CLINICAL PICTURE, DIAGNOSIS AND TREATMENT OF POISONING BY ORGANOPHOSPHATE INSECTICIDES

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General principles of organophosphorous insecticide poisoning in humans have been reviewed in this paper. Special attention has been paid to the clinical picture of poisoning, its diagnosis and treatment. Discussion of such problems as the importance and evaluation of the signs of poisoning, cholinesterase activity and oximes therapy has been based upon foreign and our experience.

During the Second World War chlorinated hydrocarbons and organophosphates were introduced as insecticides. These compounds enjoyed wide use, particularly DDT which has low toxicity. Recently chlorinated hydrocarbons have attracted public attention as a possible ecological hazard, because these compounds have accumulated unchanged on the earth and in the adipose tissue of mammals. Chlorinated hydrocarbons are stable and very slowly metabolized. Although there is not enough evidence at present that DDT or other chlorinated hydrocarbons in the tissues of human beings are harmful, there are opinions that the concentration may eventually become intolerably high. This concern was dramatically portrayed by Rachel Carson in her book "Silent Spring". Further apprehension for the ecological problem in general led the USA and some states in Europe to take measures to reject DDT except for uses essential to human health and welfare.

Since future and civilization are greatly dependent on insecticides in agriculture, forestry and vector control, particularly in malaria control, substitutes for chlorinated hydrocarbon insecticides are required. Presently organophosphate insecticides are considered to be the most practical substitutes because they are potent insecticides and are relatively rapidly hydrolyzed after application. Many organophosphate compounds have been synthesized in the past 30 years and many of them have been widely used as agricultural insecticides. Useful as they are, organophos-
phate insecticides are so toxic (LD₉₀ for most insecticides varies from 1—400 mg/kg) that every year a number of victims of organophosphate poisoning are reported in every part of the world (1).

| Table 1 |
|------------------|------------------|
| **Oral Toxicity of Parathion, Malathion, DDT and Aspirin** |
| 50% lethal dose in rats (mg/kg) | Estimated lethal dose in man (mg/kg) |
| Parathion | 13.0 | 1.4 |
| Malathion | 1375.0 | 858.0 |
| DDT | 217.0 | 429.0 |
| Aspirin | 1360.0 | 400.0—500.0 |

* Data from T. Namba, Medical Times (Vol. 100, No.6, p. 103, June 1972).

Since a great range of concentrations or doses of various organophosphates may be involved in causing harm, categories of toxicity have been divided on the basis of the compounds toxicity-amounts necessary to produce harm. An example of such a categorization is:

I. Relatively harmless

II. Practically nontoxic

III. Slightly toxic

IV. Moderately toxic

V. Toxic

VI. Highly toxic

VII. Extremely toxic

more than 15 g/kg

5.0 to 15.0 g/kg

0.5 to 5.0 g/kg

50.0 to 500.0 mg/kg

1.0 to 50.0 mg/kg

0.025 to 1.0 mg/kg

less than 0.025 mg/kg

Generally the incidence of organophosphate poisoning is higher in warm farm areas. However, large cities are not immune to the poisoning, since most of the household insecticides also contain organophosphates.

POSSIBILITY AND WAY OF POISONING

Occupational poisoning most frequently develops after prolonged exposure, whereas accidental, suicidal and homicidal poisonings are often acute without previous exposure to the substance. The rate of absorption of insecticides is an important factor regarding the period of latency before symptoms appear and the seriousness of reactions. Most organophosphate insecticides are absorbed through intact skin at a rather low rate (6 to 12 hours). However, the absorption of insecticides is rapid
through the mucosa of the conjunctiva, nose, mouth and gastrointestinal tract. This also applies to pulmonary absorption after inhalation of vapors, sprays and mists. The first symptoms of poisoning appear most frequently between a few minutes and about 6 hours after exposure depending upon the site of absorption and dose. Manifestations that occur more than 24 hours after the last exposure usually cannot be attributed directly to organophosphorous insecticides.

CHEMISTRY OF ORGANOPHOSPHATES

Most insecticides are esters of phosphoric acid, thiophosphoric acid or pyrophosphoric acid. The basic formula appears in Fig. 1, in which $R_1$ and $R_2$ may be amides, alcohols, mercaptans, phenols, etc., and where $X$ may be paranitrophenol, phosphates, thiophosphates, etc.

![Chemical Structure](image)

Fig. 1. The basic formula of organophosphorous insecticides

Some examples of substances belonging to various chemical groups:

- Derivatives of thiophosphoric acid: parathion
  (0,0-diethyl-0-p-nitrophenyl phosphorothioate)
- Phosphates: paraoxon
  (0,0-diethyl-0-p-nitrophenyl phosphate)
- Dithiophosphates: malathion
  (S/-1,2-bis/ethoxy carbonyl/ethyl/0,0-diethyl phosphorodithioate)
- Phosphonates: dipterex
  (dimethyl 2,2,2-trichloro-1-hydroxyethyl phosphonate)
- Carbamate: physostigmine

PHYSIOLOGY AND PHARMACOLOGY

Above mentioned anticholinesterase compounds belong to a group of widely different substances and their effects differ qualitatively and quantitatively. Consequently, the following account can be only synoptic. The substances in their effects may be either reversible or irreversible inhibitors of cholinesterases. Reversible compounds act by competitive
inhibition, noncompetitive inhibition, or a combination of the two. Inhibitors with reversible effects may be removed by dialysis; a free equilibrium exists between enzyme and inhibitors, which is not the case with inhibitors of irreversible effects. They form loose or firm complexes with enzyme which may be reactivated in certain cases. Thus the term irreversible is correct in a limited sense of the word.

Several of organophosphorous insecticides are rather weak anticholinesterases in themselves. In the organism, however, they are transformed into very strong inhibitors (e.g. parathion into paraoxon, malathion into malaoxon, etc.).

Cholinesterases are classified into two types: acetylcholinesterase (true cholinesterase, specific cholinesterase) and butyrylcholinesterase (pseudo cholinesterase, non-specific cholinesterase).

In man, synapses, erythrocytes, nerves and skeletal muscles contain mainly acetylcholinesterase; and serum (plasma) and liver contain mainly pseudocholinesterase. The function of non-synaptic cholinesterase is not known. Clinically, reduction of serum cholinesterase (synthesized in the liver) is used as an indicator of liver dysfunction. A genetically inherited syndrome resulting in reduction serum cholinesterase occurs, and individuals with this syndrome are hypersensitive to succinylcholine, a cholinesterase inhibitor, used as a muscle relaxant in anesthesia.

Very low concentrations of organophosphorous compounds inhibit the activity of both types of cholinesterases. Inhibition of these enzymes by organophosphate is a result of firm binding of phosphate radicals of organophosphates to the active sites of the enzymes, forming phosphorylated enzymes. The pharmacologic and toxicologic effects of organophosphates are primarily, if not entirely, due to inhibition of acetylcholinesterase of the nervous system, resulting in accumulation of acetylcholine at the synapses. The over-abundance of acetylcholine initially stimulates and then paralyzes transmission in cholinergic synapses, sparing adrenergic synapses.

Today acetylcholine is supposed to be of importance for:

— transmission of the nervous impulse,
— neurohumoral transmission,
— permeability of membranes,
— local hormonal function (e.g. in the heart).

Phosphorylated cholinesterase complex is inactive and very stable in contrast to acetylated cholinesterase which is a normal complex in organism produced during decomposition of acetylcholine. Spontaneous hydrolysis of the phosphorylated enzyme takes place only to a very short extent. Consequently cholinesterase activity does not reach the normal level till after the formation of new enzyme. This process takes several weeks, possibly months, depending upon the kind of organophosphate which produced inhibition of cholinesterase.
Inhibition of cholinesterase in blood is a specific test for proving systemic absorption of organophosphate compounds. Normal cholinesterase activity of the blood excludes poisoning by these compounds.

It could be very often seen in literature that severity of poisoning, beside clinical manifestations, is classified on basis of the degree of cholinesterase inhibition in blood (plasma and erythrocytes). Also, the level of cholinesterase inhibition serves as a guide for prognosis of poisoning and efficiency of therapy. Generally, signs and symptoms of acute poisoning occur when more than 50% of the plasma or erythrocyte cholinesterase is inhibited (1, 2).

Table 2

<table>
<thead>
<tr>
<th>Signs and symptoms of acute organophosphate poisoning</th>
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<tr>
<td><strong>Muscarinic-like manifestation:</strong></td>
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<tr>
<td>Ocular symptoms</td>
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<tr>
<td>Miosis, occasionally unequal, blurring of vision,</td>
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<tr>
<td>headache (ciliary pain);</td>
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<tr>
<td>Glandular symptoms</td>
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<tr>
<td>Increased sweating, lacrimal, salivary, nasopharyngeal</td>
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<td>and bronchial secretion;</td>
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<td>Bronchial tree and pulmonary symptoms</td>
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<tr>
<td>Sensation of constriction, possibly light pain in</td>
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<tr>
<td>the thorax, increased secretion with coughing,</td>
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<td>possibly pulmonary edema, dyspnea, cyanosis;</td>
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<tr>
<td>Cardiovascular symptoms</td>
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<tr>
<td>Bradycardia, fall in blood pressure, initially</td>
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<td>dilatation of blood vessels of skin and mucosa;</td>
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<td>Gastrointestinal symptoms</td>
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<tr>
<td>Anorexia, nausea, vomiting, tenesmus, abdominal pain,</td>
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<td>diarrhoea, involuntary discharge of feces;</td>
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<td>Urinary tract symptoms</td>
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<td>Pollakisuria, possibly involuntary discharge of urine;</td>
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<td><strong>Nicotinic-like manifestation:</strong></td>
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<tr>
<td>Striated musculature symptoms</td>
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<tr>
<td>Fatigue, flaccidity, twitching, fasciculation,</td>
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<tr>
<td>convulsions;</td>
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<tr>
<td>Sympathetic ganglion symptoms</td>
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<tr>
<td>Tachycardia, initial elevation of blood pressure,</td>
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<tr>
<td>pallor (constriction of blood vessels of skin and</td>
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<tr>
<td>mucosa);</td>
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<tr>
<td><strong>Central nervous system manifestations:</strong></td>
</tr>
<tr>
<td>Giddiness, anxiety, tension, emotional lability,</td>
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<tr>
<td>excessive dreaming, insomnia, nightmare, headache,</td>
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<tr>
<td>tremor, apathy, difficulty in concentration,</td>
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<tr>
<td>confusion, slurred speech, ataxia, phobia, hallucina-</td>
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<tr>
<td>tions, generalized weakness, convulsions, coma with</td>
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<tr>
<td>absence of reflexes, Cheyne-Stokes respiration,</td>
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<td>depression of respiratory and circulatory centers;</td>
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</table>
POISONING PICTURE

Organophosphate insecticides may exert their influence locally and generally. Signs and symptoms of such poisoning are attributable mainly to the accumulation of acetylcholine at the cholinergic synapses and may be traditionally classified into muscarine-like (parasympathetic), nicotin-like (sympathetic and motor) and central nervous system manifestations according to the site of action of acetylcholine (Table 2). This division has also some importance in understanding the treatment of poisoning caused by organophosphates.

Signs and symptoms of acute organophosphate poisoning shown in Table 2 are generalized and could serve to recognize the degree of severity of poisoning picture. The most serious manifestation and the usual cause of death is respiratory insufficiency which is a result of the following progression: a) bronchoconstriction; b) depression of the respiratory center; and c) paralysis of respiratory muscles. Cardiovascular function is usually maintained until the terminal stage.

Chronic poisoning by organophosphorous compounds most frequently presents a very complex clinical picture. Thus prolonged exposure to small doses of organophosphorous insecticides (e.g. laboratory workers) may provoke appearance of symptoms referable to the central nervous system (psychic symptoms), peripheral nervous system (paresis, possibly paralysis) and digestive system. These effects may cause serious symptoms, but some of them are reversible upon drug withdrawal and some of them can persist for weeks, months or years.

DIAGNOSIS

The diagnosis of illness or death caused by an organophosphorous insecticide is not simple. Such diagnosis depends upon a great deal of information:

1. Case history (For acute poisoning evidence of exposure to organophosphates within the previous 24 or exceptionally 48 hours. For subacute or chronic poisoning evidence of exposure for last weeks or months in connection with occupation.)

2. Clinical observation (Signs and symptoms of poisoning shown in Table 2.)

3. Laboratory tests (Cholinesterase activity of the blood. Detection of organophosphate or its metabolites in gastric aspirate, skin, blood, urine or clothing.)

4. Effectiveness of antidotal therapy (Improvement or recovery from signs and symptoms of poisoning.)
TREATMENT

The treatment of acute poisoning by organophosphorous compounds should be started without waiting for the results of laboratory tests. In order to be effective the treatment of poisoning by organophosphorous insecticide should consist of combinations of antidotal therapy and general measures:

1. Decontamination

Generally speaking, a wide range of chemicals could be used as decontaminants, the choice depending upon the particular agent which has to be neutralized, the type of surface that needs to be treated, the extent of contamination and the amount of the time available. In any case the termination of exposure by removal of the patient or application of a protective mask will be necessary if the atmosphere is contaminated.

a) Skin — organophosphate by which skin was contaminated can be destroyed and removed by using solutions of peroxides, hypochlorous acid (Clorox), dilute alkali, soap and water or plain water. By removal of contaminated clothing further contamination is also terminated.

b) Eyes — if organophosphate insecticides have splashed into the eyes, they should be immediately irrigated with water or with physiological saline, or sodium bicarbonate if at hand.

2. Antidotal therapy

Atropine — in sufficient dosage antagonizes very effectively the muscarinic-like manifestations of poisoning at periphery and to a moderate extent the central respiratory paralysis and other central actions. It is comparatively ineffective against the autonomic ganglionic actions and it has virtually no effect against the peripheral neuromuscular paralysis. Atropine acts by blocking directly the parasympathetic receptor sites from acetylcholine.

Atropine should be given in «heroic» doses until muscarinic-like symptoms are relieved and signs of mild atropinization (mydriasis, dry mouth and dry flushed skin, heart rate over 140 beats/min.) appear. Following an initial injection of 2 to 4 mg given intravenously if possible, otherwise intramuscularly, the 2 mg dose should be repeated every 5 to 10 minutes until muscarinic-like symptoms disappear, and also, if they reappear. As much as 10 to 50 mg of atropine may have to be administered over a twenty-four hour period (3, 4, 5, 5). A mild degree of atropinization should then be maintained by the oral administration of 1 to 2 mg at intervals of several hours, as long as such symptoms are in evidence.

Cholinesterase reactivators (Oximes) — the therapeutic action of reactivator substances may be explained in two ways: first, reactivation of inhibited cholinesterase will allow the enzyme to perform its physi-
ological (primary) function of destroying the accumulated acetylcholine; and second, a complex of the reactivator substance with the anticholinesterase agent is formed which will «neutralize» anticholinesterase before it reaches the active site on the enzyme.

Several substances which accelerate the reactivation of cholinesterase have been established for human use (5, 7—26). They are known as oximes, and among the best known for the treatment of human organophosphorous poisoning are:

— **PAM-2, P2AM, PAM, Pralidoxime, Protopam**
  (Pyridine-2-aldoxime methiodide or methchloride)
— **P5S, Contrathion**
  (Pyridine-2-aldoxime methyl methane sulfonate)
— **TMB-4, Trimedoxime, Dipiroksin**
  (1,1’-trimethylene bis-/4-pyridinium-4-aldoxime dibromide or dichloride)
— **LüHö, Obidoxime, Toxogonin**
  (1,1’-oxydimethylene bis-/4-pyridinium-4-aldoxime dibromide or dichloride).

In comparison with pralidoxime, the experience in using trimedoxime and obidoxime in humans poisoned by organophosphorous compounds is relatively insufficient. Although trimedoxime and obidoxime are effective in smaller doses for the treatment of organophosphate poisoning, they are more toxic than pralidoxime.

It is essential for successful management of the treatment that these substances be administered soon after poisoning. This is because phosphorylated enzyme passes rapidly from an unstable phase, when it can be reactivated, to a stable form after which it cannot be reactivated («aging»).

The intravenous or intramuscular injection of oximes produces the effect in 5 to 15 minutes. Oximes are also effective when administered orally, but previously mentioned routes are preferred for prompt effect. Pralidoxime should be administered in the dose of 1 to 2 g intravenously or intramuscularly. This should be repeated in one hour if respiration weakens or muscular fasciculation recurs. We would like to stress that a continuous infusion of oxime at rates up to 0.5 g per hour is more effective than repeated single injection of 0.5 or 1.0 g, probably because of the maintenance of continuously higher concentration of this substance in the blood.

Trimedoxime and Obidoxime should be administered in the dose of 0.25 g intravenously or intramuscularly, and all procedures described for pralidoxime could be applied for these oximes as well. However, the combined use of an oxime and atropine is more effective than the application of either of them alone.
3. Maintenance of patient airway and artificial ventilation

According to the degree of poisoning picture severity the treatment may also include:

— removal of fluids collected in the mouth and pharynx before medical treatment (atropine, etc.) by suction or by sweeping with cloth-covered fingers and postural drainage;
— a prone, head-down position of the patient;
— elevation of the mandibulae of a patient in the supine position and pulling forward of the tongue;
— insertion of an endotracheal catheter if practicable.

In the moderate to severe case of poisoning, because of pulmonary deficiency, artificial respiration may be needed using a positive-pressure method. As soon as cyanosis has been overcome, atropine and oxime should be promptly given intravenously or intramuscularly. Atropine is contraindicated in a cyanotic patient because of the possibility of inducing ventricular fibrillation.

4. Other general measures

When the patient is unconscious, a catheter should be used to observe the urinary flow for early detection of oliguria.

In cases with convulsions a short action barbiturate (e.g. thiopental sodium) may be administered intravenously, or after intubation d-tubocurarine, which counteracts the nicotine-like manifestations of organophosphorous poisoning. Morphine, aminophylline and phenothiazines are specifically contraindicated.

Other measures of non-specific therapy should be also undertaken depending on the course of illness (e.g. intravenous fluids, antibiotics, cardiotonics, etc.).

COMMENTS

Signs of poisoning

The most helpful signs in diagnosis of organophosphorous poisoning are miosis (especially due to the local exposure to poison) and muscular fasciculations, which are almost always present in moderately severe or severe poisoning. Other signs that are helpful in diagnosis include excessive sweating, salivation, lacrimation and bronchial secretion. The ingestion of organophosphorous compounds is often followed by severe abdominal pain, diarrhoea and vomiting.

As a guide for the efficiency of antidotal therapy pupil diameter seems to be a misleading parameter (4, 5, 27) because there is no correlation between the appearance of mydriasis and an improvement in the clinical condition. Therefore, dryness of the mouth or red flush of the face could be more useful signs as a guide in the efficiency of antidotal therapy.
Cholinesterase activity

What relationship, if any, exists between general tissue levels of cholinesterase and erythrocyte enzyme activity is difficult to determine since patients may have blood cholinesterase levels as low as 15% of normal without toxic signs (28, 29). Estimation of erythrocyte cholinesterase activity is theoretically preferred, since it would reflect the degree of inhibition of synaptic cholinesterase (1) and also it is a better parameter for the efficiency of oxime therapy than are plasma cholinesterase activities (30, 31, 32). On the other side, the estimation of plasma cholinesterase has an advantage because the measurement is simpler and more accurate than the estimation of erythrocyte cholinesterase.

However, it should be kept in mind that plasma (serum) cholinesterase, whether tested by sensitized paper or a more elaborate method, is subject to problems of interpretation in view of the changes of pseudocholinesterase found with liver disease, influence of phenothiazines and under other conditions. Another problem concerns what constitutes a normal range of cholinesterase for the method in use. Most studies are based upon standards of activity derived from fresh adult venous (or capillary) blood. These standards of comparison may not be applicable to blood obtained from different age groups not already standardized. To avoid difficulties which may appear in diagnosis of poisoning, especially in the workers occupationally exposed to organophosphorous insecticides, it is necessary to have their enzyme values checked at regular time intervals.

The individual who has been acutely poisoned and has shown marked cholinesterase depression, should not be allowed to return to work with organophosphate insecticides until his cholinesterase activity levels have returned to approximately 75–85% of the normal.

Finally, one conclusion could be drawn from the facts mentioned: that in practice the cholinesterase activity test is more valuable as a confirmatory, rather than a diagnostic procedure. This is why clinician should set on his clinical impression and on the history of exposure rather than wait for the laboratory results.

Oximes therapy

Although the therapeutic principles of poisoning with organophosphates insecticides are largely accepted, several points still remain open to discussion. These points mainly concern the oxime therapy where in some cases reactivation of inhibited cholinesterase was found, whereas it was absent in others. Also, some authors propose a repeated injection of oximes and others give only two injections early in intoxications. Many authors state that the oxime must be given in repeated doses especially in cases when the poison has to metabolize before acting, as for instance nitrostigmin (33) or where a redistribution from other depots (34) or a continuous absorption from the intestinal tract (1) may occur.
On the other hand some authors (30, 35, 36) propose in an early phase of poisoning one or two administrations of an oxime in an appropriate dose. They stress that reactivation of cholinesterases by oximes is most pronounced early after inhibition and that further injections could only have minor effects. If on the contrary the oximes have no effect at the beginning of therapy of organophosphorous poisoning they remain ineffective.

In our opinion the absence of activity as well as the absence of reactivation by oximes (pralidoxime, trimedoxime and obidoxime) in vitro and in vivo indicates the ineffectiveness of prolonged oxime therapy and the "ageing" of the enzyme-inhibitor complex.

In some cases hepatic damage was seen which was imputed either to the oxime therapy or to organophosphate poison or to both (27, 30, 31, 32, 36).

Animal experiments had shown that high doses of oximes did not produce liver damage, whereas high doses of organophosphate did (36, 37, 38). Also, our results of investigation of oximes (pralidoxime, trimedoxime) in healthy men-volunteers have shown that therapeutic doses of mentioned substances did not affect liver function (22, 25, 26). These controversial facts suggest that further studies are needed in order to reach a clear conclusion about the relationship concerning the usage of oximes and liver damages.

In the past few years, in some cases obidoxime and trimedoxime have been used in the treatment of human organophosphorous poisoning instead of pralidoxime. The explanation lies in the fact that obidoxime and trimedoxime are in many respects superior to pralidoxime as antidotes in animal poisoning with organophosphates (e.g. stronger and more rapid reactivation of inhibited cholinesterase) (39—47). It is interesting to point out that until today obidoxime and trimedoxime have not replaced pralidoxime for use in man, probably because on a weight basis in animals obidoxime and especially trimedoxime show a higher toxicity than pralidoxime.

Comparing obidoxime and trimedoxime it could be very often found in literature that obidoxime is given preference on account of low toxicity in animal experiments on weight basis. However, animal studies have failed to show any superiority of obidoxime over trimedoxime as an antidote in animal poisoning (48—50). On the contrary our results (25) show that 28% of the dose of trimedoxime injected intramuscularly in healthy men is excreted in urine in two hours. This is only approximately half of the amount excreted in the urine after the injection of obidoxime (51). Under conditions where the duration of the oxime level in blood is a critical factor, any advantage which obidoxime might have because of its slightly lower toxicity in animals, is diminished by its shorter persistence in blood and its faster urinary excretion.

It is really very difficult to give an advantage to any of the oximes mentioned because the antidotal action very often depends on the kind
of poisoning which has to be treated. Thus for example we have found that trimedoxime is even superior as an antidote in experimental poisoning by organophosphorous compounds of GD—42 and GD—7 types (52).

Finally, opinions on the therapeutic efficiency or inefficiency in the treatment of poisoning differ depending on way of penetration of the poison in the body, time of application of the oxime after poisoning and the kind of organophosphorous compounds which should be treated.

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Sažetak

KLINICKA SLIKA, DJAGNOSTIKA I TERAPIJA OTROVANJA ORGANOFOSFORNIM INSEKTICIDIMA

Izneti su opšti principi delovanja organofosfornih insekticida na ljudima. Posebna pažnja posvećena je kliničkoj slici trovanja, dijagnozi i terapiji. U radu su razmotreni problemi kao što su: vrednost znaka trovanja, aktivnost holinesteraze i naročito terapija upotrebe reaktivatora holinesteraze oksima, i to na osnovu stranih i naših podataka.

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