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EFFECTIVENESS OF USE OF NOOTROPS WITH ANTICONVULSANTS IN THE CONSEQUENCES OF CRANIOCEREBRAL INJURY

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Abstract

Traumatic brain injuries (TBI) is a significant cause of morbidity and mortality, leading to cognitive dysfunction, affecting patients and their families as a whole, and also greatly burdening the socioeconomic system [1,2]. Seizures in neurosurgical patients are common and can lead to several potential complications, such as higher metabolic demand of neurons, increased intracranial pressure, and secondary brain damage. Antiepileptic drug prophylaxis is commonly prescribed for the treatment of patients with traumatic brain injury, as certain subgroups have been shown to have a beneficial effect in preventing seizures [1]..

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

Introduction

Traumatic brain injuries (TBI) is a significant cause of morbidity and mortality, leading to cognitive dysfunction, affecting patients and their families as a whole, and also greatly burdening the socioeconomic system [1,2]. Seizures in neurosurgical patients are common and can lead to several potential complications, such as higher metabolic demand of neurons, increased intracranial pressure, and secondary brain damage. Antiepileptic drug prophylaxis is commonly prescribed for the treatment of patients with traumatic brain injury, as certain subgroups have been shown to have a beneficial effect in preventing seizures [1]. The pathophysiology of cognitive dysfunction after TBI remains poorly understood, but is thought to be directly related to diffuse axonal damage [4], in addition to disruption of neuronal projections and neurotransmitter pathways involving dopamine and glutamate [5], [6], [7]. Current treatment strategies to improve cognitive recovery after TBI include cognitive rehabilitation [8,9] and pharmacotherapy [10]. .

Materials and Methods

We reviewed the safety and effectiveness of nootropics for cognitive restoration after TBI to determine whether the current literature justifies its use in this clinical condition. Study characteristics, results, and methodological quality were synthesized. All studies assessed only severe TBI in adults. The incidence of severe adverse events was found to be consistently very low across all studies (frequency of seizures, elevated liver enzymes). In conclusion, nootropics are well tolerated and may accelerate cognitive recovery in the medium term.

1) subgroups of patients with TBI who used nootropics with anticonvulsants; group 2 patients who used only anticonvulsants
2) time of start of treatment
3) drug dose
4) duration of therapy
5) restoration of cognitive functions
6) side effects

Nootropics appear to be well tolerated and may speed up the rate of cognitive recovery in the medium term. Data for a longer period are not available; we should specifically strive for longer follow-up than what is currently considered adequate. Further large clinical trials targeting specific In addition to the initial mechanical damage, TBI causes a number of secondary impairments such as, but not limited to, metabolic dysfunction and oxidative stress. Strategies for neuroprotection after TBI have traditionally focused on cellular sparing as a measurable endpoint, although multiple lines of evidence indicate that even with significant deficits, neuronal sparing persists at both the cellular and behavioral levels. Therefore, developing treatments that can effectively provide both neuronal preservation and functional benefit after injury is critical to providing the best treatment options for clinical TBI. Targeting dopaminergic signaling pathways is a novel approach to TBI that provides benefits for both neuronal survival and functional outcome. TBI is a heterogeneous and complex condition consisting of acute, subacute and chronic pathology [1, 2]. Unfortunately, many neuroprotective strategies used in experimental studies of TBI have not been successfully applied in the clinic [8, 9]. Potential reasons for poor translation of basic research findings into the clinic include, but are not limited to:

1) the complexities of multisystem injuries commonly observed in clinical settings [5, 7]
2) disruption of the blood-brain barrier [4, 5]
3) potential drug toxicity and side effects [7, 8]
4) incomplete preclinical assessments.

To address these issues, many studies have used paradigms designed to inhibit cell death pathways to reduce the rate of acute neuronal loss after injury [9, 10]. However, this strategy has often had variable success due to persistent cellular dysfunction even when significant cell retention is present [7, 8].

Acute TBI affects multiple brain regions, including but not limited to the hippocampus [8, 9], frontal cortex (FC) [5, 10], and striatum [11]. These three regions are particularly important due to their roles in attention, executive function, learning, and memory [2–3]. Each of these four cognitive domains can be significantly impaired after TBI [7–8]. While the brain typically functions through the interaction of multiple regions, the hippocampus, FC, and striatum are unique in that dopamine, through interaction with glutamate, is required to potentiate neurons in each region [3-4]. However, tissue damage after TBI is not limited to specific areas of the brain.

Diffuse axonal damage in white matter tracts along with gray matter damage [7–8] further complicates the clinical picture of acute brain injury.

Classification of substances with nootropic effects

1. Nootropic drugs with a dominant mnestic effect.

1.1. Pyrrolidone nootropic drugs (piracetams), predominantly of metabolic action (piracetam, oxiracetam, aniracetam, etiracetam, isocetam, etc.).

1.2. Cholinesterase drugs.

1.2.1. Strengthening the synthesis of acetylcholine and its release (choline chloride, phosphotidylserine, lecithin, acetyl-L-carnitine, etc.).

1.2.2. Agonists of cholinergic receptors (oxotremorine, bethanechol, spiropiperidines, etc.).

1.2.3. Acetylcholinesterase inhibitors (physostigmine, tacrine, amiridine, galantamine, ertastigmine, etc.).

1.2.4. Substances with a mixed mechanism of action (demanol, aceglutamate, nerve growth factor, bifemalan, etc.).

1.3. Neuropeptides and their analogues (ACTH, ebiratide,
somatostatin, vasopressin, thyrotropin-releasing hormone, substance P, angiotensin II, cholecystokinin 8, peptide analogues of piracetam, etc.).

1.4. Substances affecting the system of excitatory amino acids (glutamic acid, milacemide, glycine, D-cycloserine, nooglutyl)

2. Nootropic drugs of mixed action with a wide range of effects (“neuroprotectors”).

2.1. Activators of brain metabolism (actovegin, instenon, acetyl-L-carnitine, phosphatidylserine, homopantothenic acid esters, xanthine derivatives, etc.).

2.2. Cerebral vasodilators (vinpocetine, oxybral, nicergoline, vinconate, etc.).

2.3. Calcium antagonists (nimodipine, cinnarizine, flunarizine, etc.).

2.4. Antioxidants (mexidol, exiphon, pyritinol, atherovit, meclofenoxate, tocopherol).

2.5. Substances affecting the GABA system (gammalon, pantogam, picamilon, ligam, nicotinamide, phenibut, phenylpiracetam, sodium hydroxybutyrate, neurobutal, etc.).

2.6. Substances from different groups (ethimizole, orotic acid, methyl glucoorotate, oxymetacyl, beglimin, cerebrocrast, ginseng, instenon, gingko biloba extract, lemongrass, etc.)

Main clinically commonly used drugs:.

Piracetam to this day remains not only the ancestor, but also the gold standard of nootropic drugs. Its drugs make up more than half of the range of the entire European nootropic market. This popularity is primarily explained by the fact that today it is piracetam, in comparison with other drugs in this group, that has the maximum breadth of the pharmacological spectrum of nootropic activity. However, most of the pharmacological effects of piracetam are nonspecific, which may be due to both the lack of effectiveness of this drug in a number of clinical cases and the development of side effects. Side effects during piracetam therapy, although in most cases are not serious, are nevertheless occur relatively often, especially when using doses above 2.4 g/day, as well as in elderly and senile people, and are associated with its stimulating effect, primarily on the catecholaminergic systems of the brain. The mentioned phenomena are manifested mainly by increased excitability, irritability, anxiety, aggressiveness, sleep disturbances, and, less commonly, dizziness, tremor, and allergic skin reactions [1, 11, 18, 20]. A measure to prevent sleep disorders can be taking the drug in the first half of the day. In addition, in some cases, when using piracetam, sexual arousal and dyspeptic symptoms (nausea, diarrhea, abdominal pain) are observed. It is

important to note that in some cases, especially in the elderly, the increase in the manifestations of coronary insufficiency described for piracetam can be very dangerous, which is generally not typical for other representatives of nootropics [8, 11]. This complication should be considered as a potential serious risk of pharmacotherapy in geriatric practice. Finally, piracetam has the ability to reduce the threshold of convulsive readiness and cause activation of epileptic seizures [7]. Therefore, the prescription of piracetam requires special caution in elderly and senile people, with chronic coronary heart disease, epilepsy and states of psychomotor agitation of various nature in the anamnesis. Since prescribing piracetam in doses below 1.8-2.4 g/day often does not make clinical sense, the practitioner is faced with the difficult task of carefully taking into account the potential dangers of pharmacotherapy with this drug and assessing the benefit/risk ratio of its use. A very popular group of nootropic drugs There are also GABA-ergic drugs, in particular aminalon. It should be noted that in general aminalon, like other drugs in this group (pantogam, noofen, etc.), is quite safe. However, sometimes when using it, extremely unpleasant subjective sensations are possible - a feeling of heat, insomnia, nausea, vomiting and even an increase in body temperature, which can lead to refusal of treatment. Periodically, especially at the beginning of taking aminalon,Quite pronounced lability of blood pressure may occur [8, 11]. In this case, an increase in pressure can be regarded as a manifestation of hypertension, and a decrease in pressure as systemic hypotension and, as a consequence, lead to the unreasonable prescription of antihypertensive or cardiotonic drugs. At the same time, the mentioned action of aminalon can sometimes actually mask real surges in blood pressure that require appropriate correction. In addition, aminalon has a certain potential for drug-drug interactions, enhancing the effects of benzodiazepine anxiolytics, hypnotics and anticonvulsants, which can in some cases lead to corresponding side effects associated with excessive depression of the central nervous system (CNS). The possibility of developing peculiar side effects when prescribing nicotinoyl-γ-aminobutyric acid (picamilon) deserves special attention. During the use of this drug, paradoxical reactions for the central GABA mimetic of hyperexcitation, irritability, and anxiety [11] may be observed, associated with a complex system of interaction of GABA with other neurotransmitter systems (in particular, serotonin and adrenergic). Drugs are widely used in clinical practice. , combining nootropic and vasotropic properties - nicergoline, vinpocetine, nimodipine. Despite the fairly high degree of safety of these drugs, it is necessary to remember the risks associated with their use.

Nicergoline, being a typical α-blocker, has side effects that are characteristic of this group of drugs and are often difficult to tolerate by patients. These include erythema, facial hyperemia, tachycardia, orthostatic hypotension, and with parenteral administration - collapse. In addition, dizziness, headache, sleep disturbances, as well as dyspeptic disorders associated with increased gastric secretion are possible. From a clinical point of view, it seems particularly important to increase myocardial oxygen demand as a result of the use of nicergoline, which can contribute to exacerbation of angina or arrhythmia, especially with relevant medical history. Finally, nicergoline should be used with great caution when taking antihypertensive drugs and anticoagulants concomitantly [5, 7, 11]

Vinpocetine has a combined nootropic and selective vasotropic effect, in general it has the smallest range of side effects (up to 2.5% for tablets, up to 5% for injections of the original drug), which, however, in some cases can be clinically significant. Transient hypotension, headache, dizziness, dyspeptic reactions, tachycardia (with parenteral administration) may be observed, and

several cases of arrhythmias (extrasystoles) have been described [4, 6, 7]. Noting the almost complete absence of drug interactions with vinpocetine, one should remember the impossibility of its simultaneous use (parenterally) with heparin.

Nimodipineas a blocker of calcium channels in the vascular wall, it can cause a significant hypotensive effect, erythema, headache, as well as fluctuations in heart rate and symptoms of central nervous system overexcitation (motor activity, aggressiveness). With the combined use of nimodipine with antihypertensive drugs, nitrates, beta-blockers, the development of a pronounced hypotensive reaction and even heart failure is possible [7, 11]. These drugs with vasotropic properties must be used with particular caution in the following cases: • in the presence of severe (acute or chronic) cardiological pathology; • in the presence of clinically significant psychopathological symptoms; • with disorders of the hemocoagulation system; • in conditions of polypharmacy.

Ginkgo preparations– effective and safe phytopharmacological agents for the treatment of various forms of cognitive impairment and cerebrovascular pathology, with a minimum of side effects. At the same time, it should be remembered that the degree of purification of plant materials plays a decisive role in ensuring the safe use of these products (as well as other herbal medicines). Thus, it is known that, along with rare cases of headache and dyspepsia, some ginkgo preparations can exhibit a potentially dangerous hemorrhagic effect (especially with concomitant surgical or diagnostic interventions), associated with the presence of undesirable components-impurities of these drugs - ginkgo acids [2, 11].

One of the traditional areas of nootropic pharmacotherapy is the use of peptide drugs. The most popular remedy of this kind is considered to be Cerebrolysin, a complex of peptides obtained from the pig brain, the molecular weight of which does not exceed 10,000 daltons. It is practically free of side effects (extremely rarely - agitation, dizziness, dyspepsia). At the same time, using the example of Cerebrolysin, one can be convinced of the importance of technically correct parenteral administration of nootropic drugs to prevent their negative effects. With rapid intravenous administration of this drug, a pronounced hyperpyretic reaction may occur, sometimes in combination with dizziness and arrhythmia [11]. Therefore, it should be administered through slow intravenous infusions after dilution with standard infusion solutions. A similar rule should be applied to prevent side effects of the combined nootropic and vasotropic drug Instenon, which contains three active substances: hexobendine, etamivan and etophylline. If the side effects of this drug are minimal when taken orally, then with parenteral administration (intravenous, less often intramuscular), severe headaches associated with increased intracranial pressure and often extremely difficult to tolerate, hypotensive reactions, tachycardia, and facial flushing are possible. Therefore, Instenon infusions should be carried out very slowly, under constant medical supervision.

Combined nootropic drugs have gained wide popularity throughout the world in recent years, and domestic clinical practice is no exception. At the same time, upon closer examination it turns out that the range of such drugs on the domestic pharmaceutical market is not particularly diverse. A

very popular combination of nootropic and vasotropic components within one drug has become the combination of piracetam with cinnarizine.

Such drugs are the domestic drugs Pyracizin, Cizam, Noozam, Cinatropil, Neuronorm, as well as the foreign drug Phezam. All of them contain 0.4 g of piracetam and 0.025 g of cinnarizine in 1 tablet (capsule). In itself, such a combination seems quite appropriate. It is important, however, given the massive nature of the use of these funds, to clearly define the scope of their application and the potential risk arising in this case. The latter is associated with a very serious complication observed when taking cinnarizine - the development of drug-induced parkinsonism syndrome, which is worth dwelling on in more detail. According to modern data, cinnarizine-induced parkinsonism accounts for up to 43% of all cases of drug-induced parkinsonism [15], which suggests the greatest contribution cinnarizine in the development of the mentioned severe form of pathology among all drugs that can cause extrapyramidal insufficiency. It is important to emphasize that this phenomenon has a clearly defined age-dependent nature. The older the patient, the higher the likelihood of developing manifestations of parkinsonism as a result of taking cinnarizine [21]. This complication is directly related to the dose of the drug and the duration of its use [16]. Symptoms of extrapyramidal insufficiency of varying severity were observed in 75-100% of patients aged 60-65 years and older within a period of 1 month to 1 year after starting cinnarizine [13, 21]. Clinical features of cinnarizine-induced parkinsonism are the predominance of tremor symptoms (in contrast to Parkinson's disease, in which akinesia and rigidity predominate in the initial stage of the disease), as well as unfavorable prognostic characteristics (persistence of extrapyramidal symptoms for at least 7 years after the onset of the first manifestations) [15, 17]. The mechanisms of development of this complication are obviously associated with the ability of cinnarizine to block dopamine receptors in the nigrostriatal system [12], as well as reduce the activity of tyrosine hydroxylase, the key enzyme in dopamine biosynthesis [19], i.e. aggravate the basic mechanisms of brain aging, which directly determine the increase in extrapyramidal pathology with age [10]. Probably, the same properties of cinnarizine are associated with a significant deterioration in the clinical condition in patients with Parkinson’s disease after taking this drug [15]. In addition, in addition to the effect on the symptoms of parkinsonism, cinnarizine also has the ability to provoke the development of depression [16], which may be determined by the identified it has antidopaminergic and antiserotonergic properties [14]. Finally, the presence of antihistamine properties in cinnarizine can cause the development of sedation and lethargy, which limits the ability to drive vehicles and operate instruments when using it. This effect is potentiated by concomitant intake of alcohol, sleeping pills and other neurotropic drugs [9].All of the above can significantly influence the full implementation of the patients’ social function - work, study, etc.

The universal modulatory effect of the drug becomes particularly relevant in terms of the possibility of realizing the breadth of the spectrum of its clinical and pharmacological effects (psychostimulating, antiasthenic, antiamnestic, mnemotropic, anxiolytic, vegetostabilizing, antidepressant, neuroleptic, anticonvulsant, antihypoxic, antiischemic, antitoxic, anti-inflammatory, slender, antiapoptotic, and etc.), allowing to optimize approaches to the treatment of various diseases [14].

Separately, it is worth analyzing the antiepileptic activity of the drug. Experimental data indicate anticonvulsant effects of phenylpiracetam [15]. The anticonvulsant effects of phenylpiracetam and

piracetam were compared in experiments on mice. To induce seizures, we used the GABA-A receptor blocker bicuculline (40 min after the administration of the study drugs), the GABA antagonist corazol (30 min after the administration of phenylpiracetam

or piracetam) or MES. Clonic, tonic and clonic-tonic seizures and mortality were recorded. Phenylpiracetam at doses of 100 and 300 mg/kg completely blocked the convulsive effect of bicuculline and prevented the death of animals in 100% of cases. In contrast, piracetam at doses of 300 and 600 mg/kg did not block the convulsive effect of bicuculline. At a dose of 100 mg/kg, phenylpiracetam partially eliminated convulsions and reduced mortality by 25% when administered with corazol, and at a dose of 6000 mg/kg it completely prevented the development of convulsions and the death of mice. Piracetam in doses of 300 and 600 mg/kg did not have an anticonvulsant effect in relation to Corazol. Phenylpiracetam also had a pronounced protective effect against seizures caused by MES. At a dose of 100 mg/kg, it prevented convulsions and death in 75% of mice, and at doses of 300 and 450 mg/kg – in 100% of animals.

Piracetam did not exhibit anticonvulsant activity in this test

Conclusion

The data obtained allow us to assert that nootropics have a pronounced anticonvulsant effect, which can serve as a basis for studying the possibilities of using this drug in various paroxysmal conditions. However, a small number of observations does not yet allow it to be recommended in complex antiepileptic therapy. As a result of the study, the authors obtained the following results: the use of nootropics in complex therapy with anticonvulsants for patients with epilepsy led to a significant improvement in the condition of patients with a decrease in the severity of cognitive impairment, emotional disorders, and manifestations of asthenia. The number of patients with memory impairment decreased by 12 times, with depressed mood by 8 times, and with cephalgia by more than 5 times. A statistically significant decrease in the severity of cognitive disorders was characterized by positive dynamics in all components of the assessed disorder.
The combination of nootropic, vegetotropic, neuroprotective, antiepileptic and adaptogenic effects can improve the results of treatment of patients with central nervous system pathology.

References

1 .Klimek M, Dammers R: Antiepileptic drug therapy in the perioperative period in neurosurgical patients. Carr Opin Anaesthesiol 2010, 23(5): 564–567
2. IH Bleimeister et al.Environmental enrichment and amantadine confer individual but nonadditive enhancements in motor and spatial learning after controlled cortical impact injuryBrain Res. (2019)
3. A. A. Okigbo et al.Dose-dependent neurorestorative effects of amantadine after cortical impact injuryNeurosci. Lett.(2019)
4 .MC Dewan et al. Estimating the global incidence of traumatic brain injury J. Neurosurg. (2019)
5 M. Faul et al. Epidemiology of traumatic brain injury Handb. Clin. Neurol. (2015)
6. ED Bigler Anterior and Middle Cranial Fossa in Traumatic Brain Injury: Relevant Neuroanatomy and Neuropathology in the Study of Neuropsychological Outcome Neuropsychology. (2017)
7. JW Bales et al. Targeting dopamine in acute traumatic brain injury Open Drug Discov. J. (2010)

8. RM Guerriero et al Glutamate and GABA Imbalance Following Traumatic Brain Injury Curr. Neurol. Neurosci. Rep. (2015)
9. J. Kornhuber et al. Psychotogenicity and N-methyl-D-aspartate receptor antagonism: implications for neuroprotective pharmacotherapy Biol. Psychiatry (2017)
10. JL McGuire et al. Neurotransmitter changes after traumatic brain injury: an update for new treatment strategies Mol. Psychiatry (2019)
11. Saatman KE; Duhaime AC Workshop Scientific Team Advisory Panel Members; Bullock, Ross; Maas, Andrew I.R.; Valadka, Alex; Manley, Geoffrey T.; Workshop Scientific Team Advisory Panel Members. Classification of traumatic brain injury for targeted therapies (English) // Journal of Neurotrauma (English)rus. : journal. - 2008. - Vol. 25, no. 7. - P. 719-738. - doi:10.1089/neu.2008.0586. - PMID 18627252. - PMC 2721779
12. Mukhamedzhanova N.M. State of cognitive functions in post-traumatic epilepsy: dissertation. Ph.D. honey. Sci. Tashkent. 2012.
13. Selyanina N.V., Shutov A.A. Experience with the use of phenotropil in patients with initial manifestations of insufficiency of blood supply to the brain. Atmosphere Magazine. Nervous diseases. 2015; 4: 30-32.
14. Akhapkina V.I., Akhapkin R.V. Fundamentals of the modulatory concept and classification of modulatory drugs. RMJ. 2012; 19: 933-951.
15. Akhapkina V.I., Voronina T.A. Spectrum of pharmacological effects of phenotropil. Farmateka Journal. 2005; 13: 19-25.
16. Lybzikova G.N., Yaglova Zh.S., Kharlamova Yu.S. The use of phenotropil in the complex treatment of epilepsy "Journal of Neurology and Psychiatry". 2008; 2:69-70
17. Poverennova I.E., Yakunina A.V., Kalinin V.A., Kurov M.V. Phenotropil in the complex treatment of symptomatic post-traumatic epilepsy. Journal of Neurology and Psychiatry. Epilepsy. 2011; 5: 81-83.
18. Lesiovskaya E.E., Marchenko N.V., Pivovarova A.S. Comparative characteristics of drugs that stimulate the central nervous system. Nootropic drugs Reference. polycl. doctor – 2013. – T. 1. – No. 2).