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PHARMACOTHERAPY OF CEREBRAL EDEMA

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Abstract

Edema and swelling of the brain (OCS) is one of the main causes of mortality in traumatic brain injury [1], neuroinfections, and liver failure [2, 14]. Also, cerebral edema is observed with tumors of the central nervous system, cerebral circulatory disorders, intoxication, and complicates some mental and infectious diseases, renal failure, and hypoxic conditions [3]. For example, mortality in severe traumatic brain injury (TBI) reaches 70% [4], while, according to various authors, swelling and dislocation of the brain are the main cause of death (about 40% of cases) [5,6]. Therefore, ONGM remains one of the main problems of intensive care.

Keywords: To analyze pharmacotherapeutic approaches to the correction of cerebral edema based on the results of our research and analysis of the literature.

Introduction

Edema and swelling of the brain (OCS) is one of the main causes of mortality in traumatic brain injury [1], neuroinfections, and liver failure [2, 14]. Also, cerebral edema is observed with tumors of the central nervous system, cerebral circulatory disorders, intoxication, and complicates some mental and infectious diseases, renal failure, and hypoxic conditions [3]. For example, mortality in severe traumatic brain injury (TBI) reaches 70% [4], while, according to various authors, swelling and dislocation of the brain are the main cause of death (about 40% of cases) [5,6]. Therefore, ONGM remains one of the main problems of intensive care.

Despite many years of studying and introducing into clinical practice a wide arsenal of decongestants with different mechanisms of action, prevention and pharmacotherapy of ONGM is not always successful [7,8]. In the pharmacotherapy of ONGM, the empirical-symptomatic approach with a focus on dehydration still often prevails, and this approach often leads to the development of serious complications .

Materials and Methods

the material was based on data from patients in the Department of Neurosurgery of the Multidisciplinary Clinic of Samarkand State Medical University with edema and swelling of the

brain due to traumatic brain injury (TBI). Traditionally, diuretics and hypertonic solutions are used in the treatment of ONGM. The osmotic diuretic mannitol (mannitol) and hypertonic sodium chloride solution are still used as first-line drugs for the treatment of acute cerebral edema. These drugs promote the mobilization of water from the brain tissue into the vascular bed. Mannitol has the most pronounced dehydrating property of all osmodiuretics and is used most often [9,10]. .25 g/kg to 2 g/kg, with recent studies showing that high doses (1.4 g/kg) are more effective than standard doses (0.7 g/kg) in the case of acute cerebral edema due to TBI. Bolus administration is recommended instead of continuous infusion [11,12]. To prevent acute kidney injury, mannitol is recommended to be administered at plasma osmolarity no higher than 320 mOsm/L [13,14]. Mannitol can cause a "recoil" phenomenon, penetrate the BBB and cause a reverse flow of fluid from the vessels into the brain. This can be prevented by subsequent administration of saluretic or repeated administration of mannitol. In case of severe cardiac, renal, or liver failure, the use of mannitol is not recommended or is sharply limited [11]. Of the osmotic diuretics, glycerin and urea can also be used (intravenously and orally). Urea acts quickly and for a long time (up to 10 hours). However, it causes an even more pronounced "recoil" phenomenon and stress on the heart, liver and kidneys [12]. The attitude towards the prescription of hypertonic sodium chloride solution for acute urinary tract infections is not clear. Some authors consider its use inappropriate due to the lack of evidence and the negative impact on a number of cellular systems (immune system, microcirculation). However, recent studies have revealed its greatest effectiveness in comparison with mannitol in reducing intracranial pressure in severe TBI [13]. In addition, hypertonic sodium chloride solution improves cerebral oxygenation, which allows its use in TBI [14].

Saluretics (primarily furosemide) are used for ONGM if osmotic diuretics are contraindicated, or to enhance their effect. It has been proven that furosemide reduces the volume of intracranial fluid in proportion to the reduced volume of fluid in the body, but this decrease in intracranial pressure is short-lived and mild. An important place in the treatment of ONGM is given to corticosteroids. By stabilizing the membranes of brain cells, these substances reduce the permeability of cell membranes to water, and also reduce the secretion of cerebrospinal fluid, which normalizes the function of the BBB. However, corticosteroids are capable of deactivating the inflammatory cytokine cascade that occurs as a result of brain cell necrosis [6,] and should be used with caution. Representatives of corticosteroids such as prednisolone and dexamethasone are potent drugs; they significantly inhibit the adrenal cortex, so they are used only in exceptional cases. For example, direct indications for their use may include terminal conditions, adrenal insufficiency, severe shock, and hypotension that cannot be corrected [14].

This is explained by the fact that progesterone reduces both vasogenic and cytotoxic cerebral edema. In addition, under the influence of the drug, the inflammatory cytokine cascade decreases, free radical and lipid oxidation decreases, autoregulation of water in brain cells (aquaporin channels) is stabilized and apoptosis is reduced [14].

Some authors call L-lysine aescinate a worthy alternative to corticosteroids in terms of anti-edematous action in TBI [12]. The active ingredient of the drug is a water-soluble salt of horse chestnut saponin - escin and the amino acid L-lysine. The drug inhibits the exudative stage of inflammation and increases vascular resistance. The effectiveness of L-lysine aescinate has been studied in the prehospital and hospital stages of treatment of TBI. According to MRI data, already on the 3-5th day of therapy, a significant decrease in the area of edema around hemorrhagic foci was noted. L-lysine escinate reduced, and in some situations prevented, swelling of the membranes of the brain, which was manifested by normalization of cerebrospinal fluid pressure and a decrease

in congestive changes in the fundus. Researchers note the effectiveness of L-lysine fascinate in the acute period of TBI and consider the widespread practical use of the drug appropriate [14].

The above-mentioned cytokine cascade is closely related to the kallikrein-kinin system. An increase in its plasma components, including bradykinin, contributes to secondary brain damage, increasing the degree of acute brain injury and inflammation. Therefore, in severe TBI, it is recommended to administer the natural kallikrein protease inhibitor aprotinin (centrical) intravenously at a dose of 60 thousand units/day [12]. Modern studies have found that activation of blood clotting factor XII stimulates the release of bradykinin, which contributes to cerebral edema. Pharmacological blocking of activated factor XII a with the substance rHA-Infestin-4 (Germany) reduced post-traumatic inflammation and the formation of cerebral edema [8].

With TBI, as well as with cerebrovascular accidents caused by other causes, there is a high risk of developing thromboembolism ical complications. Therefore, direct anticoagulants are often used, especially low molecular weight heparins (Clexane, Fraxiparin, etc.) [9]. Their administration helps improve microcirculation, but it may contribute to the development or progression of cerebral edema, so some authors recommend using erythrocytopheresis instead of such therapy. At the same time, recent clinical studies have shown that heparin and its low-molecular-weight derivative enoxaparin reduce the incidence of clinical vasospasm and delayed cerebral infarction after subarachnoid hemorrhage. In addition to vasospasm, heparin prevents inflammation and restores the integrity of the blood-brain barrier, thereby reducing swelling. This is a more important aspect of its therapeutic effectiveness than the prevention of vasospasm [12]. Antihistamines (chloropyramine, diphenhydramine, etc.) are often used to treat various diseases of the central nervous system, including ONGM. However, data confirming their effectiveness in cerebral edema in clinical studies have not been obtained and are limited to individual clinical observations [6]. Reducing cerebral metabolism and brain oxygen demand, minimizing pain stimuli from areas of traumatic injury makes analgosedation an integral part of intensive care for the acute period of TBI. By reducing cerebral blood flow, cerebral blood volume, cerebral metabolism, reducing CPP, sedatives can prevent and reduce the consequences of primary brain damage associated with cerebral edema and increased ICP. These drugs are most often used today for traumatic brain injuries. They have various side effects, the most dangerous of which is a decrease in systemic blood pressure. There is still no convincing evidence of the clinical benefit of any sedative drug [4]. Most often, propofol, benzodiazepines and narcotic analgesics are used for analgosedation. Of the benzodiazepine drugs, midazolam is mainly used due to its faster onset of action and short duration of action compared to lorazepam or diazepam. Benzodiazepines lower ICP and reduce seizure activity; however, bolus infusions can significantly reduce systemic blood pressure and ICP. Other disadvantages of benzodiazepines are depression of breathing and cough reflex, development of tolerance, and after cessation of administration, dangerous withdrawal symptoms requiring long-term use of benzodiazepines [4,5]. The drug has antioxidant, neuroprotective, vasodilator (reduces the tone of cerebral vessels, increases cerebral blood flow, without causing the “steal” phenomenon, but, on the contrary, increasing perfusion in damaged areas of the brain) effects. According to foreign sources, nimodipine is the most effective drug for relieving cerebral vasospasm [6, 7]. Modern studies using multiparametric MRI have proven that the use of nimodipine after hypoxia changes the intracellular calcium flux and can reduce the development of cytotoxic cerebral edema [4]. It is known that magnesium sulfate administered intravenously is also capable of blocking calcium channels. Clinical observations have shown that the use of low doses of magnesium sulfate in combination with nimodipine, as well as the use of high doses of magnesium sulfate in patients with rupture of a central aneurysm, improves treatment outcomes,

which is manifested by recovery without neurological deficit and with minimal neurological deficit [9]. In the treatment of ONGM of various origins, nootropics are often used due to their high efficiency in terms of normalizing energy metabolism [5]. By activating plastic processes in the central nervous system, they improve the exchange of nucleic acids, increase the synthesis of phospholipids and proteins in nerve cells, inhibit lysosomal enzymes, remove free radicals, and improve the penetration of glucose through the BBB. Nootropics have a positive effect not only on metabolic processes, but also on the main neurotransmitter synaptic systems - cholinergic, adrenergic, dopaminergic, GABA and glutamatergic. This feature of the mechanism of action of nootropics is reflected in many synonyms to designate their action (neuroregulatory, neurometabolic, neuroprotective, cerebroprotective, angioprotective, etc.) [3]. A number of studies have studied the effectiveness of nootropics in TBI. The ability of piracetam and pyritinol to improve the results of treatment of patients with TBI, reduce the duration of coma, and relieve neurological symptoms has been described [13]. In general, it should be noted that nootropics are used today in many areas of medicine and have high prospects for further use in traumatic and vascular lesions of the brain, including acute brain injury. Cerebral edema resulting from TBI, in acute or chronic cerebrovascular accidents, triggers a complex multi-link pathophysiological process determined by the development of cerebral hypoxia. Further, an increase in calcium concentration inside neurons causes activation of membrane phospholipases, which leads to the destruction of membrane phospholipid structures and the release of free fatty acids [3]. Such changes contribute to the aggravation of microcirculatory disorders and neurometabolic disorders. As a result of weakened glycolysis, lactic acidosis develops under conditions of oxygen deficiency, which contributes to the progression of cerebral edema [12]. An increase in the concentration of reactive oxygen species causes structural damage to cell components, including the outer and inner mitochondrial membranes, and increases the permeability of the BBB [7].

Results

Many drugs with neuroprotective, neurometabolic, and nootropic types of action have an antioxidant and antihypoxic effect to one degree or another. However, in almost all of them, these effects do not allow for a full-scale effect on the pathophysiological processes caused by reactive oxygen species. In recent years, active experimental and clinical research has been carried out on antihypoxants and antioxidants of various chemical structures, and their mechanisms of action in various diseases are studied. Next, we consider the literature data regarding the study of antioxidants in the post-traumatic period of TBI, their effect on the development of acute cerebral trauma, limiting our analysis only to those compounds that have well-established antioxidant activity. The clinical study also showed a significant reduction in mortality and improvement in long-term outcomes with the introduction of tocopherol in dose of 400 IU/ml intramuscularly for 7 days after TBI [93]. Some experimental studies on TBI models show the neuroprotective effect of xanthines, such as astaxanthin, fucoxanthin, and bexarotene. Trimetazidine is a promising drug with antihypoxic and antioxidant activity. By preventing the development of lactic acidosis in brain tissue, increasing the activity of lipid peroxidation processes, and reducing the activity of antioxidant systems, trimetazidine has proven itself to be a powerful cerebroprotective agent [56]. Under various hypoxic conditions, including TBI, the antihypoxic properties of thiol compounds (gutimin, amtizol, etc.) have been studied. In our laboratory, we studied the effect of amtizol, etomersol and bemythyl (metaprot) on the water balance in brain tissue in a model of TBI in rats. All three substances effectively prevented the formation of ONGM [27, 37]. Of course, further

study of the above-described agents with antioxidant and antihypoxic activity is necessary due to their promise as cerebroprotectors that can reduce the development of negative reactions after hypoxic, ischemic and traumatic effects on the brain.

Conclusion

Despite the fact that many pathophysiological mechanisms of the formation of ONGM are known and in the arsenal of practical medicine there are many drugs that quite effectively influence the severity of cerebral edema, therapy for this pathology remains largely empirical. Diuretics continue to be widely used, and the osmotic diuretic mannitol and hypertonic saline are still used as first-line agents for the treatment of acute cerebral edema. Corticosteroids play an important role in the treatment of ONGM, but their prescription is treated with caution and is used only in exceptional cases. Terminal conditions may be direct indications for their use. According to indications, complex pharmacotherapy for ONGM sometimes includes inhibitors of the kallekrein-kinin system and low molecular weight heparins.

For vascular and traumatic brain injuries. Nootropics, antioxidants and antihypoxants have high prospects for further use in traumatic and vascular lesions of the brain, including acute brain injury. New directions are being developed in the pharmacotherapy of traumatic and vascular brain lesions, including the development of ONGM, associated with effects on molecular targets (water channels, ion transporters, matrix metal prostheses, etc.). The possibility of pharmacological preconditioning is being studied as a separate area of neuroprotection. However, new approaches to pharmacotherapy of ONGM require in-depth experimental study and thorough clinical studies to substantiate their therapeutic effectiveness.

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