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Review

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Possibilities of Application of Ethylmethylhydroxypyridine Succinate in the Treatment of Acute Poisoning

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ABSTRACT In recent years, there has been a trend of increasing poisoning by various substances among the general population throughout the world. For the complex treatment of these patients, modern toxicology uses a combination of drug and non-drug methods that have universal mechanisms aimed at restoring body functions. Currently, antihypoxants and antioxidants are actively used in medical practice in all situations where there are oxygen deficiency and certain manifestations of the ischemic cascade in order to interrupt the mechanisms of hypoxia progression as early as possible. The widespread use of ethylmethylhydroxypyridine succinate (Mexidol®, NPK PHARMASOFT LLC, Russia) both in the form of monotherapy and in combination with various methods of non-pharmacological intervention (mesodiencephalic modulation, hyperbaric oxygenation, etc.) is becoming quite interesting for practical use in toxicological practice for the treatment and rehabilitation of conditions developing after acute poisoning by neurotropic substances (psychodysleptics, drugs, ethanol and its substitutes).

Keywords: ethylmethylhydroxypyridine succinate, antihypoxants, antioxidant properties/antioxidants, lipid peroxidation, neurotoxicity, acute poisoning, toxic-hypoxic encephalopathy

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CNS – central nervous system
HBOT – hyperbaric oxygen therapy
MDM – mesodiencephalic modulation

INTRODUCTION

An urgent problem in toxicology today is the rationale for the use of modern medicinal and non-medicinal methods that have universal mechanisms aimed at restoring body functions in the complex treatment of patients with acute poisoning. The incidence of acute poisoning in the Russian Federation, according to data on emergency medical care, ranges from 2.7 to 5 cases per thousand population (average - 3.9). More than a quarter of a million people are hospitalized with acute poisoning every year. Of the fatal poisonings recorded by forensic medical authorities, more than 80% occur at the prehospital stage. The structure of acute poisonings, according to data from various toxicological centers, varies widely: from 40 to 74% of cases - by medications, mainly of psychotropic

action; from 6 to 49% - by ethyl alcohol and its substitutes; from 12 to 20% - by narcotic drugs [1, 2].

In 2022, the Rospotrebnadzor Central Office registered 2,748 cases of acute poisoning of chemical etiology at home [3]. In addition, often people taking medications for one or another medical condition accidentally or intentionally increase the dose, which causes an overdose of the drug with the development of toxic effects. According to the American organization that deals with the effects of toxicants on the human body (National Poison Data System), the most common cause of poisoning among people over 20 years of age is the use of: analgesics (11.9%), sedatives and antipsychotics (10.4%), antidepressants (6.7%), cardiovascular drugs (6.1%), cleaning products (5.7%), alcohol (4 .6%), anticonvulsants (3.7%), pesticides (3.5%), and antihistamines (3.1%) [4].

Poisoning in adults can also develop as a result of taking narcotic drugs. The UN report (2018) noted that today about 150 million people use marijuana, 30 million use amphetamine derivatives, 15 million use opiates, 13 million use cocaine and 10 million use heroin. Due to addiction, drug addicts increase the dose of drugs they take, which often leads to poisoning [5].

According to the US National Institute on Drug Abuse (2021), 88,000 Americans died from drug overdoses of various types in 2020, an increase of 27% from 2019. And in the previous few years, the death toll only grew: from 21,000 people in 2010, to 46,600 in 2017, and 75,000 in 2019. Most die from fentanyl, followed by heroin, oxycodone and cocaine [6–8]. As you can see, the problem is widespread throughout the world, and there is a trend towards an increase in the number of deaths, which dictates the need for modern and timely provision of the right type of treatment.

Today, poisoning by such a group of drugs as psychotropic drugs (antipsychotic, neuroleptic and antidepressant drugs) used in psychiatric practice is not uncommon. Poisoning by them ranks third (9.6%) in the structure of acute poisoning after alcohol (34.7%), and drugs from the group of sedatives, hypnotics and anticonvulsants (9.8%) [9].

Antipsychotics (neuroleptics) are a large group of drugs with psychotropic properties that have an inhibitory effect on the functions of the central nervous system (CNS), can relieve mental disorders, and may cause neurotoxicity. Antipsychotics are toxic and may cause poisoning. The cause of poisoning is often the intentional (suicidal) use of these drugs, but poisoning also occurs if these drugs are used in large doses during a deterioration in a person's psychological/mental well-being and iatrogenic overdose [10–12]. It should be noted that, according to the WHO, more than once a minute people all over the world deliberately commit suicide, annually this figure is more than 700,000 people, and one of the most common methods is the use of various medications [13]. Also, according to some sources, suicide is the second most common cause of death among people aged 18-29 years. As a rule, suicide attempts are a manifestation of depression, and therefore these patients require hospitalization in a psychiatric hospital, where they will be treated under appropriate supervision [14, 15].

One of the leading pathogenetic components of poisoning by psychotropic drugs is neurotoxicity, that is, the ability of chemical substances, acting on the body, to cause disruption of the structure and (or) function of the nervous system [16–18].

In the works of E.A. Luzhnikov, G.A. Livanov and Kalmanson M.L. "toxic-hypoxic encephalopathy" is described, which is a certain brain damage that occurs when exposed to toxic substances, resulting in the development of hypoxia that disrupts the structure and functions of various parts of the central nervous system [19–24].

Poisoning by some antidepressants manifests itself, in addition to the syndrome of overall brain dysfunction (encephalopathy), also as a soporous state, superficial and deep coma, peripheral and central cholinolytic (anticholinergic) syndrome; and when combined with amphetamines, it is also characterized by toxic damage to the heart, which is the main cause of death in the toxicogenic stage of poisoning [25–28].

Severe poisoning is characterized by a deep disorder of consciousness (coma). In 24.6%, a coma leads to a mixed type of external respiration disorder (a combination of mechanical and central components). Cholinergic syndrome develops only after recovery from coma and initially proceeds according to the central type, turning into the peripheral cholinergic syndrome. In addition, convulsive syndrome may occur, which is observed in 6% of patients. A characteristic manifestation is the presence of a primary cardiotoxic effect with QRS complex prolongation to at least 0.11–0.12 s, up to complete transverse block, accompanied by bradycardia, which acts as an unfavorable prognostic sign [2].

Poisoning in adults nowadays, with timely and correct provision of basic medical care, ends favorably [9]. In addition to fundamental approaches to normalize impaired breathing and maintain adequate hemodynamics, specialized therapy is used: specific, detoxification and symptomatic one. In recent years, modern agents with membrane stabilizing, antioxidant and antihypoxic effects have found increasing use for the treatment and rehabilitation of conditions developing after poisoning [29–31].

Aim: To study literature data on the effectiveness of the use of ethylmethylhydroxypyridine succinate in the complex treatment of patients with acute poisoning by psychoactive substances.

MATERIAL AND METHODS

An analysis of literature was carried out in the search engines of PubMed, Google Scholar, Cochrane Library, Scince Direct, eLIBRARY in English and Russian using keywords: “ethylmethylhydroxy-pyridine succinate”, “antihypoxants”, “antioxidant properties/antioxidants”, “lipid peroxidation”, “neurotoxicity”, “acute poisoning”, “toxicohypoxic encephalopathy”, “Mexidol”, “intoxication”. More than 100 sources were reviewed for the period from 1997 to 2023. The review included research that examined the use of antihypoxants and antioxidants in toxicology.

RESULTS AND DISCUSSION

In practice, a significant number of drugs have an antihypoxic effect, but there are few sources containing information on the effectiveness of such drugs in acute poisoning by antipsychotic drugs. Due to the presence of antihypoxic and antioxidant properties, the use of drugs with an antihypoxic effect makes it possible to disrupt the chain of pathological events in acute severe poisoning by substances of neurotropic action associated with deep depression and disruption of the metabolism of the central nervous system, the development of hypoxia, leading to worsening disorders of tissue metabolism, decreased activity of the antiradical defense system, and activation of lipid peroxidation [32–38].

Thus, it was shown that one of the effective ways to treat toxic-hypoxic injuries may be a set of pharmacological correction measures aimed at restoring cellular metabolism in order to prevent, first of all, cerebral disorders that play a causal role in the development of encephalopathy. In critical conditions of various etiologies, antihypoxants are used as a pathogenetic agent in a complex of therapeutic measures and in acute poisoning [24].

The use of the Mexidol®, which has antioxidant, antihypoxic and membrane-stabilizing effects, is promising. Among synthetic and natural antioxidants, it occupies a special place, has a multimodal mechanism of action and, importantly, is a domestic development. The mobile hydrogen atom of the hydroxyl group can interact with peroxy and alkoxy radicals formed during the processes of lipid peroxidation and inactivate them. The presence of succinate in its structure is of fundamental importance for the manifestation of the pharmacological effects of the drug, and, since this fragment of the molecule is functionally significant for many processes occurring in the body, succinate is a substrate for increasing energy metabolism in the cell. Important components of the pharmacodynamics of ethylmethylhydroxypyridine succinate are its antioxidant, membranotropic action, ability to modulate the functioning of

receptors and membrane-bound enzymes, as well as to restore neurotransmitter balance, since the functioning of neuronal membranes as an integral structure depends on the coordinated work of chemical and physical processes during the transmission of information [39, 40]. The mechanism of its work is that it inhibits the processes of free radical oxidation of lipids, affects the physicochemical properties of the membrane, reduces the viscosity of the lipid layer, modulates the activity of membrane-bound enzymes, activates the energy-synthesizing functions of mitochondria, and improves energy metabolism in the cell, which enhances the cell's protection and increases its viability [40, 41].

In 2017, Russian scientists I.Yu. Berezina et al. scientifically substantiated the inclusion of ethylmethylhydroxypyridine succinate in the complex rehabilitation of both acute and delayed manifestations and complications that develop from poisoning by neurotoxicants. Psychopharmacological agents, drugs and ethanol acted as neurotoxicants. All the examined patients had toxic-hypoxic encephalopathy. In addition, several treatment options were compared: medication alone – intravenous drip administration of a 5% Mexidol® solution at a dose of 4 ml/day for 5–10 days along with basic treatment for poisoning; a combination of pharmacological and non-pharmacological interventions – Mexidol® and mesodiencephalic modulation (MDM) along with basic therapy; and non-pharmacological approach alone – MDM and hyperbaric oxygenation (HBO) along with basic therapy. The comparison group consisted of patients who received only basic therapy including enhanced natural detoxification (gastric lavage, intestinal cleansing, forced diuresis), restoration of effective hemocirculation, vitamin therapy, nootropic and symptomatic therapy, and, if indicated, sedatives. To control and evaluate the results obtained, the researchers used electroencephalography, auditory event-related potentials, a set of psychological tests: the Mini Mental State Examination (MMSE), the Frontal Assessment Battery (FAB) – a brief battery of neuropsychological tasks designed to assess frontal lobe function, Münsterberg tests, verbal reasoning tests, the number connection tests A; the clock-drawing test and Schulte tables. Based on electroencephalographic data, the authors revealed that disturbances in the spontaneous electrical activity of the brain of varying degrees of severity were observed in all the patients with encephalopathy due to acute poisoning by neurotoxicants at the rehabilitation stage; moreover, in 68% of cases they were moderate, and in 25% - pronounced in nature, with dominating signs of disruption of the functional activity of diencephalic and mesodiencephalic level formations. It is important that electroencephalographic positive dynamics were noted only after treatment using Mexidol® or a combination of Mexidol® with HBO and MDM. During an initial neuropsychological examination before treatment, in 97.5% of those examined, the authors identified impairments in cognitive functioning of varying severity (from mild cognitive impairment to severe impairment) due to acute poisoning by various neurotoxicants [29]. It should be noted that the work of I.Yu. Berezina et al. (2017) proved the presence of cognitive dysfunctions and disorders previously described by other researchers [42, 43], which confirms the pathogenetic significance of neurotoxicity in poisoning by psychotropic substances. In the examined patients, changes in cognitive functions are manifested by impairment of auditory verbal memory, directed attention, dynamic praxis and spatial gnosis, which may indicate fronto-parietal and temporal brain dysfunction [29].

Thus, the authors conclude that during treatment with Mexidol®, there was an improvement in indicators that reflect both the functional state of the brain as a whole and the state of cognitive functions. Moreover, the best results were obtained when Mexidol® was used in combination with non-pharmacological interventions; the maximum positive effect was observed when Mexidol® was combined with MDM (70% of cases), as well as with

HBO and MDM (80% of cases) for the vast majority of psychophysiological indicators, reflecting the processes of directed attention, dynamic praxis, spatial gnosis, speed of sensorimotor reactions, as well as auditory verbal memory and working memory for events [29].

In modern literature, there are works on the use of Mexidol®, a Russian-made antioxidant and antihypoxant, in case of poisoning by psychodysleptics, natural and synthetic substances, under the influence of which the processes of perception, memory, learning, and thinking are disrupted, as a result, conditions can be formed that manifest themselves as inadequate behavioral reactions [30]. The danger of psychodysleptics for young people lies in the ease of their use (inhalation and oral administration are possible), the difficulty of predicting the effect of their use and calculating the dose taken [30]. A.A. Stakanov and A.V. Chuprikov (2019) analyzed the condition of intensive care patients with signs of acute poisoning by psychodysleptics and a clinical picture of toxicohypoxic encephalopathy in the form of deep depression of consciousness - stupor, who in addition to basic therapy (detoxification, vitamin therapy) received Mexidol® at a dose of 500 mg (10 ml) per day intravenously for 4 days [30].

As a result of their research, it was proven that in patients with psychodysleptic poisoning and a clinical picture of deep depression of consciousness, this drug, when added to basic therapy, contributed to a faster recovery of the patients from the state of toxicohypoxic encephalopathy (consciousness was assessed as clear after 24–36 hours), with less cognitive deficit; and the patients showed greater motivation, were less aggressive and less exhausted when performing mental activity [30]. All this, according to the authors, allows recommending the use of Mexidol® in toxicology and intensive care departments for the treatment of patients with poisoning by psychodysleptics.

Another possible positive point of the pathogenetic application of ethylmethylhydroxy-pyridine succinate may be patients with acute intoxication by synthetic drugs and the presence of withdrawal states as a result of their use, which is the focus of the work of the staff of the Department of Psychiatry, Narcology, Psychotherapy and Clinical Psychology of the V.I. Razumovsky Saratov State Medical University [31]. It is worth noting the increase in drug use in all countries in general, especially among young people. Moreover, in the modern world, cases of acute intoxication by so-called “designer” drugs, which are psychoactive substances (surfactants) (“salts”, “spices”, “flowers”) and easily combined with each other or with natural narcotic substances, yielding new “effects” that are still poorly studied clinically, and, therefore, require further study and, especially, the selection of methods for managing intoxicated patients.

In her research, A.Yu. Mishukova (2019) used Mexidol® together with standard therapy for acute intoxication by surfactants and drug withdrawal parenterally at 100–400 mg 2 times a day (200–800 mg/day) for 15 days [31]. Before treatment, all the patients had a high level of drug addiction, manifested by drug-themed fantasies and dreams, sleep disturbances, depressive states of varying depths, and a clinically significant anxiety. As a result of treatment with the inclusion of Mexidol® for acute intoxication by psychoactive substances and withdrawal syndrome, those examined showed positive dynamics of their condition; they also lost cravings for drugs (a decrease in obsessive thoughts on drugs from 86% to 13%, dreams on drugs from 80% to 20%), and rates of anxiety and depression decreased [31]. The author considers it necessary to continue further study of the use of Mexidol® in the complex therapy of patients with intoxication by synthetic surfactants.

It should be noted, that according to V.G. Kosenko et al. (2006), this drug exhibits an antiparkinsonian effect in neuroleptic syndrome during acute intoxication by antipsychotics, which manifests itself already from the day 2-3 of therapy and consists in reducing the severity of hyperkinetic movement disorders, their complete reduction by the 7th–14th day of treatment, leveling of weakness,

lethargy, stiffness, hypokinesia and hypomimia, orthostatic phenomena, dizziness and blood pressure fluctuations. The effect of Mexidol® persists for 3–5 days after its discontinuation [44, 45].

When toxic substances enter the gastrointestinal tract, most of them are metabolized in the liver. In case of intoxication and overdose of antipsychotic drugs, the leading pathomorphological syndrome is cytolysis caused by increased permeability and destruction of the membranes of hepatocytes and their organelles, which manifests itself in the cellular and molecular links of the pathogenesis of toxic liver damage. To correct cytolytic syndrome, it is currently considered advisable to include in modern pharmacotherapy agents with a membrane-stabilizing effect, for example, synthetic antioxidants. The use of Mexidol® in the treatment of toxic hepatitis leads to faster correction of cytolysis. Its administration potentiates the effect of standard therapy, which is manifested in an earlier onset of reduction of the clinical picture and more rapid regression of cytolysis [46]. Thus, A.V. Chuprikov (2019) studied the effect of ethylmethylhydroxypyridine succinate on the clinical symptoms of acute poisoning by alcohol-containing liquids with predominant liver injury complicated by acute toxic hepatitis. In this case, to the standard regimen, consisting of ademetionine 1200 mg combined with prednisolone 40 mg and detoxification therapy, Mexidol® was added at a dose of 500 mg (10 ml) intravenously for 14 days, followed by oral administration of the drug, 2 tablets (250 mg) 3 times a day for 3 months [46]. The author notes that the general condition of the patients significantly improved after only a week of treatment: the symptoms of asthenia were leveled, appetite improved, nausea and skin itching disappeared; while in the comparison group an improvement in general condition was observed only after two weeks of inpatient treatment. At the same time, in the Mexidol® group after a week of hospital treatment, positive dynamics of cytolysis indicators were noted (correction by approximately 50%), but in the group without Mexidol® therapy this indicator was not so significant (decrease in cytolysis by only 20%) [46]. According to a number of authors, in the treatment regimen for cytolytic syndrome, the use of the parenteral form of this drug is extremely relevant [47, 48].

The work by A.V. Alenkhovich back in 2009 showed that the use of Mexidol® in the complex treatment for pneumonia complicating the course of acute poisoning by neurotoxic drugs, and when applied topically in patients with necrotizing ulcerative burns of the stomach, enabled to obtain positive clinical results. It was possible to achieve improved microcirculation and stabilization of cell membranes, which was confirmed by laboratory tests [49].

Thus, the domestic ethylmethylhydroxypyridine succinate (Mexidol®) has proven pathogenetic substantiated points of application in toxicology [29–49].

CONCLUSION

Currently, antihypoxants and antioxidants are actively used in medical practice in all situations where oxygen deficiency and certain manifestations of the ischemic cascade are present, in order to interrupt the mechanisms of hypoxia progression as early as possible. In this regard, Mexidol® becomes quite interesting for practical use in toxicological practice for acute poisoning by various psychoactive substances, and the studies conducted allow us to actively recommend it for inclusion in combination therapy, where it has shown its effectiveness and safety. The authors of the research cited in the article consider it necessary to continue studying the clinical and pathogenetic effects of ethylmethylhydroxypyridine succinate (Mexidol®) in acute poisoning in general on a wider sample of patients.

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