UDC 615.9; 615.917; 615.279 DOI: 10.33273/2663-4570-2021-91-2-79-90

MODERN ASPECTS OF DEVELOPMENT OF BASIC THERAPY AND PREVENTION MEANS OF ORGANOPHOSPHORUS COMPOUNDS ACUTE POISONING (review of literature)

M. Zinovieva, Y. Kurdil. M. Prodanchuk, O. Kravchuk, P. Zhminko
LI Medved's Research Centre of Preventive Toxicology, Food and Chemical Safety, Ministry of Health, Ukraine (State Enterprise), Kyiv, Ukraine

ABSTRACT. Introduction. *Despite large experience in the use of basic therapies for acute poisoning by organophosphorus compounds (OPs)of anticholinesterase action and the results of research conducted in the world, the current methods of treatment of such poisonings are insufficient and do not meet requirements for effective treatment and health.*
Purpose. *Based on the analysis of scientific publications to outline the main directions of modern developments of drugs for basic therapy and prevention of acute OPs poisoning at the stages of their experimental assessment.*
Methods. *A systematic content analysis of literature data using the PubMed database was performed.*
Results. *Modern principles of pharmacotherapy of acute anticholinesterase OPs poisoning are based on the use of anticholinergic drugs (mainly atropine), cholinesterase reactivators and anticonvulsant action. M-cholinolytic therapy remains a mandatory basic component of the treatment of acute OPs poisoning. Today, research is aimed at finding less toxic M-cholinolytics with a wider range of therapeutic effects. A cholinesterase reactivator has not yet been developed that has such a spectrum of action that is able to prevent the central effects of OPs poisoning. The effectiveness of the combined action of AChE reactivators has also been insufficiently studied. One approach to solving the problem of protecting the central nervous system in OPs poisoning may be to find a combination of peripheral cholinesterase reactivators with neuroprotectors capable of overcoming the blood-brain barrier. The development of anticonvulsant therapeutic agents requires further study of the mechanism of status epilepticus in acute OPs poisoning.*
Conclusions. *There is an intensive search for OPs poisoning treatments around the world. But in time the relevance and importance of finding and implementing a unified methodology for studying the therapeutic efficacy of a wide range of pharmacological agents at the stage of their preclinical evaluation. Efforts to find means of pharmacologically correcting OPs poisoning should be accompanied by the development of a more prudent regulatory policy in the field of pesticide use. It is also necessary to create a clear and consistent policy on information measures that would focus on the dangers of OPs, as well as contribute to the prevention of mental disorders that provoke suicidal consequences.*
Key Words: *organophosphorus compounds, acute poisoning, means of basic therapy, means of prevention.*

Introduction. Organophosphorus compounds (OPs) were synthesized in 1854. Approximately 80 years later, OPs were proposed as potent insecticides of neurotoxic action. Subsequently, within this class of chemicals the deadliest neuro-paralytic substances ever synthesized by man were developed. Paradoxically, OPs have a double force. On the one hand, their use is necessary for insecticidal action as pesticides, i.e. vital substances in the national economy. On the other hand, these compounds are toxic warfare agents that affect all living things.

Although global measures are currently being taken to regulate the use of organophosphorus pesticides, the health risks associated with them remain high. More than three million people worldwide are exposed to OPs every year. This leads to approximately 300,000 (10%) deaths, most of which are reported in developing countries [1]. Although, almost 8,000 cases of such poisonings are registered annually in the United States. Most of them occur in agriculture sector due to the use of pesticides, poisoning by OPs-containing household drugs – means to neutralize ants and cockroaches [2]. The global assessment of OPs pesticidepoisoning rate shows that the mortality rate ranges from 2 to 25%. As well as in the world as a whole, in Ukraine acute poisonings by organophosphorus compounds during the last 30 years remain an urgent problem. Hospital mortality in the period from 1987–1999 was 6,3%, in 2001–2010 – 13,7%, and after 2010 – 16,3% [3].

According to world statistics, a third of suicides are OPs poisonings, among which the most common fatalities due to pesticides are associated with four compounds – fenitrothion, dichlorvos, malathion and trichlorophenol (chlorophos) [4]. According to other data, the OPs pesticides, as classified by WHO,

belong to the toxicity classes Ia, Ib and II – insecticides monocrotophos, forate, methylparathion, and dipyridyl herbicide paraquat, topping the list of pesticides that have become suicidal in the last fifty years [5]. Despite the fact that the risk factors for personal poisoning have their own specifics in different countries, it is shown that both in cases of abuse and accidental exposure (both in everyday life and at work), the most common important risk factors for acute poisoning are young age of victims, insufficient experience in agriculture, low socio-economic status of the victim, level of general education, non-compliance with the rules of use and storage of pesticides, lack of awareness of health threats, as well as significant use of these pesticides [6].

Ukraine, like the whole Europe in general, is one of the countries with the highest level of pesticide use. In this regard, we can outline the most relevant risk factors for poisoning in Ukraine: a high level of use, including misuse; availability of places of storage (warehousing), which allows accidental or intentional distribution; intensive transportation across the territory; ongoing institutional changes in the health care system (transformation of sanitary and epidemiological services); insufficient information about the risks associated with these substances both at work and at home; lack of a clear risk management system in production, industrial and domestic applications. The scientific community of Ukraine has repeatedly stressed the need to provide effective antidotes to OPs poisoning of both civilians and emergency services [7, 8].

Considering the risks associated with the use of toxic warfare agents, including OPs, a number of important steps have been taken at the international level to minimize them. However, it should be noted that no country has achieved the complete elimination of its chemical weapons stockpiles, which, according to the 1997 OPCW Convention, was to be completed by April 2007.Against this background, there is an increase in the activity of international terrorism, which increases the risk of using both known toxic substances of OPs and new compounds with an unknown chemical structure. Neuro-paralytic poisons of series A (tabun, sarin, soman, VX, Novichok class substances – A-230, A-232, A-234 [9]) and their analogues are found during investigations of resonant political events (terrorist incidents, murders and attacks on life), cause extreme concern from both international defense organizations and society as a whole. Confirmation of the above is the use by international criminal structures of war poisons in the United Kingdom of Great Britain and Northern Ireland, the city of Salisbury (poisoning of Sergei and Julia Skripal, 2013) and in the Russian Federation (poisoning of A. Navalny, 2020). [10–11].

Thus, in the current state of existence of a real global chemical threat to human life and the environment of its vital activity the development of measures of minimization of harmful influence of dangerous chemical factors, among which areOPs, is an issue of great relevance. This justifies the need for scientific developments in the field of health protection of servicemen and civilians in case of such poisonings. An important task is the development of pharmacological agents for human health in acute OPs poisoning, which is based on understanding the interaction of the toxicant with the body, the pathogenesis and clinical manifestations of poisoning.

The specific features of most highly toxic OPs are high lipophilicity and electrophilicity, which determine their ability to easily overcome the physiological barriers of the body, to bind and phosphorylate numerous enzymes and proteins [12]. It should be noted that the clinical relevance of the full spectrum of these reactions remains unclear. But the key mechanism of acute poisoning by such OPs is the inhibition of carboxylesterases, mainly acetylcholinesterase (AChE, EC 3.1.1.7). This is due to the structural similarity of OPS to the neurotransmitter acetylcholine – a natural substrate of AChE. The structure and catalytic function of AChE have been studied in detail and refined during the last two decades of the last century [13, 14]. OPs inactivate this enzyme by phosphorylation of the hydroxyl group of serine, what leads to the accumulation of acetylcholine in cholinergic synapses, hyperstimulation of receptors, blockade of nerve impulses. Clinically acute poisoning is characterized by symptoms of muscarinic hyperactivation (miosis, bronchorrhea, bronchospasm, lacrimation, salivation, activation of urination, defecation, gastric secretion) and nicotinic receptors (muscle spasms, paresis of the diaphragm, transient hypertension) body functions and respiratory arrest. Damage of

the brain cholinergic synapses causes severe neurological and mental disorders. In addition to hyperactivity of the cholinergic part of the nervous system, an excess of acetylcholine induces a parallel excitotoxic effect, which mechanism is not definitively elucidated. The release of glutamate causes excessive calcium intake to neuronal cells and their following apoptosis [15]. Depending on the anticholinesterase OPs chemical structure specifics, the AChE-OPs complex formed in the body during poisoning may be more or less stable. Conformational changes leading to formation of a stable complex (so-called "aging" AChE), make it impossible to restore the activity of the enzyme [16]. It should be taken into account in the development of therapies for poisoning.

The clinical signs of acute OPs intoxication unfolds extremely quickly.It requires life-saving means of prehospital, as well as self- and mutual assistance, especially in emergencies. At the same time, the forced readiness for the possible terrorist use of organophosphorus nerve agents demands to create stocks of a significant number of antidotes. Today we need a global consolidation of scientific, industrial and military resources and coordination of efforts to develop and test new treatments aimed at saving the lives of victims of both pesticides and warfare OPs use [17, 18].

Purpose. To outline the main directions of modern developments of drugs for basic therapy and prevention of acute OPs poisoning at the stages of their experimental assessment and clinical testing.

Methods. A systematic content analysis of literature data using the PubMed database was performed.

Results and Discussion. Modern principles of pharmacotherapy of acute anticholinesterase OPs poisoning were formed in the 1960s and 1970s, developed taking into account the specific mechanisms of action of these compounds, as well as the symptoms and pathogenesis of intoxication. Today, they are based on the use of anticholinergics (mainly atropine), cholinesterase reactivators and anticonvulsants [19, 20]. The generalized modern scheme of clinical application of such combination is given in the table.

Thus, modern treatment standards include a symptomatic agent – M-cholinolytic, antidote – AChE reactivator and anticonvulsant. However, given the likely likelihood of massive OPs damage, there are a number of challenges in providing adequate care for acute OPs poisoning. First, it is the effectiveness of the existing drug care scheme, which is relatively difficult to implement and requires trained medical staff, and second, the standard stock of basic therapies in health care facilities may be insufficient to provide care [19]. The latter aspect is only partially related to the risk of mass poisoning, as individual poisonings require the creation (and maintenance) of certain stocks of specific therapies. All this necessitates the improvement of existing schemes and the search for effective alternatives to existing basic therapies.

M-cholinolytics. The competitive muscarinic receptor antagonist atropine remains today a key symptomatic treatment used since the 1950s in anticholinesterase poisoning. It penetrates well through the blood-brain barrier (BBB), but can cause central toxic effects – development of seizures and coma.Long-term clinical experience has optimized the use of atropine, which minimizes the toxic effects of this drug [22, 23]. In addition, the use of peripheral cholinolytic glycopyrrolate can reduce the toxic effects of atropine on the CNS [24]. Unfortunately, this does not protect the CNS from the cholinergic effects of OPs. The literature describes the experience of successful use of scopolamine, which is faster than atropine penetrates the CNS in a patient with severe manifestations of extrapyramidal disorders [25]. In addition, the use of other available M-cholinolytics in some cases may be due to individual insensitivity of individual patients to the action of atropine [23, 26]. According to the literature, the results of aerosol application of the atropine derivative – ipratropium [27] in combination with intravenous atropine, which improves the condition of the respiratory system [28]. In recent years, another Atropa belladonna alkaloid anisodamine has attracted scientific attention. Being a less effective cholinolytic than atropine and scopolamine, it is less toxic. In addition, anisodamine exhibits anti-inflammatory, antioxidant, antiarrhythmic, anticoagulant activity [29], which is important for the correction of the whole complex of disorders due to acute OPS poisoning.

Cholinesterase reactivators. While anticholinergic drugs alleviate the manifestations of muscarinic intoxication, specific antidotes

Table

The scheme of use of drugs in acute OPs poisoning [21]

Drug	Type	Dose
Atropine	M-cholinolyticк	— entering a bolus loading dose of 0,6–3,0 mg, rapidly intravenously; — every 5 minutes the dose is doubled and administered until the onset of signs of atropinization of the patient (heart rate – 80 beats per minute; systolic pressure – 80 mm Hg; clean lungs); — in case of atropinization of the patient, 10–20% of the dose required for atropinization in 0,9% sodium chloride solution is infused every hour; — closely monitor the patient for manifestations of recurrent cholinergic toxicity, or toxic effects of atropine (see below) — in case of return of cholinergic toxicity, repeated bolus administration of atropine is performed before the onset of atropinization of the patient and hourly infusion of increased to 20% of the dose required for atropinization is performed in 0,9% sodium chloride solution; — if the patient has signs of toxic effects of atropine (tachycardia, absence of intestinal murmurs, hyperthermia, delirium, urinary retention) stop infusions for 30 minutes, then resume them, reducing the dose of atropine by 20%;
Pralidoxime	oxime cholinesterase reactivator	— a patient is given a loading dose – 20–30 mg/kg for 30 minutes; — this dose can be re-administered in 6–8 hours; — alternatively, an infusion can be performed at a dose of 5–10 mg * hour/kg in 0,9% sodium chloride solution; — the duration of administration is not defined - can be stopped after 48 hours and then resumed in case of deterioration of the clinical condition or the results of electrophysiological examination. It is advisable to monitor the activity of erythrocyte acetylcholinesterase;
Obidoxime	oxime cholinesterase reactivator	— a patient is given a loading dose of 250 mg/kg for 30 minutes; — conduct a continuous infusion of 750 mg every 24 hours until the clinical condition of the patient improves;
Diazepam	GABA-A receptor agonist	— a patient is given 10–20 mg intravenously to the patient in case of excitation or respiratory distress, provided the possibility of artificial ventilation.

use is aimed at restoring the function of OPs-inhibited acetylcholinesterase by dephosphorylating the active site of the enzyme [30-32]. In 1951, I. Wilson (USA) [33] demonstrated in vitro reactivation of cholinesterase inhibited by tetraethyl pyrophosphate, a nucleophilic compound – hydroxylamine. Shortly afterwards, the reactivity of a group of tertiary oximes was evaluated – monoisonitrosoacetone (MINA), diisonitrosoacetone (DINA), isonitrosoacetophenone (INAP), isonitrozoacetylacetone (INAA) and diacetylmonoxime (DAM) [34]. Although those compounds were capable to penetrateBBB, tertiary oximes were toxic at reactivating doses. Further studies were aimed at the synthesis of a reactivator with an electron-donor group (nucleophile), structurally similar to acetylcholine and with a stable positive charge, due to the presence of quaternary nitrogen. This structure provided affinity for

the active site of acetylcholinesterase and efficient reactivation of the enzyme, but prevented penetration through the BBB. The parallel efforts of I. Wilson (USA) and A. Green and D. Davies (UK) resulted in the synthesis of pralidoxime (2-PAM). The drug was successfully used in 1956 in parathion poisoning in Japan and still remains the leading antidote for OPs poisoning. The drug is currently recommended by the WHO and is commercially available in the UK, Japan, India and Australia. In 1959, in the United States, I. Wilson and colleagues synthesized a derivative of pralidoxime, the bis-pyridine aldoximetrimedoxime (TMB-4), which showed even greater affinity for inhibited acetylcholinesterase [35], but was the most toxic among other oximes used at the time. In continuation of the search for reactivators of the bis-pyridine oxime group, A. Luttringhaus and I. Hagedorn (Germany) developed reactivator LuH-6 (obidoxime) in the early 1960s [36]. The compound successfully reactivated acetylcholinesterase inactivated by tabun, sarin and VX, but was not effective in soman poisoning. In 1966, K. Schoene and I. Hagedorn proposed HS-6, effective in soman poisoning, and later its analogue HI-6 (azoxim) effective in poisoning by soman, sarin and VX, but ineffective in tabun poisoning [37]. Thus, in the mid-1960s, all five cholinesterase reactivators that are allowed to be used today were identified (Fig. 1). Later, in 1986, oxime HLo-7 (I. Hagedorn and M. Loffler, Germany) was synthesized [38]. The compound was effective in defeating all four major warfare OPs, but its own high toxicity and instability in solutions did not allow consider it as an alternative to 2-PAM.

In the 1970s, on the basis of the current Scientific Center for Preventive Toxicology, Food and Chemical Safety named after academician L.I. Medved, the Ministry of Health of Ukraine synthesized and studied a reactivator from the group of non-quaternary oximes – diethyxime. Studies have shown its low toxicity and ability to reactivate AChE in both the peripheral and central nervous systems in poisoning of rats with anticholynesterase OPs and carbamates [40]. According to the authors of the study, the concentration of the antidote in the brain was almost twice as high as in the serum. Diethyxime normalized the bioelectrical activity of the brain of experimental animals and the functional state of spinal cord motoneurons, prevented the development of histopathological changes in spinal cord fibers after OPs intoxication. The results of later studies are concised and contradictory [41-43], which generally confirms the fact that the search for a "universal" AChE reactivator is an ambiguous and complex issue.

In the Russian Federation, the AChE carboxime reactivator (Fig. 2), developed at the beginning of the century, has been registered as a medicinal product [44]. Carboxime is able to overcome BBB, in vitro study demonstrated that it also exhibits the properties of a non-

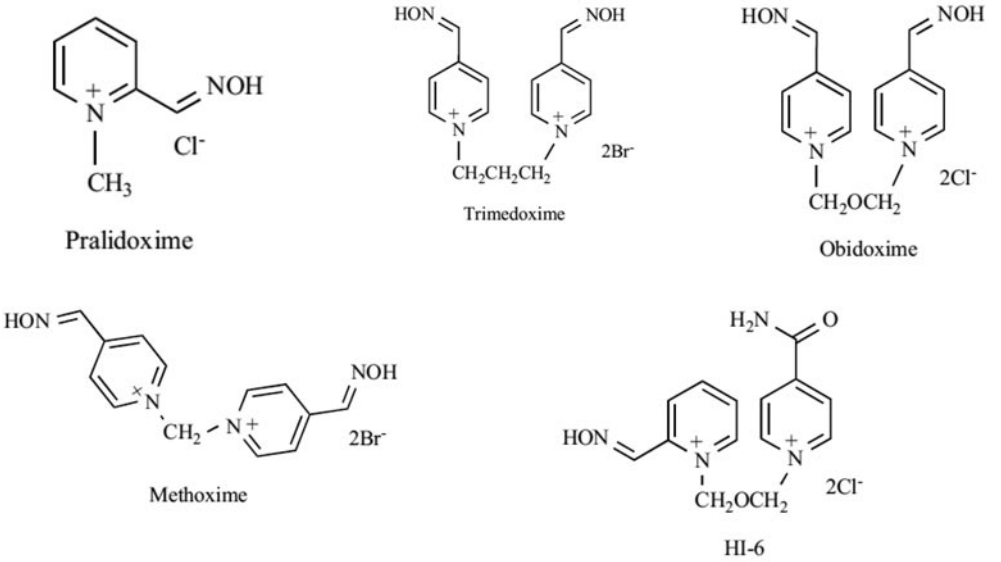

Fig. 1. Structural formulas of oximes that are allowed for clinical use (Antonijevic B., Stojiljkovic M.P., 2007) [39].

competitive inhibitor of AChE, what allows to consider it as a prophylactic agent at the situation of expectedOPs poisoning.

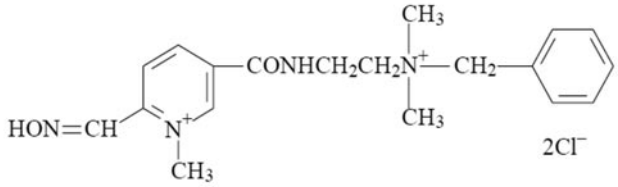

Fig. 2. Carboxime (Prozorovsky V.B., Skopichev V.G., Panchenkova O.A., 2008) [44].

Development and research of oxime reactivators continues. Last decades, more than 300 oxime reactivators have been synthesized and studied, and steps have been taken towards the synthesis of new compounds (for example, K-27, K-48, BT-07-4M, BT-08) [45-47]. However the significant disadvantage of oximes is their inability to overcome BBB and protect the CNS from toxic damage. As an alternative to quaternary oximes, lipophilic amidine oximes, which are able to penetrateBBB, have been considered [48]. However, they have significant disadvantages – low affinity for cholinesterases and a high risk of toxic effects. In order to reactivate AChE in the CNS, it was proposed to consider uncharged, zwitterionic oximes. The class of these substances revealed RS 194B (Fig. 3), which is able to restore AChE in the CNS and is less toxic compared to 2-PAM [49].

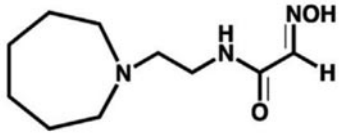

Fig. 3. Zwitterionic oxime RS 194B (Taylor P et al, 2019) [49].

Recently, a number of phenoxyalkylpyridine oxime compounds have been synthesized (US Patent 9,277,937) [50]. It is reported that some members of this series are able to restore the activity of AChE in the brain of rats up to 35% within 2 hours after poisoning by nitrophenyl isopropyl methylphosphonate (sarin surrogate) and paraoxon [51].

Nowadays there is a return of scientific interest to tertiary oximes MINA and DINA, capable to penetrateBBB. Thus, in a model of guinea pig somanpoisoning AChE reactivation in the striatum and midbrain of animals wasconfirmed [52]. The authors of the study deem that the effectiveness of this group of reactivators was underestimated, although their own relatively high toxicity must be taken into account.

In 2018, the results of a study of 15 new antidotes, structurally close to the known bispyridine K-oximes – K408 and K074, were published, in which the oxime group was preserved and the heterocyclic functional group of the molecule was modified (Fig. 4). Better results were obtained compared to standard reactivators in the model of reactivation of human brain AChE in vitro, [53].

Also, tertiary imidazole aldoximes capable of reactivating butyrylcholinesterase have recently been proposed as antidote agents, which are considered as a natural bioscavener of OPs [54]. Over the last 10 years, a number of uncharged (non-nucleophilic) oxime and non-oxime compounds with a wide range of structural elements in the molecule have been proposed as potential reactivators [55].

In order to expand the range of OPs, under the action of which antidotes would be effective, mixtures of HI-6 with trimedoxime and K203 were studied in a model of cyclosarine poisoning in rats [56]. The obtained results indicate that this direction can be promising

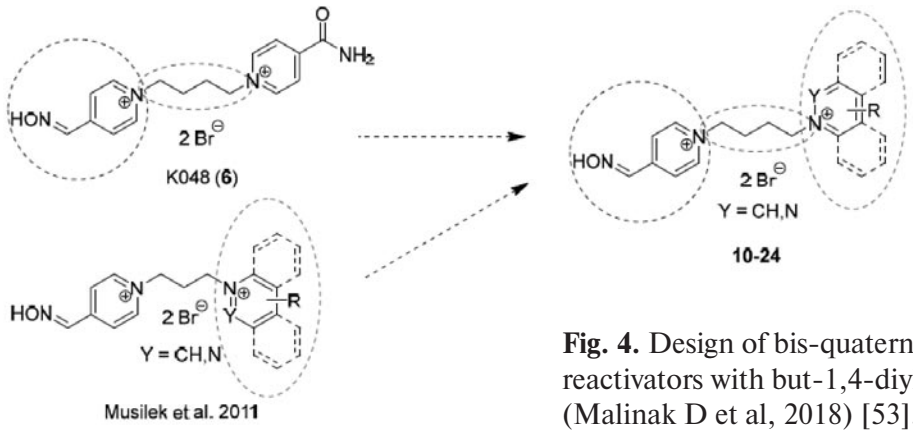

Fig. 4. Design of bis-quaternary monooxime reactivators with but-1,4-diyl lincage (Malinak D et al, 2018) [53].

for the development of more universal antidotes. In 2015, after screening almost 2,000 biologically active compounds, it was found that the antimalarial substance amodiaquine (Fig. 5) exhibits reactivation activity higher than 2-PAM, and is able to penetrateBBB. These findings expanded the range of compounds with new functional groups – common bases and Mannich phenols, to search for reactivators [57]. Although amodiaquine has been shown to inactivate human AChE by a mixed (competitive-non-competitive) type [58], the structure of this molecule is considered as a promising matrix for further search for reactivators.

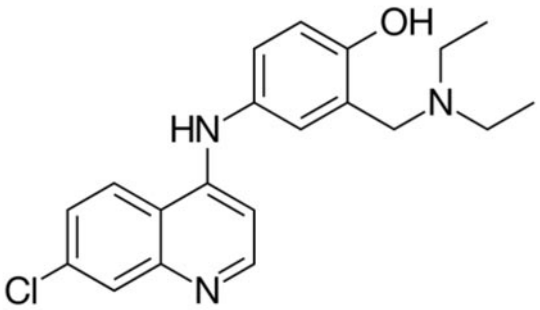

Fig. 5. Amodiaquine (Katz FS et al, 2015) [57].

Approaches to solving the problem of overcoming AChE BBB reactivators are covered in detail in the review of T. Kobrlova and co-authors [59]. The authors consider such steps to ensure the permeability of BBB for reactivators, as the use of nanoparticles as transporters, inhibition of p-glycoprotein to increase the permeability of BBB, development of lipophilic and sugar-modified oximes, prooximes that can be transformed into a reactivator after overcoming BBB, search for uncharged Quaternary oximes, the possibility of nasal administration of cholinesterase reactivators. The review emphasizes that the attempt to increase the permeability of BBB for reactivators is accompanied by the risk of their own neurotoxic effects, which can be observed on the example of tertiary oximes. As a promising approach to CNS protection in OPs poisoning, the authors proposed the use of combinations of known neuroprotective agents (parasympatholytics, antiglutamatergic and GABAergic agents) together with AChE reactivators and OPs scavengers.

Despite considerable efforts, there is no alternative to pralidoxime yet. As F. Worek and co-authors [55] rightly point out, structured, step-by-step approaches and comprehensive in vitro and in vivo studies are needed to successfully identify and select potential cholinesterase reactivators.

Anticonvulsants. Acute OPs intoxication is accompanied by epileptomorphic (prolonged and continuous) convulsions due to the accumulation of acetylcholine and subsequent activation of the glutamatergic system. The incidence of convulsions in highly toxic OPs poisoning was estimated at approximately 3% as a result of a sarin terrorist attack in the Tokyo subway [60]. However, under conditions of mass poisoning of the civilian population of OPs, pharmacological suppression of epileptomorphic states reduces their negative consequences - neuronal damage, which leads to severe functional deficit and death. Therefore, the existing therapeutic regimen includes the use of GABA-A receptor stimulants, in particular benzodiazepines. These drugs have been shown to reduce the synaptic release of acetylcholine, and the combined use of diazepam with atropine is more effective than only atropine or oxime [61]. Because the therapeutic efficacy of benzodiazepines decreases over time from the onset of convulsive symptoms [62], they are a means of emergency care. Today, diazepam is the standard of anticonvulsant therapy for OPs poisoning, but the use of midazolam is being considered. A significant disadvantage of both drugs is their ability to control the status epileptomorphic for a limited time and reduce the therapeutic efficacy of both drugs over time (from the onset of symptoms). Therefore, the search for more effective tools and their combinations continues. In particular, data from a preclinical study of the compound LY293558 [63], which is an antagonist of AMPA /GluK1 receptors, have been published. Experiments on rats have shown that LY293558 effectively stops sarin-induced convulsions, has a neuroprotective effect, is effective even 1 hour after exposure. The combined use of LY293558 with caramiphene, which is an antagonist of M1-muscarinic receptors and has the properties of an antagonist of NMDA-receptors, led to an enhancement of the therapeutic effect and, most importantly, completely prevented the loss of neurons in animals.

Today, the development of new drugs and regimens for anticonvulsant therapy in OPs

poisoning requires both a more detailed study of the mechanisms of formation of this symptom complex and an experimental paradigm that reflects the characteristics of certain parts of the population that may be affected or be more vulnerable (for example, age) to the neurotoxicants [64].

Means of prevention of acute OPs poisoning. The use of pharmacological prophylaxis at the risk of exposure to OPs anticholinesterase action can increase the effectiveness of basic therapy in case of acute poisoning, and sometimes prevent the development of its symptoms. Today, as a means of prevention, along with reversible inhibitors of AChE of non-organophosphorus nature, are also considered bioscavengers [65].

Due to the "aging" effect of AChE under the action of highly toxic OPs, for the prevention of poisoning, in an emergency, it is recommended to use pharmacological agents that temporarily inhibit cholinesterase and thus protect the active center of AChE from interaction with the OPs molecule. These include carbamates: aminostigmine, pyridostigmine, proserine, as well as alkaloids of plant origin – galantamine, guperzine A. Proserine and pyridostigmine contain in their structure a Quaternary nitrogen atom and therefore do not penetrate the BBB. Pyridostigmine is more effective than proserine because it has greater bioavailability and prolonged action. Currently, pyridostigmine bromide [66] is used in most NATO countries as a prophylactic against the threat of OPs poisoning. The compound covalently binds to AChE, after which the complex slowly hydrolyzes to release acetylcholinesterase. In the standby mode of the chemical threat of pyridostigmine bromide can be used prophylactically repeatedly at 30 mg every 8 hours, while the activity of cholinesterase remains at 60–80% of baseline [67]. A significant disadvantage of pyridostigmine is the inability to prevent the toxic effects of OPs on the CNS. Carbamate compound with a tertiary nitrogen atom – aminostigmine easily penetrates through the BBB and has a pronounced effect on M-cholinoreactive systems of the brain [43]. The alkaloid galantamine isolated from the plant Galanthus woronowii is a competitive cholinesterase blocker, which has a slow reverse effect. In addition, the compound is an allosteric ligand capable of modulating nicotinic cholinergic receptors [68, 69]. Galantamine interacts with the active center of the nicotinic receptor and specifically increases its activity in the presence of acetylcholine. The alkaloid guperzine A, isolated from the moss Guperzia serrate, compared with other reverse cholinesterase inhibitors, better penetrates the BBB and provides a longer inhibition of the enzyme. The duration of protective inhibition of AChE can be enhanced by the manufacture of specialized formulations [70].

Another group of therapeutic agents, the scientific interest in which arose in the 80s of last century – OPs-reactive proteins [66]. Such biomolecules are butyrylcholinesterase, albumin, plasma paraoxonase (PON-1), carboxylesterase, which is present in many barrier tissues of the body. Endogenous bioscaveners are present in the skin, tissues and blood in amounts that can neutralize low doses of OPs. The antidote potential of these molecules can be enhanced by replenishing the body's own pool with exogenous bioscaveners. It is assumed that the use of exogenous bioscaveners can protect the human body from the effects of approximately two LD50 anticholinesterase OPs, regardless of their structure. The toxicity of these drugs to humans is low, but their use is associated with the risk of disruption of metabolic processes in which these molecules are involved, and the development of adverse immune reactions when reintroduced into the body.

Conclusions. Standards for the treatment of OPs poisoning have remained unchanged for almost half a century. During this period, considerable experience has been gained and a large amount of research has been conducted. However, existing methods of treatment of OPs poisoning with anticholinesterase action currently remain insufficiently effective and do not always meet the requirements of health protection [71]. The principles of pharmacological therapy of poisoning with highly toxic OPs, based on the use of cholinolytics and oximes, are characterized by certain limitations, their prophylactic use remains problematic, they do not protect against the development of long-term effects of poisoning [72]. Current research aims to find less toxic M-cholinolytics with a wider range of therapeutic effects. Analysis of the experience of clinical use of 2-PAM – AChE reactivator, recommended by the WHO, did not clearly confirm its effectiveness in pes-

ticide poisoning [73]. The problem of creating a broad-spectrum cholinesterase reactivator capable of overcoming BBB and preventing CNS damage in OPs poisoning remains unsolved. In this aspect, it would be appropriate to conduct non-clinical studies at the current methodological level of diethyxime reactivator, which was developed in the 1980s in Ukraine. This would assess the prospects for its further development as an antidote to acute OPs poisoning. It should be noted that the effectiveness of the combined action of AChE reactivators is also insufficiently studied. In addition, the search for a combination of neuroprotectors capable of overcoming BBB with peripheral cholinesterase reactivators may be one approach to solving the problem of protecting the central nervous system in OPs poisoning. In this context, the data on guperzine A, which exhibits the properties of both an inverse AChE inhibitor and a channel-type NMDA receptor antagonist, are noteworthy. The development of anticonvulsant therapeutic agents requires further study of the mechanism of status epilepticus in general and in acute OPs poisoning in particular.

Given the extremely wide range of new groups of compounds proposed for screening as drugs for basic therapy of acute anticholinesterase OPs poisoning, one way to increase the effectiveness of such studies may be the use of unified methods to assess the therapeutic efficacy of a number of antidotes structures. Given the intensive research to improve the treatment of OPs poisoning worldwide, at the stage of preclinical studies it is important to unify the research methodology using relevant models of experimental evaluation of the effectiveness of therapies. Adherence to international standards and schemes in this direction will ensure the receipt of relevant data and their comparability with existing ones. It should also be noted that the development of tools and treatment regimens for poisoning at the experimental stage faces limitations due to ethical and safety issues in the work of research staff with OPs anticholinesterase action, and the organization of the clinical stage of evaluation of acute intoxication therapy is extremely difficult.

Although the literature casts doubt on the possibility of developing an effective system for the treatment of acute OPs poisoning and suggests focusing on banning the use of these compounds in the agro-industrial complex [21], such an approach to solving the problem is unlikely to be realistic. At the same time, the efforts of scientists to find means for pharmacological correction of OPs poisoning should be accompanied by the formation of a more prudent regulatory policy in the use of pesticides, promoting information measures on the dangers of OPs, prevention of mental disorders that provoke suicidal consequences.

Prospects for further research. Further research will focus on the analysis of modern models and schemes of preclinical evaluation of the treatment of acute OPs poisoning.

REFERENCES

1. Watson WA, Litovitz TL, Rodgers GC, Klein-Schwartz W, Youniss J, Rose SR, Borys D, May ME. 2002 annual report of the American association of poison control centers toxic exposure surveillance system 1. The American journal of emergency medicine. 2003;21(5):353-421.
2. Robb EL, Baker MB. Organophosphate toxicity. StatPearls [Internet]. 2020 Jul 27. [https://www.ncbi.nlm.nih.gov/books/NBK470430/]
3. Ivashchenko OV, Zozulia IS, Kurdil NV. Suchasni aspekty hostrykh otruien fosfororhanichnymy insektytsydamy. Zbirnyk naukovykh prats spivrobitnykiv NMAPO im. PL Shupyka. 2018(30):683–98.
4. Bertolote JM, Fleischmann A, Eddleston M, Gunnell D. Deaths from pesticide poisoning: a global response. The British Journal of Psychiatry. 2006 Sep;189(3):201–3.
5. Bonvoisin T, Utyasheva L, Knipe D, Gunnell D, Eddleston M. Suicide by pesticide poisoning in India: a review of pesticide regulations and their impact on suicide trends. BMC public health. 2020 Dec;20(1):1–6.
6. Marcus H, De Souza RJ. Risk Factors for Acute Pesticide Poisoning in Developing Countries: A Systematic Review. Global Health: Annual Review. 2020 Jul 4;1(5):4.
7. Prodanchuk NG. Balan GM. Krivenchuk VE. Prodanchuk GN. Kurdil NV. Babich VA. Kharchenko OA. Bubalo NN. O neobkhodimosti sozdaniya proizvodstva reaktivatorov kholinesterazy v Ukraine dlya lecheniya ostrykh otravleniy fosfororganicheskimi soyedineniyami. Suchasni problem toksykolohii, kharchovoi ta khimichnoi bezpeky. 2014;3-4:14-22.
8. Ustinova LA, Seredynska NM, Kurdil NV, Sahlo VI, Barasii MI, Yevtodiev OA. Toksykanty antykholinesteraznoi dii: mekhanizm dii, klinichni oznaky ta aktualni pytannia zabezpechennia zasobamy antydotnoi terapii. Suchasni problem toksykolohii, kharchovoi ta khimichnoi bezpeky. 2017;3:73-82.
9. Harvey SP, McMahon LR, Berg FJ. Hydrolysis and enzymatic degradation of Novichok nerve agents. Heliyon. 2020 Jan 1;6(1):e03153.
10. Vale JA, Marrs TC, Maynard RL. Novichok: a murderous nerve agent attack in the UK. Clinical Toxicology. 2018 Nov 2;56(11):1093–7.
11. Masterson J. OPCW to Investigate Navalny Poisoning. Arms Control Today. 2020 Oct 1;50(8):28–9.

12. Costa LG. Current issues in organophosphate toxicology. Clinica chimica acta. 2006 Apr 1;366(1–2):1–3.
13. Dvir H, Silman I, Harel M, Rosenberry TL, Sussman JL. Acetylcholinesterase: from 3D structure to function. Chemico-biological interactions. 2010 Sep 6;187(1-3):10–22.
14. Petrov KA. Kharlamova AD. Nikolskiy Eye. Kholinesterazy: vzglyad neyrofiziologa. Geny i kletki. 2014;9(3).
15. McDonough JH Jr, Shih TM. Neuropharmacological mechanisms of nerve agent-induced seizure and neuropathology. Neuroscience &biobehavioral reviews. 1997 Jan 1;21(5):559–79.
16. Zhuang Q, Young A, Callam CS, McElroy CA, Ekici ÖD, Yoder RJ, Hadad CM. Efforts towards treatments against aging of organophosphorus-inhibited acetylcholinesterase. Annals of the New York Academy of Sciences. 2016 Jun;1374(1):94–104.
17. Buckley NA, Roberts D, Eddleston M. Overcoming apathy in research on organophosphate poisoning. Bmj. 2004 Nov 18;329(7476):1231–3.
18. Peter JV, Moran JL, Graham PL. Advances in the management of organophosphate poisoning. Expert opinion on pharmacotherapy. 2007 Jul 1;8(10):1451–64.
19. Hulse EJ, Haslam JD, Emmett SR, Woolley T. Organophosphorus nerve agent poisoning: managing the poisoned patient. British journal of anaesthesia. 2019 Oct 1;123(4):457–63.
20. Bajgar J, Kuca K, Jun D, Bartosova L, Fusek J. Cholinesterase reactivators: the fate and effects in the organism poisoned with organophosphates/nerve agents. Current drug metabolism. 2007 Dec 1;8(8):803–9.
21. Eddleston M, Chowdhury FR. Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new. British journal of clinical pharmacology. 2016 Mar;81(3):462–70.
22. Abedin MJ, Sayeed AA, Basher A, Maude RJ, Hoque G, Faiz MA. Open-label randomized clinical trial of atropine bolus injection versus incremental boluses plus infusion for organophosphate poisoning in Bangladesh. J Med Toxicol. 2012; 8: 108–17.
23. Connors NJ, Harnett ZH, Hoffman RS. Comparison of current recommended regimens of atropinization in organophosphate poisoning. Journal of Medical Toxicology. 2014 Jun 1;10(2):143–7.
24. Arendse R, Irusen E. An atropine and glycopyrrolate combination reduces mortality in organophosphate poisoning. Human & experimental toxicology. 2009 Nov;28(11):715–20.
25. Kventsel I, Berkovitch M, Reiss A, Bulkowstein M, Kozer E. Scopolamine treatment for severe extra-pyramidal signs following organophosphate (chlorpyrifos) ingestion. Clin Toxicol (Phila). 2005;43(7):877–9.
26. Iyer R, Iken B, Leon A. Developments in alternative treatments for organophosphate poisoning. Toxicology letters. 2015 Mar 4;233(2):200–6.
27. Shemesh I, Bourvin A, Gold D, Kutscherowsky M. Chlorpyrifos poisoning treated with ipratropium and dantrolene: a case report. Journal of Toxicology: Clinical Toxicology. 1988 Jan 1;26(7):495–8.
28. Perrone J, Henretig F, Sims M, Beers M, Grippi MA. A role for ipratropium in chemical terrorism preparedness. Academic Emergency Medicine. 2003 Mar;10(3):290.
29. Eisenkraft A, Falk A. Possible role for anisodamine in organophosphate poisoning. Br J Pharmacol. 2016;173(11):1719–27.
30. Mercey G, Verdelet T, Renou J, Kliachyna M, Baati R, Nachon F, Jean L, Renard PY. Reactivators of acetylcholinesterase inhibited by organophosphorus nerve agents. Accounts of chemical research. 2012 May 15;45(5):756–66.
31. Musilek K, Dolezal M, Gunn-Moore F, Kuca K. Design, evaluation and structure-activity relationship studies of the AChE reactivators against organophosphorus pesticides. Medicinal research reviews. 2011 Jul;31(4):548–75.
32. Colovic MB, Krstic DZ, Lazarevic-Pasti TD, Bondzic AM, Vasic VM. Acetylcholinesterase inhibitors: pharmacology and toxicology. Current neuropharmacology. 2013 May 1;11(3):315–35.
33. Petroianu GA. The history of cholinesterase reactivation: hydroxylamine and pyridinium aldoximes. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2012 Oct 1;67(10):874–9.
34. Musilek K, Kuca K, Ghosh KK. Development and Structural Modifications of Cholinesterase Reactivators against Chemical Warfare Agents in Last Decade: A Review. Mini Rev Med Chem. 2015;15(1):58–72.
35. Wilson IB, Ginsburg S. Reactivation of acetylcholinesterase inhibited by alkylphosphates. Arch Biochem Biophys. 1955 Feb;54(2):569–71.
36. Lüttringhaus A, Hagedorn I. Quaternary hydroxyiminomethylpyridinium salts. The dischloride of bis-(4-hydroxyiminomethyl-1-pyridinium-methyl)-ether (lueh6), a new reactivator of acetylcholinesterase inhibited by organic phosphoric acid esters. Arzneimittel-Forschung. 1964 Jan;14:1–5.
37. Stojiljković MP, Pantelić D, Maksimović M. Tabun, sarin, soman and VX poisoning in rats: kinetics of inhibition of central and peripheral acetylcholinesterase, ageing, spontaneous and oxime-facilitated reactivation, Proceedings of VII International Symposium on Protection against Chemical and Biological Agents, Stockholm, Sweden, 2001:1–12.
38. de Jong LP, Verhagen MA, Langenberg JP, Hagedorn I, Löffler M. The bispyridinium-dioxime HLö-7: a potent reactivator for acetylcholinesterase inhibited by the stereoisomers of tabun and soman. Biochemical pharmacology. 1989 Feb 15;38(4):633–40.
39. Antonijevic B, Stojiljkovic MP. Unequal efficacy of pyridinium oximes in acute organophosphate poisoning. Clin Med Res. 2007;5(1):71–82.
40. Kokshareva NV, Kovtun SD, Kagan YuS, Mizyukova IG, Medvedev BM. Effect of a new cholinesterase reactivator, diethyxime, on the central nervous system. Byull. Eksp. Biol. Med.1977;83:29–32 (Abs. in English).
41. Kenley RA, Howd RA, Mosher CW, Winterle JS. Nonquaternary cholinesterase reactivators. Dialkylaminoalkyl thioesters of alpha-ketothiohydroximic acids as reactivators of diisopropylphosphorofluoridate inhibited acetylcholinesterase. J Med Chem. 1981 Oct;24(10):1124–33.
42. Dube SN, Ghosh AK, Jeevarathinam K, Kumar D, Gupta SD, Pant BP, et al. Studies on the efficacy of diethyxime as an antidote against organophosphorus intoxication in rats. The Japanese Journal of Pharmacology.1986;41(3):267–71.
43. Shih TM, Koplovitz I, Kan RK, McDonough JH. In search of an effective in vivo reactivator for organophosphorus

nerve agent-inhibited acetylcholinesterase in the central nervous system. Advanced Studies in Biology 2012;4(10):451–78.
44. Prozorovskiy VB. Skopichev VG. Panchenkova OA. Otsenka reaktivatora kholinesterazy karboksima kak sredstva profilaktiki otravleniy fosfororganicheskimi ingibitorami kholinesteraz. Psikhofarmakologiya I biologicheskaya narkologiya. 2008: 8(3-4): 2457–62.
45. Petroianu GA, Hasan MY, Nurulain SM, Nagelkerke N, Kassa J, Kuca K. New K-Oximes (K-27 and K-48) in Comparison with Obidoxime (LuH-6), HI-6, Trimedoxime (TMB-4), and Pralidoxime (2-PAM): Survival in Rats Exposed IP to the Organophosphate Paraoxon. Toxicol Mech Methods. 2007;17(7):401–8.
46. Petroianu GA, Nurulain SM, Nagelkerke N, Shafiullah M, Kassa J, Kuca K. Five oximes (K-27, K-48, obidoxime, HI-6 and trimedoxime) in comparison with pralidoxime: survival in rats exposed to methyl-paraoxon. J Appl Toxicol. 2007 Sep-Oct;27(5):453–7.
47. Atanasov VN, Petrova I, Dishovsky C. In vitro investigation of efficacy of new reactivators on OPC inhibited rat brain acetylcholinesterase. Chem Biol Interact. 2013 25;203(1):139–43.
48. Kalisiak J, Ralph EC, Cashman JR. Nonquaternary reactivators for organophosphate-inhibited cholinesterases. Journal of medicinal chemistry. 2012 Jan 12;55(1):465–74.
49. Taylor P, Yan-Jye S, Momper J, Hou W, Camacho-Hernandez GA, Rosenberg Y, Kovarik Z, Sit R, Sharpless KB. Assessment of ionizable, zwitterionic oximes as reactivating antidotal agents for organophosphate exposure. Chemico-biological interactions. 2019 Aug 1;308:194–7.
50. Chambers JE, Meek EC. Novel centrally active oxime reactivators of acetylcholinesterase inhibited by surrogates of sarin and VX. Neurobiology of disease. 2020 Jan 1;133:104487.
51. Dail MB, Leach CA, Meek EC, Olivier AK, Pringle RB, Green CE, Chambers JE. Novel Brain-Penetrating Oxime Acetylcholinesterase Reactivators Attenuate Organophosphate-Induced Neuropathology in the Rat Hippocampus. Toxicol Sci. 2019;169(2):465–74.
52. Shih TM, Skovira JW, O'Donnell JC, McDonough JH. Treatment with tertiary oximes prevents seizures and improves survival following sarin intoxication. J Mol Neurosci. 2010 Jan;40(1-2):63–9.
53. Malinak D, Nepovimova E, Jun D, Musilek K, Kuca K. Novel Group of AChE Reactivators-Synthesis, In Vitro Reactivation and Molecular Docking Study. Molecules. 2018 Sep 7;23(9):2291.
54. Sit RK, Fokin VV, Amitai G, Sharpless KB, Taylor P, Radić Z. Imidazole aldoximes effective in assisting butyrylcholinesterase catalysis of organophosphate detoxification. J Med Chem. 2014;57(4):1378–89.
55. Worek F, Thiermann H, Wille T. Organophosphorus compounds and oximes: a critical review. Arch Toxicol. 2020;94(7):2275–2292.
56. Kassa J, Karasová JZ, Pavlíková R, Caisberger F, Bajgar J. The ability of oxime mixtures to increase the reactivating and therapeutic efficacy of antidotal treatment of cyclosarin poisoning in rats and mice. ActaMedica (Hradec Kralove). 2012;55(1):27–31.
57. Katz FS, Pecic S, Tran TH, Trakht I, Schneider L, Zhu Z, Ton-That L, Luzac M, Zlatanic V, Damera S, Macdonald J, Landry DW, Tong L, Stojanovic MN. Discovery of New Classes of Compounds that Reactivate Acetylcholinesterase Inhibited by Organophosphates. Chembiochem. 2015;16(15):2205–15.
58. Bierwisch A, Wille T, Thiermann H, Worek F. Kinetic analysis of interactions of amodiaquine with human cholinesterases and organophosphorus compounds. Toxicol Lett. 2016;246:49–56.
59. Kobrlova T, Korabecny J, Soukup O. Current approaches to enhancing oxime reactivator delivery into the brain. Toxicology. 2019;423:75–83.
60. Okumura T, Takasu N, Ishimatsu S, Miyanoki S, Mitsuhashi A, Kumada K, et al. Report on 640 victims of the Tokyo subway Sarin attack. Ann Emerg Med 1996;28:129–35
61. Bajgar J, Fusek J, Kuca K, Bartosova L, Jun D. Treatment of organophosphate intoxication using cholinesterase reactivators: facts and fiction. Mini Rev Med Chem. 2007;7(5):461–6.
62. Trinka E, Kälviäinen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure. 2017 Jan 1;44:65-73.
63. Aroniadou-Anderjaska V, Figueiredo TH, Apland JP, Braga MF. Targeting the glutamatergic system to counteract organophosphate poisoning: A novel therapeutic strategy. Neurobiology of disease. 2020 Jan 1;133:104406.
64. McCarren HS, McDonough JH Jr. Anticonvulsant discovery through animal models of status epilepticus induced by organophosphorus nerve agents and pesticides. Ann N Y Acad Sci. 2016 Jun;1374(1):144-50.
65. Masson P, Nachon F. Cholinesterase reactivators and bioscavengers for pre- and post-exposure treatments of organophosphorus poisoning. Journal of neurochemistry. 2017 Aug;142:26–40.
66. Philippens I, Jongsma M, Joosen M, Bouwman G, Vanwersch R. Prophylaxis against nerve agent toxicity: Physiological, behavioral, and neuroprotection of current and novel treatments. InHFM-149 Symposium'Defense against the Effects of Chemical Hazards: Toxicology, Diagnosis and Medical Countermeasures', Edinburgh, Scotland (GBR), 8-10 October 2007 2007 Jan 1.
67. Dunn MA, Sidell FR. Progress in medical defense against nerve agents. JAMA. 1989 Aug 4;262(5):649–52.
68. Wessler I, Kirkpatrick CJ. Acetylcholine beyond neurons: the non-neuronal cholinergic system in humans. Br J Pharmacol. 2008;154(8):1558–71.
69. Pohanka M. Cholinesterases, a target of pharmacology and toxicology. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2011 Sep;155(3):219–29.
70. Wang T, Wang Y, Zhang L, Han B, Wang H, Li Y, Fu F. A novel approach to medical countermeasures against organophosphorus compound toxicity. Biomed Rep. 2013;1(6):901–906.
71. Bajaj P, Tripathy RK, Aggarwal G, Datusalia AK, Sharma SS, Pande AH. Refolded Recombinant Human Paraoxonase 1 Variant Exhibits Prophylactic Activity Against Organophosphate Poisoning. Appl Biochem Biotechnol. 2016 Sep;180(1):165–76.
72. Doctor BP, Saxena A. Bioscavengers for the protection of humans against organophosphate toxicity. Chem Biol Interact. 2005 Dec 15;157–158:167–71.
73. Worek F, Thiermann H, Wille T. Oximes in organophosphate poisoning: 60 years of hope and despair. Chem Biol Interact. 2016 Nov 25;259(Pt B):93–8.

СУЧАСНІ АСПЕКТИ РОЗРОБКИ ЗАСОБІВ БАЗОВОЇ ТЕРАПІЇ ТА ПРОФІЛАКТИКИ ГОСТРИХ ОТРУЄНЬ ФОСФОРОРГАНІЧНИМИ СПОЛУКАМИ (огляд літератури)

М.Л. Зінов'єва, Н.В. Курділь, М.Г. Проданчук, О.П. Кравчук, П.Г. Жмінько
Державне підприємство «Науковий центр превентивної токсикології, харчової та хімічної безпеки імені академіка Л.І. Медведя Міністерства охорони здоров'я України», м. Київ, Україна

РЕЗЮМЕ. Вступ. *Незважаючи на значний досвід застосування базових засобів терапії гострих отруєнь фосфорорганічними сполуками (ФОС) антихолінестеразної дії та результати пошукових досліджень, проведених у світі, існуючі наразі методи терапії таких отруєнь виявляються недостатніми та не відповідають сучасним вимогам щодо ефективного лікування та збереження здоров'я людини.*
Мета*. На підставі аналізу наукових публікацій зробити огляд сучасних лікарських засобів базової терапії та профілактики гострих отруєнь ФОС на етапах їхнього експериментального дослідження, визначити основні напрямки подальшої розробки цих засобів.*
Методи. *Проведено системний контент-аналіз даних літератури з використанням бази даних PubMed.*
Результати. *Сучасні принципи фармакотерапії гострих отруєнь антихолінестеразними ФОС базуються на застосуванні антихолінергічних засобів (переважно атропіну), реактиваторів холінестерази та антиконвульсивної дії. М-холінолітична терапія залишається обов'язковим базовим компонентом терапії гострого отруєння ФОС. Сьогодні дослідження спрямовані на пошук менш токсичних М-холінолітиків з більш широким спектром терапевтичних ефектів. Нині ще не створений реактиватор холінестерази, який має таку характеристику спектру дії і здатний запобігти центральним ефектам при отруєннях ФОС. Недостатньо досліджена й ефективність комбінованої дії реактиваторів АХЕ. Одним з підходів до вирішення проблеми захисту центральної нервової системи при отруєнні ФОС може бути пошук комбінації реактиваторів периферичної холінестерази з нейропротекторами, здатними долати гематоенцефалічний бар'єр. Розробка антиконвульсивних терапевтичних агентів потребує подальшого дослідження механізму епілептичного статусу за гострого отруєння ФОС.*
Висновки. *Триває інтенсивний пошук засобів лікування отруєнь ФОС в усьому світі. Але на часі важливість пошуку і впровадження уніфікованої методології дослідження терапевтичної ефективності широкого спектру фармакологічних засобів на етапі їх доклінічної оцінки. Зусилля щодо пошуку засобів фармакологічної корекції отруєнь ФОС мають супроводжуватися формуванням більш зваженої регуляторної політики у сфері застосування пестицидів. Також необхідно створити чітку і послідовну політику щодо інформаційних заходів, які б зосереджували увагу на небезпечності ФОС, а також сприяли профілактиці ментальних розладів, що провокують суїцидальні наслідки.*
Ключові слова: *фосфорорганічні сполуки, гостре отруєння, засоби базової терапії, засоби профілактики.*

СОВРЕМЕННЫЕ АСПЕКТЫ РАЗРАБОТКИ СРЕДСТВ БАЗОВОЙ ТЕРАПИИ И ПРОФИЛАКТИКИ ОСТРЫХ ОТРАВЛЕНИЙ ФОСФОРОРГАНИЧЕСКИМИ СОЕДИНЕНИЯМИ (обзор литературы)

М.Л. Зиновьева, Н.В. Курдиль, Н.Г. Проданчук, А.П. Кравчук, П.Г. Жминько
Государственное предприятие «Научный центр превентивной токсикологии, пищевой и химической безопасности имени академика Л.И. Медведя Министерства здравоохранения Украины», г. Киев, Украина.

РЕЗЮМЕ. Введение. *Несмотря на значительный опыт применения базовых средств терапии острых отравлений фосфорорганическими соединениями (ФОС) антихолинэстеразного действия и результаты поисковых исследований, проведенных в мире, существующие в настоящее время методы терапии таких отравлений оказываются недостаточными и не отвечают современным требованиям эффективного лечения и сохранения здоровья человека.*
Цель. *На основании анализа научных публикаций провести обзор современных лекарственных средств базисной терапии и профилактики острых отравлений ФОС на этапах их экспериментального исследования, определить основные направления дальнейшей разработки этих средств.*
Методы. *Проведен системный контент-анализ данных литературы с использованием базы данных PubMed.*
Результаты*. Современные принципы фармакотерапии острых отравлений антихолинестеразными ФОС базируются на применении антихолинергических средств (преимущественно атропина), реактиваторов холинэстеразы и антиконвульсивного действия. М-холинолитическая терапия остается обязательным базовым компонентом терапии острого отравления ФОС. Сегодня исследования направлены на поиск менее токсичных М-холинолитиков с более широким спектром терапевтических эффектов. Сейчас еще не создан реактиватор холинэстеразы, который имеет такую характеристику спектра действия и способен предотвратить центральные эффекты при отравлениях ФОС. Недостаточно исследована и эффективность комбинированного действия реактиваторов АХЕ. Одним из подходов к решению проблемы защиты центральной нервной системы при отравлении ФОС может быть поиск комбинации реактиваторов периферической холинэстеразы с нейропротекторами, способными преодолевать гематоэнцефалический барьер. Разработка противосудорожных терапевтических агентов требует дальнейшего исследования механизма эпилептического статуса при остром отравлении ФОС.*
Выводы. *Продолжается интенсивный поиск средств лечения отравлений ФОС во всем мире. Ныне актуальным является поиск и внедрение унифицированной методологии исследования терапевтической эффективности широкого спектра фармакологических средств на этапе их доклинической оценки. Усилия по поиску средств фармакологической коррекции отравлений ФОС должны сопровождаться формированием более взвешенной регуляторной политики в сфере применения пестицидов. Также необходимо создать четкую и последовательную политику относительно информационных мероприятий, которые сосредоточивали бы внимание на опасности ФОС, а также способствовали профилактике ментальных расстройств, провоцирующих суицидальные последствия.*
Ключевые слова: *фосфорорганические соединения, острое отравление, средства базисной терапии, средства профилактики.*

Received 04/27/2021