinical correlates and antidotal treatment

Finkelstein Y.*, Taitelman U.*, Biegon A.**

* *Israeli National Poison Control Center and Intensive Care Unit, Rambam Medical Center, Haifa*

** *Weizmann Insitute of Science, Rehovot, Israel*

The present review was designed to integrate both experimental and clinical data and to focus on the problems of management of severe cases of acute organophosphate poisoning, which always show CNS involvement. AChE activity, in discrete regions of the human brain, was studied by quantitative histochemistry of 40 μ thick sections. The regional effects of AChE inhibition by organophosphates was examined in a comparative study of the brains of two victims and two control brains, matched for age and sex. The pattern of AChE inhibition was regionally selective. The most significant decreases were observed in the neocerebellum, thalamic nuclei and the cortex. This specific distribution of AChE inhibition may be correlated with some of the clinical characteristics of acute organophosphate poisoning. The diagnostic value of blood AChE levels was examined in a personal series of 53 patients, who needed artificial ventilation, intensive care monitoring and antidotal treatment. The effects and side-effects of the antidotal treatment were reassessed. Recommended regimen of therapy was outlined, based upon experience in this series and in recent animal studies. The logical therapy would be and almost always in the co-administration of an anticholinergic drug (usually atropine) and an AChE reactivator (oximes) in order to rapidly obtain the most beneficial effect in the critically ill patient. Seizures that do not respond to the specific antidotal therapy, should be treated with I.V. benzodiazepines. Artificial respiration and supportive measures are essential for patient' survival. They enable the patient to gain the necessary time for sufficient recovery of AChE activity.

Key-Words: Organophosphate poisoning – acetylcholinesterase – quantitative histochemistry – central nervous system – atropine – obidoxime.

Introduction

Acute poisoning by organophosphorous ester (OP) pesticides is of great concern throughout the world. Pesticides are responsible for 4% of fatalities due to all types of unintentional poisoning [58].

The acute toxic effects of OP are primarily due to inhibition of acetylcholinesterase (AChE) activity in the nervous system. Most reported instances of

acute OP poisoning have been due to parathion (Diethyl-p-nitro-phenyl-phosphorothioate or methyl-parathion [24]. Following absorption, parathion is converted in the liver to the active AChE inhibitor paraoxon and transported to the cholinergic synapses, where it causes accumulation of acetylcholine (AChE) [40]. The excess of AChE at the synaptic gaps leads to initial stimulation and later inhibition of neurotransmission [57]. The degree of severity of poisoning is dependent on the degree of inhibition of synaptic AChE [57].

The major cause of death is respiratory failure, which is the result of weakness of respiratory muscles (nicotinic syndrome), and pulmonary muscarinic syndrome, including bronchospasm and bronchorrhea; and depression of the CNS respiratory centers [72]. In the non-fatal cases of acute poisoning, major clinical sequelae may be caused by persistent toxic effects within the CNS which may be regionally selective. This issue could be best investigated by measuring AChE activity in discrete brain regions, in cases of rapid fatality after exposure to parathion. Traditionally, quantitative results with limited neuronatomical resolution could be obtained by measuring enzyme activity in brain homogenates [36], while qualitative results with high resolution were achieved by histochemical staining [38]. Recently, we have employed a computerized method of quantitavie histochemical analysis [4,32]. This method enabled us to define the fine regional pattern of inhibition of AChE activity by parathion, in cases of fatal intoxication [14,15]. This detailed knowledge of the OP effects on the human CNS may help elucidate the basic mechanisms underlying the clinical manifestations of OP neurotoxicity.

The present review integrates the experimental and clinical data, and focuses on the problems of management of the severe cases, which always show CNS involvement.

The pattern of AChE inhibition in CNS

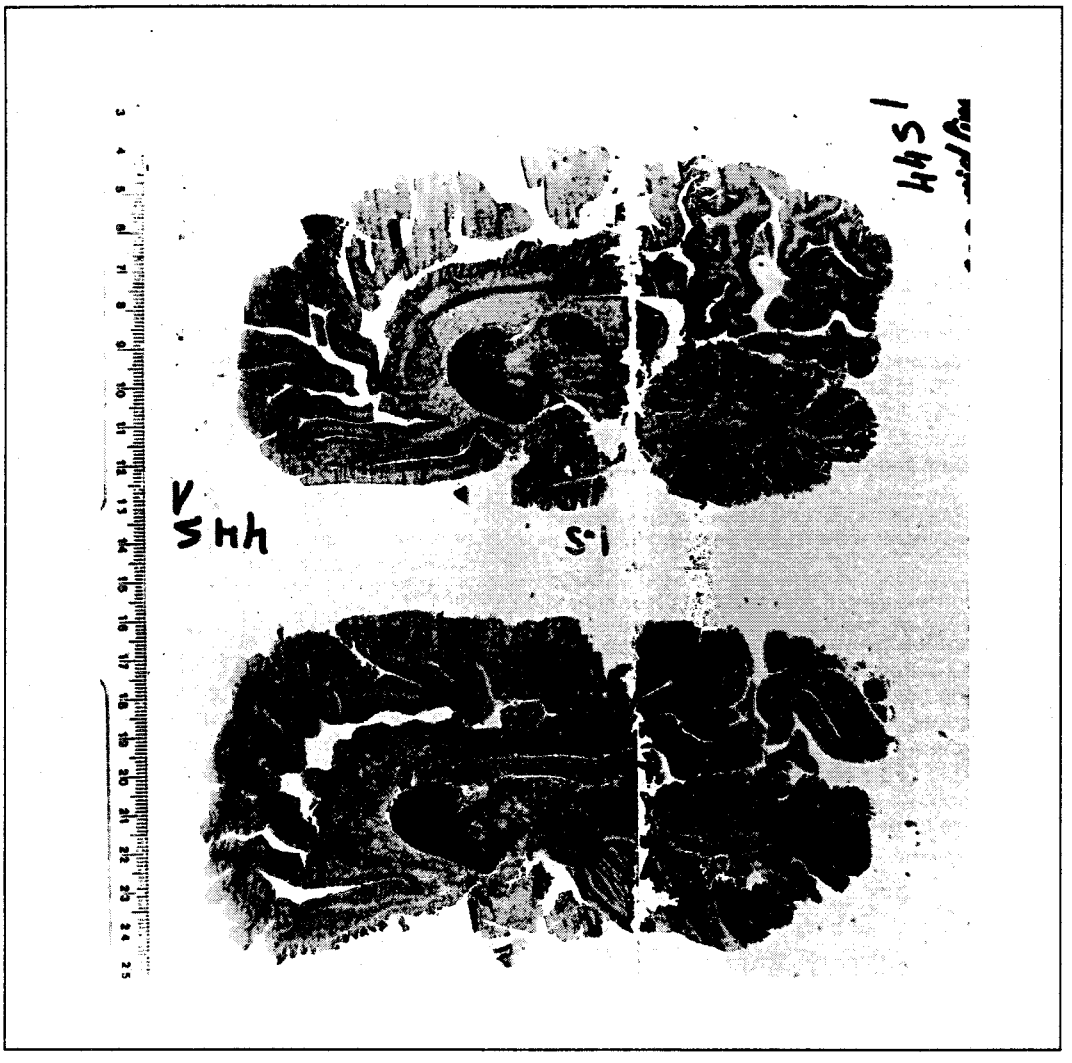
The neuroanatomical distribution of AChE inhibition in the human brain postmortem was examined in a comparative study of the brains of two victims of lethal parathion intoxication and two control brains matched for age ad sex. AChE activity in discrete brain regions was studied by quantitative histochemistry of 40 μ thick sagittal or coronal cryostat sections from the 4 brains [4]. The sections were stained for AChE activity [38] alongside with tissue standards containing known amounts of purified AChE. The staining density was quantified by a computerized image analysis system and converted to enzyme content units via the standard curve [32].

In general, all the AChE activities were within the same order of magnitude which we determined previously for brains with post-mortem delay up to 48 hours [4]. In the first pair, we esamined coronal sections at the level of the anterior basal ganglia from the right hemisphere. In the second pair, sagittal section were taken from the left hemisphere, about 1 cm lateral to the midline.

Case 1, control brain: the distribution of AChE acrivity was heterogeneous. Measurements in different brain regions exhibited AChE activities in the range of 5-50 ng/mg protein, in agreement with previous findings [4,52]. In the frontal and temporal cortex, AChE activity from 6 to 15 ng/mg protein. In the basal ganglia, the activity was relatively high, reaching levels up to 50 ng/mg protein. The activity within the white matter was rather low.

Parathion-poisoned brain: examination of AChE activity, in the same areas mentioned above, showed a region-specific pattern of AChE inhibition. In the cerebral cortex, the most marked decrease was observed in the frontal gyri, the inferior (8%) an the superior (70%). The degree of inhibition in other frontal and temporal areas ranged between 33%-60%. It should be emphasized that the absolute values of activity, measured within the cortex, were very low. In the ganglia, the inhibition was relatively moderate (24%-39%). No effect was seen in the white matter.

Case 2, control brain: AChE activity, in the grey matter regions examined, was heterogeneous (Fig. 1) and ranged from 6 to 60 ng/mg protein, overlapping the distribution observed in the control brain of Case No. 1. In the frontal and temporal cortices, AChE activity was 6-15 ng/mg protein. A layer-by-layer analysis showed that the activity was more intense in the middle and inner cortical layers (II-VI), where it reached levels up to 18 ng/mg protein. Divergent levels of AChE activity were observed within the thalamus. In discrete nuclei of the lateral group and the metathalamus the activity was relatively high (about 30 ng/mg protein), while in a small compartment of the ventral nuclear group AChE activity was lower (appros. 10 ng/mg protein). In other diencephalic structures, the basal ganglia (head of the caudate nucleus and putamen) were noted to contain AChE activity (50-60 ng/mg protein): while only low activity (5-10 ng/mg p) was measured in the tiny subthalamic structures – Corpus Luysi and the nuclei of the zona incerta and Forel's field H (pre-rubral field). In the mesencephalon, high



The control subject was a 43-year-old male, who committed suicide by hanging. The parathion case was a 36-year-old male, who committed suicide by parathion ingestion.
The staining procedure was performed according to the method of Köelle.

Fig. 1. *AChE activity in normal brain and the brain of a parathion poisoning victim (case 2).*

AChE activity (approx. 40 ng/mg p) was found in the substantia nigra. In the cerebellum, various regions contained different levels of AChE. The highest value (appros. 40 ng/mg p) was measured in the molecular layer of the neo-cortex and in the dentate nucleus (which is intimately related to the neo-cerebellar system). Lower levels of activity (14 ng/mg p) were detected within the granular layer of the cortex, while non activity was observed in the layer of Purkinje cells. Minimal activity was measured in the white matter areas of the corpus medullare and peduncles.

Parathion-poisoned brain: the pattern of AChE activity in this brain differed substantially from the pattern defined in the control brain. As a rule, the findings were in accordance with those of the previous case. As the AChE activity inhibition was region-specific, it was greatest in the cerebellum,

in the molecular layer (85%) and the dentate nucleus (75%). Lesser inhibition (65%) was observed in the granular layer. No inhibition was found in the cerebellar white matter and peduncles. In the cerebral cortex, AChE activity was inhibited by 40%-45% in the cuneus (occipital lobe) and the cingulate gyrus (limbic system). No significant differences among the cortical layers ware detected. Diverse degrees of inhibition were seen in the thalamus (46-65%).A moderate decrease (31%-35%) was observed in the substantia nigra and the head of the caudate nucleus, while a very small decrease (10%) was measured in the putamen. A more marked decrease (49%) was noted in the subthalamic nucleus. In the subcortical white matter, AChE inhibition was mild (10%-16%) in different areas of the corpus callosum, the anterior commisure and the thalamic fasciculus (H1).

Clinical correlates of the region-specific AChE inhibition

The findings described here demonstrate that acute parathion poisoning results in varying degrees of inhibition of AChE activity in various regions of the human brain. This observation may help to explain some of the clinical characteristics of OP poisoning.

Many studies of the clinical aspects of OP poisoning were subject to methodological criticism, for their failure to determine the extent of cholinesterase (AChE) inhibition [41]. Moreover, there is relatively little information available about the pathology of OP poisoning [40]. In humans, necropsies have been of limited value [48]. Pathological studies in animals revealed non-specific edematous changes in the brain [31], similar to our own findings. In biochemical studies, the ChE activites in the brain and other organs were decreased to below 30% of normal values [36]. However, all the studies concerning the CNS were qualitative in nature. There was non systematic information regarding the quantitative changes in AChE activity within the CNS after parathion poisoning. The details of these changes are of obvious relevance, as the more complex neurologic and behavioral effects associated with cholinergic pathways are likely to be exerted in well-defined, discrete regions.

The remarkable reduction of AChE activity that we observed in the molecular layer of the cerebellar cortex may be responsible for the severe impairment of coordination, ataxia and slurring of speech, observed after marked exposure to parathion [40, 41, 53]. The cholinergic dysfunction of the cerebral cortex, following parathion poisoning, may be well correlated with the changes in AChE activity, since cortical AChE may serve as a reasonably good index of cholinergic activity [52].

The remarkable AChE inhibition in the frontal regions examined, could be correlated with the signs of reduced cognitive efficiency and psychomotor slowing [40] (frontal bilateral signs [47]), impaired reading comprehension [5], (frontal subdominant [46]) and expressive language defect [22, 57] with intermittent pauses and perseverations [5, 22] (frontal dominant [45]). These signs are the earliest to appear during acute parathion poisoning [40].

The AChE inhibition in the dominant temporal lobe may contribute [44] to the amnestic word finding disturbance [5, 22]. Dysfunction of the mesial temporal cholinergic pathways has been implicated in the pathophysiology of acute confusional state, and ACh plays a crucial role in many aspects of arousal, mood and memory [2, 8, 17, 33, 51, 53].

OP poisoning frequently precipitates a depressive syndrome and may reverse hypomanic symptoms. However, our study of AChE activity in the meso-temporal and limbic structures was incomplete and further investigation is indicated. Similarly, it may be of interest to examine the brain stem systematically, since a critical component of OP poisoning is central respiratory paralysis [29, 30] due to a direct action on the medullary respiratory centers [7, 21, 64, 65].

The levels of inhibition, required to produce central effects, might be very close to lethal level [39]. Therefore, even slight reactivation of the enzyme by oxime antidotal therapy, could have very dramatic clinical effects [43].

Thus, some of the characteristic features of acute parathion poisoning may be attributed to the specific anatomical pattern of AChE inhibition, detected within the CNS. This pattern can not be explained by regional blood flow [27] alone. In addition, it does not coincide with the observed distribution of radioactive soman in the rat brain [68], which concentrates in the basal ganglia. The difference may underlie the fact that the symptoms produced by soman-like compounds are somewhat different than those of parathion, an observation that led investigators to postulate that additional mechanisms are at work [68]. However, AChE is a highly polymorphic enzyme, existing in various molecular forms [49, 50, 54] and in both intracellular and extracellular compartments [39]. Therefore, it is reasonable to assume that the forms of AChE which predominate in different brain regions have different sensitivity to inhibitors, an idea supported by recent reports from the rat brain, showing that hippocampal and cortical AChE acrivity is more affected by some AChE inhibitors while others are more effective in the caudate [71]. If this is indeed the case in the human

brain, the different symptoms observed after exposure to various inhibitors could simply be a reflection of the brain regions preferentially involved.

The diagnostic value of blood ChE levels

The performance of blood ChE levels is helpful in confirming a diagnosis of acute OP poisoning immediately after exposure. However, blood ChE levels have no correlation to follow-up and management of CNS manifestations. ChE can be measured in red blood cells (RBC), serum or whole blood. RBC ChE level is the more accurate indicator of OP poisoning [5], but most hospital laboratories measure the serum ChE, which is simpler to perform technically [6]. Serum ChE is mainly pseudo-ChE. It hydrolyzes butyril-ChE preferentially but will hydrolyze ACh at a lower rate [35]. Regardless of the ill-defined physiological role of serum ChE, its level is depressed earlier than RBC ChE following exposure to OP [72].
It should be mentioned that the synthesis of pseudo-ChE by the liver is associated with serum albumin synthesis. Therefore, serum ChE level may be decreased in parenchymal liver diseases, including viral hepatitis, cirrhosis, congestion due to heart failure and liver metastases. Low values may also be observed in malnourished patients and following acute infections, anemias, myocardial infarctions, toxemia of pregnancy and dermatomyositis [10]. Moreover, serum ChE activity is low in 3% of the normal population, due to a defective ChE molecule which is genetically controlled [6]. In addition, it must be emphasized that there are no reliable "normal" serum ChE levels for children [18].
Certain drugs and chemicals have also been shown to decrease the activity of pseudo-ChE. These include among many others, sulfonates and sulfates, fluorides, oxalates and citrates, LSD-25, some antibiotics (streptomycin and chloramphenicol), estrogenic and cortisone-like hormones, and exogenous serum albumin due to transfusion [6]. Thus, serum ChE cannot be used for monitoring the clinical state and management in cases of acute OP poisoning. Its only clinical significance is in the early stages, when a drop of more than 50% [18, 23] may serve as an indicator of exposure [72]. In severe poisoning, ChE is less than 10% [10]. In every case, the esposure history, symptoms and clinical findings must be considered carefully, no matter what the ChE level may be.
Serum ChE levels should be drawn before obidoxime is utilized, because the antidote may increase these levels although it does not affect the RBC ChE [11]. The dibucaine number should be determined, if possible, in order to rule out genetic deficiencies [35].
Characteristically, serum ChE also recovers more rapidly, due to the synthesis of new enzymes by the liver, while the recovery of RBC ChE is dominated by the relatively slow production of new RBC. The recovery of serum and RBC ChE activities is not concomitant with the clinical recovery of the patient [42].
The measurement of whole blood ChE finds its greatest usefulness in the analysis of hemolyzed samples. When hemolysis is present, calculation of activity may be made on a volume basis and compared to the normal range of values. In the interpretation of these values, it can be assumed that the RBC enzyme contributes most of the measured activity when ACh is used as the substrate [6].

Specific treatment

Specific steps in the management of acute OP poisoning include: decontamination, respiratory assistance, antidotal therapy and supportive measures.
If the patient is fully alert, Ipecac should be given, even if a petroleum distillate is the carrier [23]. Gastric lavage should be performed in unconscious patients, following intubation of the trachea. After gastric emptyng, enteral administration of activated charcoal is indicated. When cutaneous exposure is suspected, decontamination of skin and hair should be done with soap shampoo, sodium hypochlorite or calcium hypochlorite, as most of the OP esters are unstable under alkaline conditions. A second washing of the skin with ethyl alcohol is also recommended to remove hydrocarbon solvents which contain dissolved OP compounds. The importance of adequate oxygenation cannot be overemphasized. Artificial respiration alone can be very effective in saving life, since the primary cause of death in OP poisoning is respiratory failure. Ventilation should be started prior to the use of atropine, which otherwise might precipitate ventricular fibrillation in a poorly oxygenated patient, especially when the patient clinically exhibits cyanosis [28, 55, 62, 66]. According to our protocol - patients who are cyanotic or hypoxemic and need atropine, receive 2-min treatment of 100% oxygen before every dose of atropine. Should atropine be used in patients who are in respiratory distress, cardiac monitoring is a necessity. Careful attention to blood gases is essential to proper ventilation of the patient.
The use of morphine, aminophylline, phenothiazines, and reserpine is contraindicated [55]. If dopamine or other vasopressors are given, cardiac monitoring is indicated.

The role of atropine

Atropine is a major therapeutic tool for OP poisoning, blocking the excess of ACh in the muscarinic post-synaptic sites by competitive inhibition. Since atropine hardly penetrates the blood-brain barrier and has no effect in the skeletal muscle and autonomic ganglia, it is used as the mainstay of treatment for the peripheral muscarinic manifestations only.

Several authors recommend the administration of large doses of atropine, as a diagnostic trial. Absence of observable adverse effect was claimed to be virtually diagnostic of acute OP poisoning [23]. We have not found this trial to be helpful in our own cases. An initial dose of atropine, 2 mg I.V., should be given to an adult. Atropine may then be repeated, at 10 to 60 minute intervals, until the patient demonstrates signs of atropinization. As atropine is very short-acting, continuous I.V. administration may be necessary for the critical adult patient [25]. The initial dose of atropine for children is 0.03-0.05 mg/kg (I.V.) Maintenance doses for children range from 0.03 to 0.05 mg/kg.

We use atropine for the control of the peripheral respiratory and gastrointestinal symptoms, mainly: bronchospasm and bronchorrhea, abdominal cramps and diarrea. We do not use atropine to treat impairment of vital signs. Nausea is the only CNS sympton which can be effectively treated by low-dose atropine (2 mg, in most cases). This can probably be related to the absence of blood-brain barrier in the chemoreceptor trigger zone, which is linked to the vomiting center within the medulla oblongata.

We avoid, therefore, treatment with high-dose atropine and titrate its administration be relieving the muscarinic respiratory signs clearing of the tracheobronchial secretions [13]. In this respect, we use relatively low doses of atropine, as compared to other therapeutic protocols, in which the guidelines are maximal tolerance to atropine or degree of perspiration. We do not consider the pupillary size or the heart rate as reliable clinical indicators for atropinization. Dilated and even unequal pupils (due to brain anoxia) or persistent pinpoint pupils (due to direct contact of OP) may be expected in acute OP poisoning. In a like manner, while the literature frequently mentions tachycardia as a sign of atropinization, AChE inhibition may cause either bradycardia or tachycardia, depending upon whether cholinergic stimulation is muscarinic (bradycardia) or nicotinic (tachycardia) via the sympathetic ganglia.

Atropine should be used for at least 24 hours to blok the effect of AChE while OP is being metabolized. After an initial use of atropine with no demonstrable effect, one will appreciate the fact that hundreds of milligrams of atropine have been given to such patients in the first 24 hours [28, 55, 62]. Using the guides of bronchorrhea and bronchospasm termination, we rarely exceeded 60 mg daily in adults.

Atropine should be tapered in those patients who begin showing signs of improvement, usually after 24 hours (in milder cases) or 48-72 hours (in moderate and severe cases). In cases of OP ingestion, its absorption from the GIT may last several days [23]. Consequently, atropine treatment may by prolonged. One can taper the dose and lengthen the time interval between doses. Close observation is needed, as the effects of toxicity may rebound. Delayed pulmonary edema has been described [28, 55].

Signs of excessive atropinization include fever, delirium, and muscle twitching. This may develop as the effect of OP begins to wear off, and thus serve as the sign for the physician to begin tapering the dose of atropine.

The role of oximes

Oximes, the group of quaterinized bispyridinium aldoximes, exert their effect by cleaving the phosphorylation-AChE bond, thus releasing AChE from its combination with the OP ester. AChE is reactivated and restored to its normal function [9]. Another desirable effect of oximes is the direct reaction with and the detoxification of OP molecules [43]. Oximes have selective access to different regions of the CNS, which might have different clinical effects [16, 70]. In a single case report, a patient regained consciousness after treatment with oximes alone for acute parathion poisoning [56]. A similar case was observed by us, using ovidoxime only. Low-dose oximes have an anticholinergic atropine-like effect [25], while high-dose oximes can inhibit AChE activity and lead to mild cholinergic signs [60]. These effects may be explained by the change of equilibrium between inhibited AChE and increased ACh [1, 9]. An alternative explanation is the depolarizing action of oximes on post-synaptic sites. Depolarization may account also for the slight therapeutic effect of obidoxime-analogues, which do not have any reactivating power [60]. Phosphorylated AChE gradually undergoes irreversible binding ("aging"). Therefore treatment with oximes is more effective if started early [72]. If oximes are started more than 24 hours after exposure, they may be useless, unless a highly fat-soluble OP is implicated or sustained absorption has occured after ingestion.

The most commonly used oximes are Pralidoxime Chloride (2-PAM) and Obidoxime Chloride (Toxogonin). The chemical structure of the oximes may influence the level of reactivation ob-

served [19]. Obidoxime, which contains two active sites per molecule, is considered a more effective reactivator [60, 70] than pralidoxime chloride. Low-dose oximes act upon the nicotinic sites only [69] and are thought not to cross blood brain barrier easily [67]. When administered I.V. in high doses, oximes reach plasma peak levels and penetrate blood brain barrier, reactivating AChE at the CNS muscarinic sites [43, 70]. Therefore, toxogonin should be injected I.V. in bolus doses and not in continuous infusion. Patients with spontaneous breathing are treated I.V. by 4 mg/kg toxogonin every 4 hours. The dose is limited by the mild cholinergic side effects of toxogonin. Patients who are undergoing respirator treatment may be treated by 8 mg/kg I.V. every 4 hours. In our patients, we administer each dose I.V. in 20 minutes. The adverse effects of obidoxime are relatively mild, although oximes were claimed to cause prolongation of Q-T interval and consequent cardiac arrhytmias in certain Eastern European countries. We believe that oximes are valuable pharmacological tools. However, in the literature reviewed, the combined effects of OP and oximes have never been established. In addition, there is no direct evidence for the cause-effect linkage between oximes and arrhythmias. Moreover, the possible effect of phosphorylated AChE on heart muscles has not yet been excluded. Hepatotoxicity, following obidoxime, has reported [12].
In our animal studies (with dogs) I.V. injections of high-dose toxogonin have never been followed by cardiac arrhythmias, but by hepatic damage. Consequently the logical therapy would be and almost always is the co-administration of atropine and obidoxine in order to rapidly obtain the most beneficial effect in the critically ill patient.
This combination of atropine and obidoxime is much more effective than the mere summed effects [72].

Additional drugs

Seizures that do not respond to antidotal therapy should be treated with I.V. benzodiazepines [69], the mechanism of action of which might be related to its partial indirect antagonism to central effects of A Ch [20].
Other oximes used less commonly are: Trimedoxime (TMB-4), reported mainly in the Russian literature [34, 37] and Pralidoxine Mesylate (P2S). TMB-4 is water-soluble and stable in heat and therefore contained in automatic syringe, mixed with atropine and benactyzine. The automatic syringe is included in the personal equipment of soldiers for self-administration in emergency. P2S has the advantage to be well absorbed from GIT and is included in tablet form in personal antidotal kits [59].
Benactyzine is an anticholinergic agent, with antispasmodic and muscle relaxant properties [26]. Benactyzine readily crosses the blood-brain barrier and exert central cholinolytic effect [34]. Benactyzine is contained in the automatic syrynge, due to its physical stability [59] and its synergism with atropine and TMB-4.
Scopolamine has been suggested to replace atropine in therapy, since it crosses the blood brain barrier eight times more easily than atropine [3, 39]. Its clinical use was only reported once, in a case of accidental poisoning with OP war gas. In that case, delayed effects of sleep disturbances and depression were treated effectively with scopolamine [61].
Dexetimide, a drug with strong central anti-cholinergic activity, was claimed to be effective in rabbits, intoxicated with up to 60 × LD50 of paroxon.
Dexetimide was used in that experiment in conjunction with obidoxime. There are no details regarding the side-effects and hazards in the use of Dexetimide [3].
Experimentally, pharmacologic administration of carbamate-producing 10% inhibition of AChE is an effective prophylactic treatment, especially for OP with a very short aging period [63].

Prognosis

Death from acute OP poisoning usually occurs within 24 hours in untreated cases, and within 10 days in treated cases [72]. In our view, if treated promptly to avoid anoxic brain damage due to respiratory failure on the one hand, and ischemic brain damage due to cardio-circulatory arrest on the other, a patient's prognosis depends mainly on the availability of good intensive care and appropriate use of specific drug therapy.

Sommario

Questa relazione si propone di correlare i dati clinici e sperimentali e i problemi di comportamento nei casi di avvelenamento acuto da organofosfati nei quali vi è sempre coinvolgimento del sistema nervoso centrale. L'attività dell'acetilcolinesterasi (AChE) è stata studiata in diverse regioni cerebrali con metodiche di istochimica quantitativa. Gli effetti regionali della inibizione della AChE da parte degli organofosfati sono stati comparati sui cervelli di 2 vittime e di 2 controlli paragonabili per sesso e per età e si è visto che il danno è re-

gionalmente selettivo. Il maggior difetto è stato constatato nel neocervelletto, nei nuclei talamici e nella corteccia. Questa distribuzione così specifica nella inibizione di AChE può essere correlata con alcune caratteristiche cliniche dell'avvelenamento da organofosfati. Il dato diagnostico dei livelli ematici di AChE è stato esaminato in una serie di 53 pazienti che hanno avuto necessità di ventilazione artificiale, di cure intensive e di trattamento con antidoti. Gli effetti e i controeffetti del trattamento sono stati riconsiderati ed è stato elaborato e raccomandato uno schema di terapia ricavato da questa esperienza e da recenti ricerche eseguite su animali. La terapia più logica vuole sempre l'associazione di un farmaco anticolinergico (solitamente l'atropina) e di reattivatori dell'AChE, gli ozimi, per poter ottenere rapidamente effetti benefici. Le crisi convulsive, poi, che non rispondono al trattamento di base, devono essere sedate colle benzodiazepine. La respirazione artificiale è essenziale per la sopravvivenza del malato e va unita ad altre terapie di supporto capaci di guadagnare il tempo necessario per la ripresa dell'attività della AChE.

Address reprint requests to: Yoram Finkelstein, M.D.
Israeli Poison Information Center
Rambam Medical Center
Haifa 31 096, Israel

References

[1] BARNES J.M.: *Anticholinesterases: Some problems in understanding their effect in whole animals.* In Ballantyne B (ed): Foresnic Toxicology, Wright, pp. 79-85, 1974.

[2] BARTUS R.T. DEAN R.L., BEER B., LIPPA A.S.: *The cholinergic hypothesis of geriatric memory dysfunction.* Science 217: 408-417, 1983.

[3] BERTRAM U., KASTEN A., LULLMANN H., ZIEGLER A: *Improved treatment of OP intoxication by use of scopolamine or dexetimide.* Experientia (Basel), 33:1196-1197, 1977.

[4] BIEGON A., WOLFF M.: *Quantitative histochemistry of acetylcholinesterase in rat and human brain postmortem.* J. Neurosci. Meth. 16:39-45, 1985.

[5] BOWERS M.B., GOODMAN E., SIM V.M.: *Some behavioral changes in man following acetylcholinesterase administration.* J. Nerv. Ment. D. 138:383-391, 1964.

[6] CRANE C.R., SANDERS D.C., ABBOTT J.K.: *Use and interpretation of AChE measurements.* In Sunshine I (ed): Methodology for Analytical Toxicology. West Palm Beach, Florida, CRC Press, pp. 86-87, 1975.

[7] CE CANDOLE C.A., DOUGLAS W.W., LOVATT-EVANS C., HOLMES R., ET AL: *The failure of respiration in death by anticholinesterase poisoning.* Brit. J. Pharmacol. 8:466-475, 1954.

[8] DRACHMAN D.A., LEAVITT J.,: *Human memory and the cholinergic system. A relationship to aging?* Arch Neurol. 30:113-121, 1974.

[9] DURHAM W.F., HAYES W.J.: *Organo phosphorous poisoning and its therapy, with special reference to modes of action and compounds that reactivate inhibited cholinesterase.* Arch. Environ. Health 5:21-28, 1962.

[10] ECHOBICHON E.J.: *OP ester insecticides.* In Echobichon E.J. Joy RM (eds): Pesticides and Neurological Diseases. Boca Raton, CRC Press, pp. 151-204, 1982.

[11] ECHOBICHON E.J., OZERE R.L., REID E., CROCKER J.F.S.: *Acute phenitrothon poisoning.* Can. Med. Assoc. J. 116-377-379, 1977.

[12] ERDMANN W.D.: *Antidotal therapy in OP poisoning.* Arch. Toxikol 24:30-40, 1968

[13] FINKELSTEIN Y., KUSHNIR A., TAITELMANN U.: *Antidotal treatment for CNS manifestations of acute OP poisoning: effects and side effects.* Isr. Neurol. Assoc., Annual Meeting, Abst. p. 24, 1987.

[14] FINKELSTEIN Y., WOLFF M., BIEGON A.: *Differential inhibition of AChE activity in discrete regions of the human brain after parathion intoxication: a quantitative histochemical study.* Int. Neurotoxicol. Assoc. Meeting Abst. 1:82, 1987.

[15] FINKELSTEIN Y., WOLFF M., BIEGON A.: *Brain AChE after parathion poisoning: a comparative quantitative histochemical analysis postmortem.* Toxicol., in press, 1988.

[16] FIREMARK H., BARLOW C.F., ROTH L.J.: *The penetration of 2-PAM-C^{14} into brain and the effect of ChE inhibitors on its transport.* J. Pharmacol. Exp. Ther. 145:252-265, 1964.

[17] FRANCIS P.T., PALMER A.M., SIMS N.R.: *Neurochemical studies of early-onset Alzheimer's disease.* N. Eng. J. Med. 313:7-11, 1985.

[18] GOLDFRANK L.R., BRESNITZ E.A., KIRSTEIN R.H., HOWLAND M.A.: *Organophosphates.* In Goldfrank L.R., Flamenbaum N.E., Lewin N.A., Weismann R.S., Howland M.A., Kulberg A.G.: Toxicologic Emergencies. Norwalk, Conn., Appleton-Century-Grofts, 3rd ed., pp. 686-696, 1986.

[19] GRAY A.P.: *Design and structure-activity relationships of antidotes to OP anti-ChE agents.* Drug. Metab. Rev. 15:557-589, 1984.

[20] GREEN D.M., MUIR A.W., STRATTON J.A., INCH T.D.: *Dual mechanism of the antidotal action of atropine-like drugs in poisoning by OP anti-ChE.* J. Pharm. Pharmacol. 29:62-64, 1977.

[21] GROB D.: *Anticholinesterase introxication in man and its treatment.* In Koëlle G.B. (ed.): ChE anti-ChE agents. Handbuch der Experimentellen

Pharmakologie, vol. 15. Berlin: Springer, pp. 1003-1032, 1963.

[22] GROB D., HARVEY A.M.: *The effects and treatement of nerve gas poisoning.* Am. J. Med. 14:52-60, 1953;

[23] HADDAD L.M.: *The OP insecticides.* In Haddad L.M. Winchester J.F. (eds): Clinical Management of Poisoning and Drug Overdose. Philadelphia, W.B. Saunders, pp. 704-710, 1983.

[24] HAYES W.J.: *Pesticides in relation to publich health.* Ann. Rev. Entom. 5:379-384, 1959.

[25] HAYES W.J.: *Diagnosis and treatment of poisoning.* In Hayes W.U. (ed): Toxicology of Pesticides. Baltimore, Williams and Wilkins, pp. 409-417, 1975.

[26] HAZARD R., CHEYMOL J., LEVY J., BOISSIER J.-R., LECHAT P.: *Manuel de pharmacologie.* Paris, Masson, pp. 180-181, 1963 (in French).

[27] HEISS W.-D.: *Regional cerebral blood flow measurement using a scintillate scintillation camera.* Clin. Nuc. Med. 4:385-396, 1979.

[28] HENRY J.B.: *Todd-Stanford-Davidsohn Clinical Diagnosis by Laboratory Methods.* Philadelphia. Saunders W.B., 16th ed, 1979.

[29] HOLMES R.: *The mechanism of respiratory failure in the rabbit poisoned with GB.* Proton Technical Papers 275, 1952.

[30] HOLMES R.: *The effects of GB on the respiration of the monkeys.* Proton Technical Papers 316, 1954.

[31] HOLMSTEDT B., KROOK L., ROONEY D.R.: *The pathology of experimental cholinesterase-inhibitor poisoning.* Acta Pharmacol. (Koh.) 13:337-344, 1957.

[32] ISSEROFF A., LANCET D.: *An inexpensive microcomputer-based image-analysis system: novel applications to quantitative autoradiography.* J. Neurosci. Meth. 12:265-275, 1985.

[33] JANOWSKY D.A., EL-YOUSEF M.K., DAVIS J.M.: *A cholinergic adrenergic hypothesis of mania and depression.* Lancet 2:632-635, 1972.

[34] JOVIC R., MILOSEVIC M.: *Effective doses of some cholinolytics in the treatment of anti-AChE poisoning.* Eur. J. Pharmacol. 12:85-93, 1970.

[35] KALOW W., GENEST K.: *A method for the detection of atypical forms of human serum cholinesterase.* Determination of dibucaine numbers. Can. J. Biochem. Physiol. 35:339-348, 1957.

[36] KARCZAMAR A.G.: *Pharmacologic, toxicologic and therapeutic properties of anticholinesterease agents.* In Root W.S., Hofmann F.J. (eds): Physiological Pharmacology, vol. III part C. Autonomic Nervous System Drugs. New York, N.Y.: Academic Press, 163-322, 1967.

[37] KHAITOV R.K., BAYMURADOV T.B., KAYDROV U.S.: *Therapeutic efficiency for atropine and dipyroxime.* Veterinarya (Moscow) 11:86-87, 1972 (in Russian).

[38] KÖELLE G.B.: *Neurochemical transmission and the autonomic nervous system.* In Goodman L.S., Gilman A. (eds): The Pharmacological Basis of Therapeutics. New York, N.Y.: MacMillan, 404-445, 1975.

[39] KÖELLE G.B.: *Cytological distribution and physiological functions of ChE's.* In Köelle G.B. (ed): Handuch der Experimentellen Pharmakologie: ChE's and Anti-ChE agents. Berlin: Springer-Verlag, Supp. 15:187-298, 1963.

[40] KOELLER W.C., KLAWANS H.L.: *Organophosphorus introxication.* In Vinken P.J., Bruyn G.W. (eds): Handbook of Clinical Neurology, vol. 37, Amsterdam: Elsevier/North Holland Biomedical Press, 541-562, 1979.

[41] LEVIN H.S., RODNITZKY R.L.: *Behavioral effects of organophosphate pesticides in man.* Clin. Toxicol. 9:391-405, 1976.

[42] LONG K.R.: *ChE activity as a biological indicator of exposure to pesticide.* Int. Arch. Occup. Environ. Health 36:75-87, 1976.

[43] LOTTI M., BECKER C.E.: *Treatement of acute OP poisoning: evidence of a direct effect on central nervous system by PAM-2.* J. Toxicol. Clin. Toxicol. 19:121-127, 1982.

[44] LURIA A.R., KARASSEVA T.A.: *Disturbances of auditory speech memory in focal lesions of the deep regions of the left temporal lobe.* Neuropsychologia 6:97-104, 1968.

[45] LURIA A.R.: *Brain disorders and language analysis.* Language and Speech 1:14-34, 1958.

[46] LURIA A.R.: *The functional organization of the brain.* Scient. Amer. 222:66-78, 1970.

[47] LURIA A.R., HOMSKAYA E.D.: *Frontal lobes and the regulation of activation processes.* In Mostofsky D. (ed): Attention: Contemporary Theory and Analysis. New York: Appleton Century, Crofts, 1970.

[48] MARESH W.: *Die Vergiftung durch phosphosäure-ester.* Arch. Toxicol. 16:285-319, 1957.

[49] MASSOULIE J., BON S.: *The molecular forms of ChE and AChE in vertebrates.* Ann. Rev. Neurosci. 5:57-106, 1982.

[50] MEFLAH K., BERNARD S., MASSOULIE J.: *Interactions with lectins indicate differences in the carbohydrate composition of the membrane-bound enzymes acetylcholinesterase and 5'-nucleotidase in different cell types.* Biochimie 66:59-69, 1984.

[51] MESULAM M.M.: *Attention, confusional states and neglect.* In Mesulam M.M. (ed): Principles of Behavioral Neurology. Philadelphia: Davis, 125-168, 1985.

[52] MESULAM M.M., VOLICER L., MARQUIS J.K., MUFSON E.J., GREEN R.C.: *Systematic regional differences in the cholinergic innervation of the primate cerebral cortex: Distribution of enzyme activities and some behavioral implications.* Ann. Neurol. 19:144-151, 1986.

[53] METCALF D.R., HOLMES H.H.: *Psychological and neurological alterations in humans with organophosphorous exposure.* Ann. N.Y. Acad. Sci. 160:357-361, 1969.

[54] MULLER F., DUMEZ Y., MASSOULI J.: *Molecular forms and solubility of AChE during the embryonic development of rat and human brain.* Brain Res. 331:295-302, 1984.

[55] MORGAN D.P.: *Recognition and management of pesticide poisoning.* Washington D.C. U.S. Environmental Protection Agency. 3rd ed., 1982.

[56] NAMBA T., KIRAKI K.: *PAM therapy for alkylphosphate poisoning.* JAMA 166:1834-1839, 1958.

[57] NAMBA T., NOLTE C.T., JACKREL J., GROB D.: *Poisoning due to organophosphate insecticides: Acute and chronic manifestations.* Am. J. Med. 50:475-492, 1971.

[58] PELFRENE A.F.: *Acute poisoning by carbamate insecticides and oxygen therapy.* J. Toxicol. Clin. Exp. 6:313-318, 1986.

[59] REYNOLDS J.E.F., PRASAD A.B.: *Martindale,* The Extra Pharmacoloeia, 28th ed, London, pp. 389-390, 1505, 1982.

[60] SCHOENE J., OLDIGES H.: *Antidotal action of pyridi-*

nium salts for tabun and sarin poisoning in vivo and in vitro. Arch. Int. Pharmacodyn. Ther. 204:110-123, 1973 (in German).

[61] SIDELL F.R.: *The reactivability of ChE inihibited by Vx and Sarin in man.* Toxicol. Appl. Pharmacol. 27:241-246, 1974.

[62] SMITH P.W.: *Bulletin: Medical Problems in Aerial Applications.* Office of Aviation Medicine, Federal Aviation Administration, Dept. of Transportation. Washington D.C., p. 5, April 1977.

[63] STERRI S.H., ROGNERUD B., FISKUM S.E., LYNGAAS S.: *Effect of toxogonin and P2S on the toxicity of carbamates and OP compounds.* Acta Pharmacol. et Toxicol. 45:9-15, 1979.

[64] STEWART W.C.: *The effect of sarin and atropine on the respiratory center and neuromuscular junction of the rat.* Conn. J. Biochem. physiol. 37:362-367, 1959.

[65] STEWART W.C., ANDERSON E.A.: *Effect of ChE inhibitors when injected into the medulla of the rabbit.* J. Pharmacol Ex. Ther. 162:309-316, 1968.

[66] TAITELMAN U., ADLER M., LEVY I., DIKSTEIN S.: *Treatment of massive poisoning by the OP pesticide methidathion.* Clin. Toxicol. 8:277-282, 1975.

[67] TAYLOR P.: *Anticholinesterase agents.* In Goodman L.S., Gilman A. (eds): The Pharmacological Basis of Therapeutics. 6th ed., New York. MacMillan Publishing Co., pp. 100-119, 1980.

[68] TRAUB K., OLSON K., PINDZOLA M., SPENCES L.: *Quantitative autoradiography of ^{14}C-Soman distribution in the rat brain.* Abstract. J. Neurol. 232 (suppl.):552, 1985.

[69] VALE J.A., SCOTT G.W.: *OP poisoning.* Guy's Hosp. Rep. 123-13-25, 1974.

[70] VASIC B.V., MILOSEVIC M.P., TERZIC M.R.: *ACh content and ChE activity in the ponto-medullary region of brain in rats treated with armin and obidoxime.* Biochem. Pharmacol. 26:601-602, 1977.

[71] WEINSTOCK M., KAY G., RAZIN M., ENZ A.: *Selective acetylcholinesterase inhibition and acetylcholine elevation in different brain areas of the rat.* Abstracts of the Int. Symp. on muscarinic cholinergic mechanisms, Tel Aviv 41, 1986.

[72] WORLD HEALTH ORGANIZATION: *Environmental Health Criteria 63, Organophosphorous Insecticides: A General Introduction.* Geneva, W.H.O., 1986.