Correction of cognitive impairment in children and adolescents with cerebral palsy during treatment with pantocalcin

T.T. Batysheva, A.N. PLATONOVA, N.V. CHEBANENKO, O.V. BYKOVA*

Scientific and Practical Center for Child Psychoneurology of the Moscow Department of Health

Management of cognitive impairment in children and adolescents with cerebral palsy treated with pantocalcin

TT BATYSHEVA, AN PLATONOVA, NV CHEBANENKO, OV BYKOVA

Research and Clinical Center of Pediatric Psychoneurology Moscow Department of Public Health, Moscow

A randomized study of the efficacy and safety of the drug hopantenic acid (pantocalcin) and its effect on cognitive functions in children with cerebral palsy (CP) was conducted. A reliable positive effect of pantocalcin on the state of visual memory and the ability to concentrate, activity, and fatigue was established. At the same time, a decrease in the level of anxiety in children and adolescents with CP was observed. No evidence was obtained of the effect of the studied drug on the degree of acquisition of visual-motor skills. The data obtained in the study demonstrated a high safety profile of pantocalcin when used in pediatric practice.

Key words: *cerebral palsy, cognitive functions, hopantenic acid, pantocalcin.*

A randomized study on the efficacy and safety of the hopantenic acid preparation (pantocalcin) and its effect on cognitive functions in children with cerebral palsy (CCP) has been carried out. The positive effect of pantocalcin on the visual memory and attention concentration, activity and fatigability has been shown. At the same time, there was a decrease of anxiety in children and adolescents with CCP. No evidence for the effect of the drug on visual-motor skills has been found. The results of the study have demonstrated the high safety profile of pantocalcin when used in pediatric practice.

Key words: *children cerebral palsy, cognitive functions, hopantenic acid, pantocalcin.*

Cerebral palsy (CP) is one of the most common diseases in but one of the leading places in the structure of chronic disabling diseases of childhood, accounting for 1.7 to 7 cases per 1000 people [5]. The prevalence of cerebral palsy in Russia ranges from 2.5 to 5.9 per 1000 newborns [1]. Some of the most common symptoms accompanying motor disorders in children with cerebral palsy are disorders of psychoemotional development and cognitive activity. The spectrum and degree of expression of affective and cognitive disorders in patients with cerebral palsy are variable, but it is they that determine subsequent restrictions in the social adaptation of patients upon reaching adulthood.

Cerebral palsy is characterized by a wide range of cognitive impairments in the form of delayed speech development, dyslalia, attention, memory, thinking, etc. [3, 7]. Cognitive impairments aggravate the severity of disability in children due to significant limitations of their life activities during the period of formation of higher mental functions, acquisition of knowledge and skills, and personality development [2].

To correct cognitive and emotional disorders in children in Russia, nootropic drugs are widely used, which, as a result of stimulating metabolic processes and interneuronal transmission in the central nervous system

improve mental activity, attention, memory, ability to reproduce information, reduce the need of neurons for oxygen during hypoxia, increase the resistance of the central nervous system to the effects of unfavorable factors. These drugs not only have a positive effect on cognitive functions, but also contribute to the normalization of

behavior, correction of emotional and behavioral disorders [6]. Abroad, the use of nootropic drugs for the purpose of correcting cognitive disorders in children is still a topic of discussion. The main arguments against drug correction of cognitive disorders in pediatric neurological practice are the lack of evidence-based studies of its effectiveness in the context of developing intellectual and mnestic activity and convincing data on the safety of using such drugs in patients under 18 years of age [4, 8].

*e-mail: avt496709@yandex.ru

One of the drugs used is hopantenic acid (HPA, pantocalcin), a natural metabolite of GABA in nervous tissue. The drug penetrates the blood-brain barrier well due to

presence of pantoyl radical in the molecule, is practically not metabolized in the body and is excreted within 48 hours. The pharmacological effects of the drug are due to the direct effect on the GABA receptor-channel complex and the induction of acetylcholine. GPC helps to normalize GABA metabolism, improves glucose utilization and blood supply to the brain, increases its resistance to hypoxia, the effects of toxic substances, stimulates anabolic processes in neurons, has a combination of mild psychostimulating and moderate sedative effects, allows not only to activate cognitive functions in children, but also helps to normalize the emotional sphere. The nootropic effect of the drug is not accompanied by epileptosis.

genetic phenomena, which allows the drug to be used in children with epileptic seizures in combination with anticonvulsant therapy.

The aim of the study is to form an evidence base on the effect of nootropic drugs, in particular pantocalcin, on cognitive functions in children with cerebral palsy. We conducted a randomized study of the effectiveness and safety of its use in children with cognitive impairment.

Material and methods

The study involved 100 children and adolescents aged 8 to 14 years with a diagnosis of cerebral palsy. The study was conducted at the Scientific and Practical Center for Children's Psychoneurology in Moscow.

The inclusion criteria for patients in the study were as follows: patients of both sexes aged 8 to 14 years; an established diagnosis of cerebral palsy of the following forms: hemiparetic form, spastic diplegia; memorization of 2 to 5 words according to the memory for images test; an indicator of 0.91 or less according to the accuracy standard of the Toulouse-Pieron test; in the presence of a history of epileptic seizures - their absence for at least 6 months before inclusion in the program (including while continuing to take the main antiepileptic therapy); informed consent signed by the parents or legal representatives of the child to participate in the study and compliance with all its requirements.

The criteria for exclusion of patients from the study were as follows: hypersensitivity to the components of the drug; hypotrophy or obesity of grade II or higher; acute renal failure; severe, decompensated or unstable somatic diseases; the presence of epileptic seizures in the previous 6 months before inclusion in the study; difficulties in the family environment as a significant cause of the child's cognitive and behavioral disorders (conflicts between parents, frequent punishments, overprotection, etc.); admission for 3 months preceding

nootropic, sedative, desensitizing drugs, neuroleptics, antidepressants and other psychoactive drugs that were included in the study.

The following were assessed as primary parameters of effectiveness in the form of growth to age-standard indicators:

the proportion of patients with normalization of the number of reproduced words according to the Luria test; the proportion of patients with normalization of visual memory indicators according to the "memory for images" test; the proportion of patients with normalization of indicators of speed and accuracy of the Toulouse-Pieron test.

As secondary parameters of efficiency

The following were assessed: the proportion of patients with a decrease in the degree of ability to its low level on the anxiety test;
distribution of patients by the number of words reproduced according to the Luria test; distribution of patients by the number of images reproduced according to the "memory for images" test; distribution of patients by the speed and accuracy of the Toulouse-Pieron test; distribution of patients by the number of points scored in the "cipher" subtest

"rivka".

In order to minimize subjectivity and systematic errors, the study participants were randomly distributed (randomized) into groups 1 and 2. Randomization was carried out according to the following algorithm:

rhythm: each patient who met the inclusion criteria was assigned a three-digit sequential randomization number (an envelope with the corresponding number was opened). The patient's randomization number

and other data corresponding to the number were entered
by the physician-investigator in the register of randomized patients. Information was also added on the prescription of the drug pantocalcin to the patient in combination with basic therapy or on the continuation of previously prescribed basic therapy by the patient.

Group 1A consisted of 25 patients aged 8 to 10 years with a confirmed diagnosis of CP, who received a course of treatment with pantocalcin both as monotherapy and in addition to previously prescribed basic drug therapy. Group 2A (comparison group for children) consisted of 25 patients aged 8 to 10 years with CP, who continued to take previously prescribed basic drug therapy without the use of pantocalcin. Group 1B consisted of 25 adolescents aged 11 to 14 years with CP, who received a course of treatment with pantocalcin. Group 2B (comparison group for adolescents) consisted of 25 patients aged 11 to 14 years with CP, who continued to take previously prescribed basic therapy without the use of pantocalcin.

calcin.

The observation period lasted 90 days. Each patient was examined before the start of the treatment course (day 0); 45 days after the start of treatment (day 45); and at the end of the course - 90 days after the start of treatment (day 90).

Principles of Prospective Dynamic Physi-
The results of the cal, instrumental, psychoneurological, and neuropsychological examinations are presented in **Table 1.**

The drug was administered orally, in two doses (morning and afternoon), 15-30 minutes after meals, based on a daily dose of 30-50 mg/kg of the child's body weight. From the 1st to the 7th day, the drug dose was gradually increased, and from the 84th to the 90th day, it was gradually discontinued (in the first and last weeks of the patient's participation in the program) **(Table** 2).

Children with cerebral palsy included in groups 2A and 2B (comparison groups) were allowed to continue previously prescribed procedures and take symptomatic medication.

Table 1. **Scheme of dynamic examination of children with cerebral palsy and the assessment methods used**

Method of assessing the condition of patients	Day 0	Day 45	Day 90
Evaluation of compliance with inclusion/exclusion criteria Physical	+	—	—
examination (including measurement of respiratory rate, blood pressure, heart rate) Neurological	+	+	+
status examination Anxiety test (R. Temple, V.	+	+	+
Amen, M. Dorki) Toulouse-Pieron test Luria test for	+	+	+
memorizing 10 words	++ +		
and their reproduction, including delayed Memory for images test Encryption subtest Registration	+	+	+
of concomitant therapy	++ +		
Dispensing the drug Return	++ +		
of the drug and compliance assessment	+	+	+
Safety assessment	++ —		
	—	+	+
	—+ +		

Table 2. **Dosage regimen of the drug**

Age, years	Duration of patient participation in the study		
	Days 1-7	Days 8-83	84-90 days
8-10	500 mg+250 mg	500 mg+500 mg	500 mg+250 mg
11-14	500 mg+500 mg	1000 mg+500 mg	500 mg+500 mg

therapy (basic therapy) without the inclusion of nootropic drugs and metabolic agents.

Results and discussion

The number of children with the number of correctly reproduced words according to the Luria test was significantly higher in the group receiving the drug pantocalcin at visit 2 in the 2nd and 3rd attempts and at visit 3 in the 1st attempt and delayed reproduction **(Table** 3).

Comparative analysis of the number of patients with normalization of the number of words reproduced in different attempts according to the Luria test showed the absence of statistically significant intergroup differences before and 45 days after the start of therapy. Statistically significant intergroup differences were recorded on the 90th day during the assessment of delayed reproduction, when the proportion of children who reproduced the number of words corresponding to the norm was statistically significantly higher in the group receiving pantocalcin than in the comparison group (19.05% versus 2.04%; p=0.031) **(Table** 4).

The mean value of the sum of words reproduced from the 1st to the 5th attempt before the start of therapy did not differ statistically significantly in the compared groups. After 45 days of therapy, children receiving pantocalcin reproduced a statistically significantly greater number of words compared to children from the comparison group (p=0.048) **(Table** 5).

When assessing the normalization of visual memory using the “image memory” test (reproduction of 6 or more images) in the group treated with pantocalcin, the proportion of children with normal visual memory function at visits 2 and 3 was statistically higher compared to that in the group of children who received only basic therapy (p<0.001) **(Table** 6).

When assessing the speed of performing the Toulouse-Pieron test, the proportion of patients with normalization of the speed of performing the test in the compared groups in the dynamics of observation

Table 3. **Distribution of patients by the number of words reproduced in the Luria test (in %)**

Group 1 (n=50) versus Group 2 (n=50) *p*	
Visit 1	
Attempt 1	0,600
Attempt 2	0.322
Attempt 3	0,650
Attempt 4	0.247
Attempt 5	0.916
Delayed playback	0.418
Visit 2	
Attempt 1	0.310
Attempt 2	0,018
Attempt 3	0.044
Attempt 4	0.401
Attempt 5	0.307
Delayed Play Visit 3	0.319
Attempt 1	0.046
Attempt 2	0.197
Attempt 3	0.249
Attempt 4	0.194
Attempt 5	0.47
Delayed playback	0.03

the results did not differ statistically significantly regardless of from the age of the subjects (children aged 8-14 years). When assessing the distribution of patients by the accuracy of this test in the age group of 8-10 years, statistically significant intergroup differences were revealed at visit 3. The number of children with impaired test accuracy was statistically significantly lower in the group treated with pantocalcin compared to that in the group of children who received only basic therapy (64% versus 92%; p=0.024).

Table 4. **Number of patients with normalization of the number of words reproduced* according to the Luria test (50 patients in each group)**

Number of visits and attempts	1st group (pantocalcin), *n* (%)	2nd group (comparisons), *n* (%)	*p*
Visit 1			
Attempts 1-5	6 (12.0)	6 (12.0)	1,000
By the 3rd attempt	1 (2.0)	3 (6.0)	0.617
Delayed Play Visit 2	1 (2.0)	3 (6.0)	0.617
Attempts 1-5	5 (10.0)	10 (20.0)	0.171
By the 3rd attempt	0 (—)	1 (2.0)	0.495
Delayed Play Visit 3	1 (2.0)	2 (4.0)	1,000
Attempts 1-5	12 (24.0)	9 (18.0)	0.624
By the 3rd attempt	3 (6.0)	2 (4.0)	1,000
Delayed playback	8 (16.0)	1 (2.0)	0.031

Note. * — normalization means the correct reproduction of 9-10 words in at least one attempt.

Table 5. **Average value of the sum of words correctly reproduced from the 1st to the 5th attempt according to the Luria test *(M±SD)***

Visit	1st group (pantocalcin)	2nd group (comparisons)	*p*
1st	24.10±9.21	25.90±8.48	0.221
2nd	26.74±9.53	23.22±6.80	0.048
3rd	26.36±8.43	25.04±8.53	0.268

Table 6. **Number of children with normalized visual memory indicators according to the “memory for images” test (in %)**

Visit	1st group (pantocalcin), *n* (%) 0 (—)	Group 2 (comparisons), *n* (%) 0	*p*
1st	31	(—) 1	1,000
2nd	(62.0) 41	(2.0) 5	<0.001
3rd	(82.0)	(10.0)	<0.001

Note: The normal value is the reproduction of 6 or more images; *n* is the number of patients who reproduced 6 or more images at visit 1; statistical significance *(p)* was assessed using Fisher's exact test.

Normal values for test performance accuracy at visit 3 were recorded in 6 children aged 8–10 years in the pantocalcin group and in none of the children in the basic therapy group **(Table** 7).

Among children aged 11–14 years, the accuracy of the Toulouse-Pieron test at visits 2 and 3 was statistically significantly higher in the group treated with pantocalcin (p<0.001 and p=0.001, respectively), but these differences may be due to the presence of such differences before the start of therapy—at visit 1 (p=0.001). Nevertheless, if during visit 1 in both groups not a single child demonstrated a normal indicator of the accuracy of the Toulouse-Pieron test, then at visit 3 almost half of the children in the group receiving pantocalcin

cin, demonstrated normal test performance accuracy rates (12 people, 48%), whereas in the group receiving basic therapy, only 1 child showed an average level of accuracy **(Table** 8).

An assessment of intergroup differences in the proportions of patients aged 8–14 years according to the level of anxiety (test by R. Temple, V. Amen, M. Dorki) showed a statistically significant predominance of patients with a high level of anxiety in the comparison group at visits 2 and 3 **(Table** 9).

There were no statistically significant differences in the distribution of patients in the scoring of the “coding” subtest at any of the visits (p>0.05),

which indicates that the drug under study is not influenced the degree of acquisition of visual-motor skills.

During the safety assessment of pantocalcin and basic therapy during the study, the following adverse events were identified: short-term weakness - in 1 patient from the group treated with pantocalcin; symptoms of acute respiratory viral infection - in 6 children in the comparison group and in 1 child taking pantocalcin; allergic reaction of unknown etiology - in 1 child in the comparison group; abdominal pain - in 1 patient from the group

comparisons.

None of the adverse events identified was associated with the study drug. No serious adverse events were reported during the study.

Thus, the number of children with the number of correctly reproduced words according to the Luria test was significantly higher in the group treated with pantocalcin during visit 3 when assessing the performance of attempts 2 (p=0.018) and 3 (p=0.044) and during visit 3 when assessing the performance of attempt 1 (p=0.046) and delayed reproduction (p=0.031), which demonstrates an improvement in memory, attention activity and a decrease in fatigue against the background of therapy. When assessing the delayed memorization of words in the group receiving the drug

rat pantocalcin, statistically significant positive

Table 7. **Distribution of patients aged 8–10 years by the accuracy of the Toulouse-Pieron test in the compared groups (in %)**

Accuracy of the Toulouse-Pieron Test Visit 1	1st group (pantocalcin), *n* (%)	2nd group (comparisons), *n* (%)	*p*
Tall	0 (—)	0 (—)	1,000
Good	0 (—)	0 (—)	
Average (norm)	0 (—)	0 (—)	
Weak	4 (16.0)	4 (16.0)	
Pathology	21 (84.0)	21 (84.0)	
Visit 2			
Tall	0 (—)	0 (—)	0.075
Good	0 (—)	0 (—)	
Average (normal)	3 (12.0)	0 (—)	
Weak	5 (20.0)	2 (8.0)	
Pathology	17 (68.0)	23 (92.0)	
Visit 3			
Tall	0 (—)	0 (—)	0.024
Good	0 (—)	0 (—)	
Average (normal)	6 (24.0)	0 (—)	
Weak	3 (12.0)	2 (8.0)	
Pathology	16 (64.0)	23 (92.0)	

Table 8. **Distribution of patients aged 11–14 years by the accuracy of the Toulouse-Pieron test (in %)**

Accuracy of the Toulouse-Pieron test	1st group (pantocalcin), *n* (%)	2nd group (comparisons), *n* (%)	*p*
Visit 1			
Tall	0 (—)	0 (—)	0,001
Good	0 (—)	0 (—)	
Average (norm)	0 (—)	0 (—)	
Weak	13 (52.0)	2 (8.0)	
Pathology	12 (48.0)	23 (92.0)	
Visit 2			
Tall	1 (4.0)	0 (—)	<0.001
Good	2 (8.0)	0 (—)	
Average (normal)	10 (40.0)	1 (4.0)	
Weak	3 (12.0)	0 (—)	
Pathology	9 (36.0)	24 (96.0)	
Visit 3			
Tall	1 (4.0)	0 (—)	0,001
Good	0 (—)	0 (—)	
Average (normal)	11 (44.0)	1 (4.0)	
Weak	4 (16.0)	1 (4.0)	
Pathology	9 (36.0)	23 (92.0)	

Table 9. **Distribution of patients by anxiety level based on testing results (in %)**

Anxiety Level Visit 1	1st group (pantocalcin), *n* (%)	2nd group (comparisons), *n* (%)	*p*
Low	1 (2.0)	0 (—)	
Average	28 (56.0)	21 (42.0)	0.194
Tall	21 (42.0)	29 (58.0)	
Visit 2			
Low	0 (—)	0 (—)	
Medium	30 (60.0)	20 (40.0)	0.046
High	20 (40.0)	30 (60.0)	
Visit 3			
Low	0 (—)	0 (—)	
Average	40 (80.0)	28 (56.0)	0,010
Tall	10 (20.0)	22 (44.0)	

dynamics were observed by visit 3 (90th day of therapy), while in the comparison group no positive effect on delayed/long-term

memory.

In the age group of children aged 8–10 years, by the 90th day of therapy, the proportion of patients with pathology in assessing the accuracy of the Toulouse-Pieron test was statistically significantly lower and the proportion of patients with normalization of the indicators of the accuracy of its implementation was significantly higher.

In the age group of children aged 11-14 years treated with pantocalcin, when assessed on the 45th and 90th days of therapy, there was a statistically significantly lower proportion of patients with pathology when assessing the speed of the Toulouse test.

Pierona, which indicates an improvement in the ability to concentrate in this group.

A statistically significant higher proportion of patients
On the 45th and 90th days of pantocalcin therapy, the patient reproduced a greater number of images in the “image memory” test, which indicated an improvement in visual memory.

Evaluation of intergroup differences in the proportions of patients by anxiety level showed a statistically significant predominance of patients with a high level of anxiety in the comparison group at visits 2 and 3 in children aged 8 to 14 years. However, pantocalcin did not reduce the degree of anxiety

importance in children with high and medium levels to low levels.

During the study, no adverse events were observed.
no adverse reactions associated with taking the study drug were identified.

To sum up, we can say that the results of the conducted study demonstrate reliable positive
the positive effect of the drug pantocalcin, used at a dose of 1000-1500 mg per day (depending on age and body weight) with prolonged use for 3 months in children and adolescents with cerebral palsy on memory, attention activity, fatigue, visual memory and ability

ability to concentrate; the drug also reduces anxiety levels. No evidence has been found

the effect of the drug on the degree of acquisition of visual-motor skills. The data obtained demonstrated a high safety profile of the drug pantocalcin when used in children and adolescents. In the therapeutic group, no adverse events associated with taking the drug were recorded.

The analysis of the obtained data provides convincing evidence of the appropriateness, effectiveness and safety
use of the drug pantocalcin for the purpose of correcting cognitive impairment in children and adolescents with cerebral palsy.

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