METHODS FOR PREVENTION AND TREATMENT OF CONVULSIVE DISORDERS ASSOCIATED WITH CHOLINERGIC CONVULSANT INTOXICATION

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Organophosphates (OPs) and carbamates are a common cause of intoxication associated with convulsive disorders. These cholinergic substances form a bond with acetylcholinesterase (AChE), thus contributing to accumulation of acetylcholine in synapses and causing typical manifestations of toxicity, including seizures. Standard antidote therapy provides sufficient symptom control, reduces seizures and decreases mortality only in case of prescription at the early stage of poisoning or preventive administration. Traditionally, atropine is used, that blocks the activity of the muscarinic cholinergic receptors in the parasympathetic nervous system and reduce the smooth muscle contraction activity, along with oximes that reactivate the reversibly inhibited AChE in the nicotinic acetylcholine receptors found in skeletal muscle. If these are not sufficient, benzodiazepines that interact with γ-aminobutyric acid receptors are used to jugulate seizures, prevent organic brain desease and post-traumatic epilepsy. There are no unified guidelines for the cases of antidotes having no effect or insufficient efficacy of antidotes. Unwanted side effects of the existing drugs and progressive decrease of efficiency within 30 min after exposure to OPs necessitate the search for new agents. Combination therapy, new dosage forms, developing original molecules or modifying the existing ones are among the developed approaches discussed in our review.

Keywords: convulsive syndrome, neurotoxicants, organophosphates, cholinergic, anticonvulsant, antidotes, therapy, prevention

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МЕТОДЫ ПРОФИЛАКТИКИ И ТЕРАПИИ СУДОРОЖНОГО СИНДРОМА ПРИ ОТРАВЛЕНИИ КОНВУЛЬСАНТАМИ ХОЛИНЕРГИЧЕСКОГО РЯДА

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Фосфорорганические соединения (ФОС) и карбаматы — распространенная причина отравлений, ассоциированных с развитием судорожного синдрома. Эти холинергические вещества образуют связь с ацетилхолинэстаразой (АХЭ), что способствует накоплению ацетилхолина в нервных синапсах и приводит к характерным токсическим проявлениям, в том числе к развитию судорог. Стандартная антидотная терапия обеспечивает достаточный контроль симптомов, ослабляет судороги и снижает смертность только при назначении на самой ранней стадии отравления либо при профилактическом введении. Традиционно применяют атропин, который блокирует мускариновые холинергические рецепторы в парасимпатической нервной системе и уменьшает активность сокращения гладких мышц, а также оксимы, реактивирующие обратимо ингибированную АХЭ в никотиновых холинергических синапсах скелетных мышц. Если их недостаточно, для купирования судорог и профилактики развития органических повреждений головного мозга, посттравматической эпилепсии применяют средства бензодиазепинового ряда, взаимодействующие с рецепторами γ-аминомасляной кислоты. Единых официальных руководств на случай, когда антидоты не действуют или действуют недостаточно эффективно, не существует. Нежелательные побочные эффекты и прогрессирующее снижение эффективности существующих средств через 30 мин после воздействия ФОС обуславливают необходимость поиска новых средств. Среди разрабатываемых подходов — комбинированные схемы лечения, новые лекарственные формы, создание оригинальных или модификация существующих молекул, рассмотрению которых посвящен настоящий обзор.

Ключевые слова: судорожный синдром, нейротоксиканты, фосфорорганические соединения, холинергические вещества, антиконвульсант, антидоты, терапия, профилактика

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Prevalence and pathogenetic mechanisms of intoxication with cholinergic convulsants

Intoxication with chemical convulsant agents is associated with generalized seizures in the form of single/repeated seizures or symptomatic status epilepticus [1]. The mechanisms underlying the development of seizure activity include stimulation of excitation or inhibition of inhibitory pathways in the central nervous system (CNS) [2]. Neurotoxicants can affect neurotransmitters (synthesis, storage, release, reuptake), receptors (stucture, expression levels, affinity for neurotransmitters), and the mechanisms undelying coupling with the cellular effector system involved in the receptor-ligand interactions [3].

Organophosphates (OPs), produced in the form of the esther, amide or thiol derivatives of phosphoric, phosphonic or phosphinic acid are the greatest contributors to intoxication associated with seizures. Prohibition of the use and disposal

of chemical weapons have reduced, but not nullified the risk of the population exposure to OPs, since OPs are extensively used for production of agrochemicals (pesticides); OPs are components of medicines [4, 5], plasticizers, and many polymeric materials; OPs are still used for terrorist attacks [6]. Pesticides, herbicides and insecticides are key contributors to the structure of acute toxicity in the developing world [4, 6, 7], and constitute over 40% in the structure of occupational disorders in rural areas. The working-age population is mainly affected, and the percentage of cases of the long-term loss of earning capacity and disability is high. Up to million people all over the world suffer from OP poisoning every year, of them about 300,000 die. In 2020, 3 million and even 5 million cases were reported [4, 5]. Approximately 100,000 people every year die from only insecticide poisoning. Self-poisoning with high-dose insecticides often causes death from cardiovascular shock. Only 22% of poisoned patients with an out-of-hospital cardiac arrest survive to admission, and 10% survive to discharge [8].

Based on the mechanism of action, OPs are classified as cholinergic substances. When a nerve impulse is transmitted, acetylcholine, stored in the presynaptic vesicles of neurons, is released into the synaptic cleft to interact with cholinergic receptors of two types: nicotinic (directly interacting with ion channels) and muscarinic (indirectly affecting the ion channel permeability). Acetylcholine is broken down by the enzyme, acetylcholinesterase (AChE), which quickly terminates signal transmission and ensures the AChE molecule release required for the new reaction [2]. OPs are structurally similar to acetylcholine, but are able to form a strong bond with AChE, blocking its functions. OP poisoning occurs in two phases: reversible AChE inhibition, when the bond hydrolysis is still possible (spontaneous or antidote-induced), which results in the enzyme function restoration, and subsequent bond “maturation” or “aging” associated with irreversible inhibition of the enzyme [4, 7]. The heavier radicals (R^-) contained in OPs, the faster is aging [6]. AChE deficiency associated with OP poisoning contributes to excessive accumulation of acetylcholine in synapses and neuromuscular junctions of the peripheral and central nervous systems that eventually results in typical manifestations of toxicity (cholinergic syndrome), seizures, bradycardia, bronchoconstriction or even death [4, 7, 9]. The early stage of a seizure is followed by the mixed cholinergic and noncholinergic stage, which transfoms into the noncholinergic stage associated with the glutamate excitotoxicity and neuronal death [2, 9].

Inflammatory mediators that increase the severity of subsequent seizures and enhance epileptogenesis are released upon exposure to OPs. A significant increase in the levels of pro-inflammatory cytokines (IL1b, TNFα, IL6) and prostaglandin E2 2–24 h after exposure to OP has been reported [10]. Glutamate releasing actively from presynaptic terminals increases intracellular calcium concentration due to inhibition of the KCNQ2/3 potassium channels, promotes other physiological and metabolic effects. Acute OP poisoning may be followed by chronic neuropathological complications resulting from initiation of neurodegenerative processes caused by excitotoxicity and neuroinflammatory responses [9, 11–13]. In addition to cholinergic and glutamatergic effects, insecticides inhibit monoacylglycerol lipase activity, which results in the increased brain levels of 2-arachidonoyl glycerol, being the cannabinoid receptor agonist. Insecticides also inhibit the endocannabinoid-degrading enzyme, fatty acid amide hydrolase (FAAH) [8]. OPs can directly sensitize cholinergic receptors.

Biological activity of carbamates (carbamic acid derivatives), that are constituents of pesticides, herbicides, fungicides, insecticides, and medicines, including drugs for treatment of Alzheimer's disease, myasthenia gravis, glaucoma, is similar to that of OPs [7]. Carbamate poisoning, similar to OP intoxication based on the underlying mechanism, has some features [7, 8]. Carbamate activation requires no metabolic transformations [7]; clinical manifestations of intoxication are observed almost immediately after absorption [14]. The carbamate-AChE bond is weaker than that formed by OPs: the enzyme hydrolyzes spontaneously more rapidly, and there is no aging of the bond [7]. However, carbamates are comparable to OPs in terms of toxicity: cases of respiratory failure 12 h after poisoning have been reported [14]. In addition to anticholinesterase effect, carbamates have a direct cholinomimetic effect on the cholinergic receptors of synapses [3].

Analysis of the social status of individuals poisoned with OPs and carbamates produced unexpected results: 23% of victims were farmers, 27% were daily wagers, 21% were housewives, 11% were salaried employees, and 8% were students [5]. Thus, along with the risk of occupational poisoning due to harmful working conditions or terrorist poisoning, accidental and deliberate self-poisoning is rather widespread, together with toxic effects resulting from drug overdose. This determines the relevance of developing agents for jugulation of seizures.

The review was aimed to analyze published data on the existing and developed methods for prevention and treatment of convulsive disorders asssociated with the cholinergic convulsant intoxication, and to define the most promising areas for further development of medicines and comprehensive approaches to treatment. The RISC and PubMedNet databases were used. The search by keywords (antidote, organophosphorus compounds, anticonvulsant, antiepileptic agent, etc.) among the reports piblished over the last ten years was perfomed.

Standard treatment methods

In case of OP poisoning, it is extremely important to provide timely care to the affected person. Treatment with standard antidotes provides adequate symptom management, reduces seizures, and decreases mortality only in case of prescription at the early stage of poisoning or preventive administration [4].

Comprehensive treatment is commonly used: oxygen therapy, decontamination of skin and mucous membranes, and, if possible, hemodialysis. Atropine administration is started prior to administration of oxygen, since the lack of secretion management hinders oxygenation [7]. Moreover, atropine blocks the activity of the muscarinic cholinergic receptors in the parasympathetic nervous system, thus reducing the smooth muscle contraction activity [2, 4], however, it has no pronounced therapeutic effect in case of the CNS toxicity [11] due to difficulty crossing the blood–brain barrier (BBB). It also has no prominent effect on the cholinergic synapses of the skeletal muscle. Atropine cannot relieve nicotinic effects of OPs (spasms and fasciculation) [9]. In case of severe hypoxia, administration of atropine may be fatal due to blockade of the vagal nerve terminals and ventricular fibrillation [3].

The use of oximes (obidoxime, methoxime, azoxime, etc.) is recommended to reactivate AchE; pralidoxime chloride (2-PAM) is most commonly used [4, 6, 13, 15]. At an early stage of poisoning, oximes effectively reactivate the reversibly inhibited AChE in the nicotinic acetylcholine receptors found in skeletal muscle. However, oximes become almost useless after the bond maturation and irreversible AChE inactivation. Furthermore, oximes have difficulty crossing the BBB [9, 11]. First generation oximes are toxic, their interaction with OPs

may result in accumulation of the toxic OP-oxime complex in the body [3, 6]. Second generation oximes (H oximes, including HI-6, HLo-7, HGG-42) show better biological activity and bioavailability together with lower toxicity, however, many of them are unstable in aqueous solutions [6]. Among second generation oximes, levetiracetam has a good history of clinical use [16]. Carboxim, which has been developed in the USSR, is more stable in aqueous solutions and more easily crosses the BBB. It is much more effective compared to first generation oximes. New AChE reactivators are developed based on amidines and hydrazones. However, none of AChE reactivators are the broad-spectrum antidotes effective against poisoning with OPs of any type. Experimental studies of the oxime combinations, such as 2-PAM/carboxime, carboxime/atropine, are conducted in order to increase the protection index [6]. Reversible AChE inhibitors are also used (pyridostigmine, aminostigmine, physostigmine, galantamine) [3, 4, 9, 12], which have low toxicity, but are effective only in case of preventive administration.

When the effectiveness of first-line antidotes is insufficient, these are supplemented by anticonvulsants, including for prevention of the organic brain desease and post-traumatic epilepsy [4, 15]. Benzodiazepine are used, most often high-dose diazepam or lorazepam. Pharmacological efficacy of benzodiazepines results from interaction with the γ-aminobutyric acid (GABA) receptors and modulation of neurotransmission [17]. These days, the use of midazolam, the new drug that has shown benefits based on the comparative analysis of pharmacokinetics, is recommended [4, 13, 15], new drugs are developed [4, 18]. In case of OP-induced damage, benzodiazepines should be used as early as possible: benzodiazepine administration within 30 min jugulates seizures in the majority of cases [4, 19]; after 40 min their efficacy decreases significantly [4, 15], and after 60 min after the OP exposure benzodiazepines are ineffective, regardless of the total dose and amount that have passed through the BBB [9]. Despite high anticonvulsant activity and broad therapeutic range of benzodiazepines, elimination of convulsive disorder does not protect the victim's life: death may occur even in case of the complete seizure termination [3]. The cases of diazepam and midazolam resistance have been reported, which is considered to be associated with the OP-mediated disorders of binding with the target receptors or the receptor loss (benzodiazepine receptors disappear in more than 50% of neurons within 10–20 min), with the neuronal death and concomitant inflammation [9, 15, 20]. In case of BBB dysfunction, leukocytes and albumin enter the CNS. Albumin activates astrocytes, production of the seizure-provoking cytokine IL1β is increased, and excessive TGFβ is produced, which has a negative effect on the signal transmission in the CNS. The resulting inflammation affects neuromodulators, regulatory transport proteins, thus promoting seizures that cannot be managed using benzodiazepines [21].

Single administration of atropine, oximes (obidoxime, 2-PAM, HI-6) and drugs affecting GABA (diazepam, avizafone) is used for prevention or emergency therapy of the OP intoxication. In addition, pyridostigmine is sometimes used as a component of preventive antidotes [22]. Antidote auto-injectors have been designed: for example, the dual-chamber MARK-1 and DuoDote auto-injectors contain atropine (2.1 mg/0.7 mL) and 2-PAM (600 mg/2 mL), IM auto-injector contains 2 mg of atropine and 200 mg of obidoxime chloride; triple-chamber auto-injectors are available (atropine, oxime and diazepam) [4, 13, 23]. The use of the atropine sulfate and obidoxime mixture is acceptable [23], the release of auto-injectors containing midazolam instead of diazepam has been announced [13]. However, even the combination and preventive regimens for administration of antidotes that reduce immediate fatality do not necessarily suppress seizure activity, unless high-dose atropine is administered very quickly [22]. Auto-injectors have some limitations: for example, adult doses of atropine could be administered to children, however, the adult dose of pralidoxime is too much for a child [23].

Currently, there are no unified official guidelines for the cases of antidotes having no effect or insufficient efficacy of antidotes. In case of failure to respond to prehospital treatment with benzodiazepines, the status epilepticus clinical protocols are most often used for treatment [19]. Antiepileptic drugs, such as levetiracetam, phenobarbital, phenytoin, fosphenytoin and valproates, are used in clinical practice. It is known that phenytoin (fosphenytoin) stabilizes the inactivated state of the neuronal voltage-gated sodium channels, but has such side effects as arrhythmogenicity. Phenobarbital (the long-acting barbiturate) affects GABA and AMPA ionotropic glutamate receptors, inhibits the release of neurotransmitters, but is capable of providing excessive inhibition of the CNS functions, including respiratory function. Levetiracetam suppresses neurotransmitter release by means of binding to the synaptic vesicle protein 2A (SV2A); the possibility of the glutamate receptor (mainly AMPA) modulation is assumed. Lacosamide enhances slow inactivation in voltage-gated sodium channels, however, the drug is capable of causing conduction disorders [21]. Pregabalin and tiagabine block calcium channels [24]. There is no clear understanding of these drugs comparative efficacy. According to a number of clinical trials, these drugs have virtually the same efficacy of about 50% [4, 19].

In the experiment that involved rats exposed to OPs, administration of high-dose midazolam and lorazepam (four times the therapeutic dose) suppressed seizures only in 10 and 6% of cases. In another experiment, phenobarbital first showed higher efficacy against persistent or recurrent convulsive disorder compared to valproic acid (35% vs. 56%), however, the drug ensured long lasting relief only in 19% of cases [19]. When testing pregabalin, levetiracetam and valproic acid as second-line drugs (in cases of refractory status epilepticus), the rats' behavioral response was delayed by 30–60 min (compared to diazepam and ketamine). Seizures stopped only when the levels of acetylcholine decreased by more than 50%. Pregabalin and valproic acid jugulated seizures, however, animals did not regain awareness. Levetiracetam stopped seizures, rats regained awareness, but experienced tremor. Furthermore, levetiracetam was more long-acting than pregabalin and valproic acid. The mechanism of action of these drugs is unclear. It is assumed that the drugs are capable of reducing the release of acetylcholine and glutamate [16].

When antiepileptic drugs are unable to terminate seizure activity, general anesthetics, such as ketamine, pentobarbital, or propofol, are administered within 24–48 h [4, 19]. The efficiency of ketamine (inhibits ion channels of the NMDA-type glutamate receptors, interacts with opioid, monoaminergic, muscarinic and nicotinic receptors, affects L-type calcium and sodium channels, and provides cytokine modulation, including IL1, IL6, IL8, IL10, THFα) supplementation has been confirmed after using first-line antidotes and benzodiazepines. The experiment showed that the use of ketamine and propofol made it possible to jugulate seizures in benzodiazepine-resistant rats [19, 21].

Valproic (2-propyl-pentanoic) acid [16] and its derivatives (valproates) deserve special attention. Their mechanism of action involves presynaptic and postsynaptic modulation of GABAergic transmission (valproates increase synthesis, release and therefore the inhibiting activity of GABA,

potentiate GABAergic transmission, show direct effects on GABA receptors due to reduced activity of β-hydroxybutyric acid possessing excitatory effects) [25–27]. Valproic acid directly affects cell membranes, thus reducing paroxysmal discharges from neurons, provides modulation of sodium, calcium and potassium ion channels. Furthermore, valproic acid modulates glutamate activity. Valproates are capable of increasing the hippocampal extracellular levels of serotonin and dopamine. Suggestions have been also made that valproic acid has epigenetic effects and can modulate neurogenesis. Neuroprotective properties of valproates have been reported. The efficiency of valproic acid during generalized seizures in patients with epilepsy has been shown [25, 26]. However, the effective dose of valproic acid is significantly higher compared to that of benzodiazepines. During the experiments aimed at assessing the valproic acid efficiency, only high doses administered (≥150 mg/kg) to rats by intraperitoneal injection suppressed generalized seizures [28]. In case of OP-induced status epilepticus that was resistant to benzodiazepines, intravenous administration of the significantly lower dose valproic acid derivatives to experimental rats was effective [19].

Alternative treatment methods

Unwanted side effects of the existing drugs and progressive decrease of efficiency within 30 min after exposure to OPs necessitate the search for new agents. Since OPs are fast-acting agents, emergency care is often delayed, that is why versatile and fast-acting anticonvulsants are required that could be delivered via the most easy administration routes [25]. Combined treatment regimens, new dosage forms, development of original molecules and modification of existing molecules are among the approaches.

Combination therapy

Early polytherapy (for example, combining benzodiazepines with second-line drugs or NMDA receptor antagonists) may improve seizure control associated with the slightly enhanced side effects, however, there are just a few completed clinical trials [21]. Polytherapy is also capable of reducing the number of side effects due to reduction in drug dosage and drug synergism [29]. Particularly, the combination of midazolam, ketamine and valproate significantly reduced seizure severity and duration in experimental rats compared to monotherapy with higher doses [20]. The combined use of valproate and diazepam contributes to activation of neurogenesis [10]; there have been also attempts to combine valproates with carnitine [21]. The efficiency of reducing seizure activity in rats by using the combination of midazolam and dexmedetomidine (α2 adrenergic receptor antagonist) was higher compared to that of midazolam monotherapy, including when administered 60 min after initiation of seizures [29]. Prescription of sodium valproate to experimental rats after using midazolam reduced seizure frequency and duration, and supplementation of losartan (anesthetic agent) reduced the amount of brain damage [30]. In experimental rats, the combination of 3 mg/kg midazolam, 30 mg/kg ketamine and 90 mg/kg valproate showed the significant decrease in the number and duration of seizures compared to monotherapy with high-dose midazolam. The effects persisted 40 min after exposure to OPs, when midazolam became ineffective [20].

The efficiency of procyclidine supplementation was studied in experimental rats poisoned with OPs by intraperitoneal administration of triple (procyclidine 6 mg/kg, diazepam 10 mg/kg and pentobarbital 30 mg/kg) and dual (procyclidine 10 mg/kg and propofol 50 mg/kg) combinations. In the first case seizures stopped within 30–40 min after poisoning, however, mortality was 43%, and survivors had neurological disorders. In the second case seizures stopped, but 17% of rats died in 24 h. When using the combination of levetiracetam (50 mg/kg) with procyclidine (10 mg/kg) or caramiphen (10 mg/kg), seizures stopped in the majority of rats, however, mecamylamine supplementation was sometimes required. Procyclidine had a better effect than caramiphen, and preventive administration (20 min before OP intoxication) was far more effective than administration after poisoning. The combination of atropine and ketamine showed anticonvulsive effect when administered 30–120 min after poisoning [22].

In experimental animals, the effects of diazepam (10 mg/kg) were enhanced due to flupirtine supplementation (50 mg/kg) [12]. The use of memantine (neuroprotective agent) in addition to benzodiazepines showed a very narrow therapeutic index [4].

Novel non-invasive dosage forms

Increasing bioavailability and simplifying administration of the registered substances by means of developing non-invasive dosage forms (nasal dosage forms, aerosols, buccal solutions) are considered promising approches. When using intranasal drug administration, adequate circulation in the nasal mucosa can provide pharmacokinetic benefits: the drug travels directly to the CNS and systemic circulation. Delayed absorption requires dosage increase, thus increasing the risk of overdose. However, benzodiazepine-containing sprays are recommended for pediatric use as sedatives. According to meta-analysis of the experience of using nasal dosage forms in children as sedatives, midazolam is more effective than diazepam. Bioavailability of lorazepam is 80%, and the time of peak concentration is 30 min, which is almost two times faster compared to that observed after intramuscular injection; there are no significant differences in the drug effect timing and duration when comparing with the intravenous infusion dosage form. When jugulating seizures, no differences in efficiency between the nasal dosage form of midazolam and intravenous infusion or rectal dosage form of diazepam were revealed. On average, seizures terminated within 3–4 min after the midazolam administration; maximum plasma concentration was achieved in 25 min, and clinically relevant concentration was reached within 10 min [31]. The majority of nasal dosage forms of benzodiazepines and buccal form of midazolam were registered as sedatives and hypnotics only. However, the VALTOCO diazepam-containing nasal spray was registered in the USA, which was indicated to be used as anticonvulsant.

Atropine-containing nasal sprays that have been tested on rats demonstrate efficiency comparable with that of parenteral drug administration, and rapid systemic absorption. The limited clinical trial of the atropine–chitosan nasal drops was carried out, during which peak concentration was achieved within 30 min. The nano-atropine dry powder inhaler turned out to be ineffective: only a small peak in the blood was observed in volunteers after 15 min, the second peak observed after 60 min was associated with the intestinal substance absorption. During the experiment involving volunteers, six atropine poweder inhalations (in a dose of 0.4 mg per inhalation) were required to reach blood levels equivalent to single intramuscular injection (2 mg), which was considered not a promising avenue [4].

Atropine fast-disintegrating sublingual tablets were developed, comparable with the solution in terms of permeation rate.

However, bioequivalence of the sublingually administered atropine has not been defined [4].

Developing new valproic acid derivatives

The use of valproic acid as antidote is hardly acceptable due to high dose required for effective seizure termination. However, amide derivatives (for example, new derivative of valproic acid and 1,3,4-thiadiazole (valprazolamide)) demonstrate higher anticonvulsant activity and lower neurotoxicity in experimental settings. After intraperitoneal injection of valprazolamide to mice, DL_{50} and TD_{50} were 924.8 (756.9–1063.7) mg/kg and 456.7 (325.4–603.6) mg/kg [32].

Valnoctamide is more effective and has fewer side effects than sodium valproate [21]. It was tested on rats of various ages (21, 28 and 70 days), ED_{50} was 34–165 mg/kg. Only 9% of animals experienced sporadic short seizure episodes 2–3 h after the treatment initiation. The efficiency of valnoctamide intraperitoneal injection was shown in rats and guinea pigs (ED_{50} 62–80 mg/kg), including in case of delayed administration and the use in combination with diazepam in a dose of 2.2 mg/kg (monotherapy with the same dose of diazepam was ineffective) [28].

Sec-butyl-propyl-acetamide (SPD) is a more powerful homologue of valnoctamide, which has been shown in experimental rats [21]. ED_{50} of both SPD and valnoctamide is about 65 mg/kg, while ED_{50} of valproic acid is 366 mg/kg. The drug was tested on mice, rats and guinea pigs. Diazepam, valproic acid, valnoctamide were ineffective in the rat model of convulsive disorder when administered by intraperitoneal injection 30 min after exposure to OPs, and SPD suspension administered in a dose of 84 mg/kg suppressed seizures [33].

Anticonvulsant efficacy of the intraperitoneal injection of N-substituted valpromides was shown in mice [26]. The extended-release dosage form of valproic acid (metabolically activated prodrug) selectively bound to L-amino acid transporter 1 (LAT1) in experimental animals, thus contrubuting to more effective penetration into the CNS and slow release of the active ingredient [34]. Amide detivatives of valproic acid (RDG1-RDG8) are more active than sodium valproate in experimental settings [27].

Other treatment methods

Among the developed antiepileptic drugs, brivaracetam inhibits neurotransmitter release, more effectively binds to SV2A protein, is more fast-acting and has fewer side effects than levetiracetam during the preclinical testing. Preclinical studies have shown high efficiency of perampanel (selective antagonist of AMPA glutamate receptor) [21]. New antagonist of AMPA and KAR ionotropic glutamate receptors is developed [29].

It is suggested to use neurosteroids in cases OP exposure took place more than 30 min ago [9]. It is believed that neurosteroids act as positive allosteric modulators (nanomolar concentrations) and direct activators (micromolar concentrations) of all isoforms of GABA receptors (synaptic and extrasynaptic receptors). The use of endogenic neurosteroids (allopregnanolone) is not economically feasible, however, synthetic neurosteroids (alfaxalone, ganaxolone) are more active in case of oral administration and have a 4–6 times longer half-life. The efficiency of ganaxolone administered by intramuscular injection was shown in experimental rats: monotherapy prevented neuronal death, reduced the loss of inhibitory interneurons; the combination with midazolam increased the efficiency. Ganaxolone analogues SGE-516 increased GABA-evoked currents [9, 21].

The efficiency of diphenhydramine in OP poisoning was similar to that of atropine. Antidote activity of chlorpheniramine and promethazine was revealed during the experiment. It was suggested to use antihistamines that possess central antimuscarinic effects. Monotherapy with glycopyrrolate, acting through peripheral receptors, or combining glycopyrrolate with atropine makes it possible to reduce mortality. However, there are no alterations in the toxic effects severity [4, 7].

Expriments on affecting cytokine profile by administration of IL1PA in addition to diazepam were conducted. Cannabinoids enhanced the effects of valproates. However, direct anticonvulsant effects had not been proven [21].

Histone deacetylase inhibitor supplementation was studied, aimed at affecting the expression of certain genes, including increasing the expression of the heat shock proteins and brain-derived neurotrophic factor to provide neuroprotection. It was suggested to use the heat shock proteins (for example, HSP-70) preventing protein denaturation and unwanted polypeptide aggregation; certain anti-inflammatory drugs were tested [10]. Among other agents tested in order to improve seizure control there were 2-deoxyglucose, huperzine A, imepitoin, minocycline, pitolisant, glibenclamide, P2X7 receptor antagonist, bumetanide, sodium bicarbonate, infusion of calcium channel blockers, and drugs with unknown mechanisms underlying anticonvulsant effects, such as clonidine [3, 4, 8, 21]. However, all these methods are not sufficient.

CONCLUSION

Thus, standard antidote therapy of OP poisoning is effective only when started very early. There are no unified guidelines on care provision to victims with convulsive disorders in case of no response to standard therapy. There are no unified recommendations on jugulating recurrent seizures occurring during the long distance transportation of the victim. None of the registered drugs provide comprehensive protection against neurotoxicants. This dictates the need for further research aimed at developing new agents for treatment of convulsive disorders associated with the cholinergic convulsant intoxication. Developing new medications based on the combinations of registered substances in order to provide cumulative effects, creating new dosage forms to enchance bioavailability of drugs, and developing novel original substances by means of modifying chemical synthesis of compounds that possess anticonvulsant effects are considered the most promising.

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