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Attention Level and Event-Related Evoked Potentials in Patients with Cerebrovascular Disease Treated with Amantadine Sulfate – a Pilot Study

Poziom uwagi i endogenne potencjały wywołane u chorych z naczyniopochodnym uszkodzeniem mózgu leczonych siarczanem amantadyny – doniesienie wstępne

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Abstract

Background. Amantadine sulfate (AS) modulates glutaminergic transmission within the central nervous system and can thus affect attention level and other cognitive processes.
Objectives. The aim of this study was to evaluate attention level and parameters of auditory event-related potentials (ERPs) in patients with cerebrovascular disease treated with intravenous AS.
Material and Methods. The study group consisted of 15 patients, aged 57–87 years, with multifocal cerebral ischemic lesions. The Trail Making Test (TMT-B) and auditory ERPs (defining parameters of the P300 component) were performed before and five days after intravenous administration of AS. The initial P300 parameters were compared with those obtained in a control group. For the patients, TMT-B and ERP results before and after administration of AS were compared.
Results. Initial TMT-B results were abnormal in 86.6% of the patients. Mean latency of P300 was significantly longer in the patients than in the controls. The TMT-B results improved in 66% of the patients and mean P300 latency decreased significantly after treatment with AS.
Conclusions. AS given intravenously may improve attention level in patients with cerebrovascular disease (**Adv Clin Exp Med 2008, 17, 5, 553–558**).

Key words: cerebrovascular disease, cognitive dysfunction, event-related potentials, amantadine sulfate.

Streszczenie

Wprowadzenie. Siarczan amantadyny (AS) moduluje przekaźnictwo glutaminergiczne w obrębie ośrodkowego układu nerwowego, wpływając w ten sposób na poziom uwagi i inne funkcje poznawcze.
Cel pracy. Ocena poziomu uwagi i parametrów endogennych potencjałów wywołanych (ERP) u pacjentów z naczyniopochodnym uszkodzeniem mózgu, leczonych dożylnie podawanym AS.
Materiał i metody. Badanie objęło 15 chorych, w wieku 57–87 lat, z wieloogniskowym naczyniopochodnym uszkodzeniem mózgu. Przeprowadzono Test Kreślenia Drogi (*Trail Making Test* – TMT-B) oraz badanie słuchowych ERP (z określeniem parametrów potencjału P300); badania powtórzono po 5 dniach podawania chorym dożylnej postaci AS. Wyjściowe parametry P300 porównano z wynikami odpowiedniej wiekowo grupy kontrolnej. W grupie pacjentów porównano wyniki TMT-B i ERP przed i po podaniu AS.
Wyniki. U 86,6% chorych wynik TMT-B był nieprawidłowy. Średnia latencja P300 w grupie chorych była istotnie dłuższa niż w grupie kontrolnej. Po podaniu AS uzyskano poprawę wyników TMT-B u 66% chorych oraz znamienne skrócenie średniej latencji P300.
Wnioski. AS podawany dożylnie może korzystnie wpływać na poziom uwagi i parametry ERP u chorych z naczyniopochodnym uszkodzeniem mózgu (**Adv Clin Exp Med 2008, 17, 5, 553–558**).

Słowa kluczowe: naczyniopochodne uszkodzenie mózgu, zaburzenia funkcji poznawczych, endogenne potencjały wywołane, siarczan amantadyny.

Amantadine sulfate (AS) acts as a dopamine agonist (enhancing dopamine release and receptor density) and non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptors. Because of its ability to modulate glutaminergic transmission (especially in pathological conditions caused by CNS lesions), AS may exhibit neuroprotective activity (preventing excititoxic neuronal damage) and influence processes of awareness and cognition [1, 2]. Positive effects of treatment with AS on clinical outcome were shown mainly in patients after severe traumatic brain injury, especially in the area of improved vigilance, perception, and concentration [3–6]. Use of AS was suggested for states of disturbed consciousness caused by encephalitis, neurodegenerative processes. and cerebrovascular disease [7]. In patients with mild dementia and psychoorganic syndrome, treatment with AS resulted in improvement of disturbed behavior and cognition [8, 9]. A positive influence of AS on verbal fluency was also reported in patients with aphasia caused by focal or diffuse cerebral lesions [10, 11].

The aim of this study was to evaluate attention level and parameters of auditory event-related potentials (ERPs) in patients with cerebrovascular disease treated with intravenous AS.

Material and Methods

The study group consisted of 15 patients (13 men and 2 women, age range: 50–87, mean: 69.9 years) diagnosed with cerebrovascular disease and hospitalized at the Department of Neurology, Silesian Piasts University of Medicine in Wrocław. Three patients had a history of ischemic stroke, but none of them had experienced recent stroke on admission or during the stay in the hospital. On neurological examination, 14 patients presented with signs of upper motor neuron deficit, 6 with extrapyramidal syndrome, 5 with deliberations, 7 with signs of brainstem involvement (4 with oculomotor palsy, 3 with bulbar syndrome), and 3 with cerebellar ataxia. On the basis of neuropsychological assessment (including the Mini Mental State Examination, Auditory Verbal Learning Test, and Clock Drawing Test), mild cognitive impairment was recognized in 13 patients, but none of them met the criteria for a diagnosis of vascular dementia. In computed tomographic (CT) head scans at least two cerebral ischemic lesions (in remote regions) were found in all the patients, in 7 cases accompanied by diffuse ischemic changes in the periventricular white matter (leukoaraiosis). Risk factors for cerebrovascular disease were ascertained in all the patients: hypertension in 9 cases, coronary artery disease in 3, cardiac arrhythmias in 2, diabetes in 4, hyperlipidemia in 4, and smoking in 2. None of the patients had been treated with AS before and none of them were currently being treated with acetylocholinesterase inhibitors or NMDA agonists. In none of the patients were contraindications to the administration of AS found. All the patients gave their informed consent to participate in the study and the study design was approved by the Bioethics Committee at Silesian Piasts University of Medicine in Wrocław.

The patients were given 200 mg of amantadine sulfate intravenously for five consecutive days (total dose: 1000 mg). During this period they were not given any other intravenous medications or solutions. The doses of other medications they received (antihypertensive, anti-arrhythmic, or anticoagulative drugs, antiplatelet agents, insulin) remained unchanged. Attention level was examined using the Trail Making Test part B (TMT-B, source: Reitan Neuropsychology Laboratory, South Tuckson, USA) [12], with the results given in seconds (duration of task performance). Auditory ERPs were performed according to the standard "oddball paradigm", with tones of 70-dB intensity and 200-ms duration: 20% target tones (2 kHz) randomly interspersed among 80% non-target tones (1 kHz). Cerebral responses were recorded from Fz, Cz, and Pz (the 10–20 system), with the reference electrode on linked earlobes and a forearm ground and with the following analysis parameters: bandpass filter 0.30–70 Hz, sweep speed 1000 ms, and pre-stimulus baseline 250 ms. At least 30 target trials were averaged in each run and two runs were performed in every subject. Latency and amplitude of the P300 component were determined. TMT-B and ERPs were performed before the first administration of AS and after administering five doses of AS (on the day following the last dose).

Auditory ERPs were also recorded in 25 controls (10 men, 15 women, age range: 42–74, mean: 56.6 years) with normal CT head scans and without features of cognitive decline.

The mean and median values of the ERP parameters of the controls and the patient group were compared using Wilcoxon's test and adjusted for the effects of age using the analysis of covariance method. Mean and median values for the ERP parameters before and after AS treatment were compared using Wilcoxon's rank test. $p < 0.05$ was regarded as statistically significant.

Results

Initially, TMT-B results were abnormal in 8 patients (prolonged time of performance according to standardized age norms) and 5 were unable to

complete the task (they could not follow the idea of alternately joining letters and numbers and the test was stopped after five minutes). After AS administration, the results improved in 10 subjects, including 3 of those unable to perform the test initially. However, in all these subjects the TMT-B results still exceeded the normal range. In 3 patients the result was worse than initially and 2 were still unable to perform the test (Tab. 1).

The P300 component of ERPs was recorded in 14 subjects; in one patient it could not be identified. The mean latency of P300 in all the references was significantly longer in the patients than in the controls. The difference was still significant after adjusting for the effects of age (Tab. 2). No significant differences in P300 amplitude were found between these groups. After AS administration, the mean latency of P300 in the patients was significantly shorter than initially (Fig. 1). A decrease in mean P300 amplitude was also noted, but only at Cz and Pz and it was on the border of statistical significance (Tab. 3).

Discussion

Patients with multiple or diffuse cerebral ischemic lesions usually develop some cognitive impairment, ranging from mild deficit to dementia. The abnormal results of TMT-B in over 80% of the patients (including the five unable to perform the test) are indicative of disturbed attention

Table 1. TMT-B results in patients with cerebrovascular disease before and after treatment with AS

Tabela 1. Wyniki Testu Kreślenia Drogi (TMT-B) u pacjentów z naczyniopochodnym uszkodzeniem mózgu przed i po leczeniu AS

	Age – years (Wiek – lata)	Gender (Płeć)	TMT-B before treatment with AS (TMT-B przed leczeniem AS) [s]	TMT-B after treatment with AS (TMT-B po leczeniu AS) [s]
1.	80	M	165	121
2.	75	M	222	268
3.	87	F	0	0
4.	65	M	178	141
5.	57	M	285	268
6.	77	M	0	0
7.	66	F	257	125
8.	61	M	151	154
9.	76	M	229	164
10.	66	M	98	91
11.	57	M	0	390
12.	72	M	321	365
13.	78	M	0	395
14.	57	M	260	240
15.	74	M	0	291

Table 2. Comparison of P300 parameters in patients with cerebrovascular disease and controls (after adjusting for the effects of age): lat. – latency, ampl. – amplitude; Fz, Cz, Pz – placement of recording electrodes according to the 10–20 system

Tabela 2. Porównanie parametrów odpowiedzi P300 u pacjentów z naczyniopochodnym uszkodzeniem mózgu i w grupie kontrolnej (po wyeliminowaniu wpływu wieku): lat. – latencja, ampl. – amplituda; Fz, Cz, Pz – pozycja rejestrujących elektrod według systemu 10–20

	Controls (Grupa kontrolna)			Patients (Pacjenci)			*p*
	X	M	SD	X	M	SD	
P300 lat. (Fz)	333.5	334.0	23.6	375.9	381.0	26.8	0.001
P300 ampl. (Fz)	6.06	6.05	3.85	8.47	9.85	5.37	ns.
P300 lat. (Cz)	334.5	338.5	25.7	375.4	377.5	27.2	0.003
P300 ampl. (Cz)	6.66	6.05	3.57	7.97	6.25	5.66	ns.
P300 lat. (Pz)	339.3	341.0	27.0	374.3	375.0	24.1	0.007
P300 ampl. (Pz)	7.11	6.45	3.42	7.71	6.75	4.10	ns.

Table 3. Comparison of P300 parameters in patients with cerebrovascular disease before and after treatment with AS: lat. – latency, ampl. – amplitude; Fz, Cz, Pz – placement of recording electrodes according to the 10–20 system

Tabela 3. Porównanie parametrów odpowiedzi P300 u pacjentów z naczyniopochodnym uszkodzeniem mózgu przed i po podaniu AS: lat. – latencja, ampl. – amplituda; Fz, Cz, Pz – pozycja rejestrujących elektrod według systemu 10–20

	Before treatment (Przed leczeniem)			After treatment (Po leczeniu)			*p*
	X	M	SD	X	M	SD	
P300 lat. (Fz)	375.9	381.0	26.8	374.3	375.0	24.1	0.01
P300 ampl.(Fz)	8.47	9.85	5.37	7.71	6.75	4.10	ns.
P300 lat.(Cz)	375.4	377.5	27.2	358.9	363.0	31.8	0.007
P300 ampl. (Cz)	7.97	6.25	5.66	6.26	5.80	4.49	0.05
P300 lat.(Pz)	374.3	375.0	24.1	358.4	356.5	30.3	0.007
P300 ampl.(Pz)	7.71	6.75	4.10	5.71	4.80	3.00	0.006

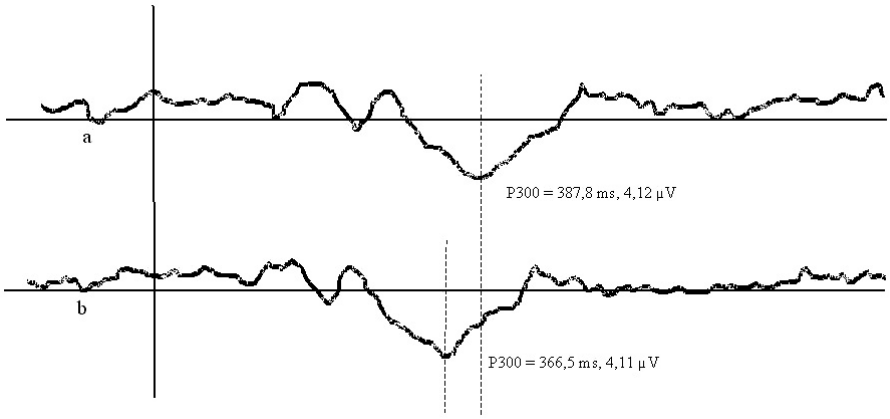

Fig. 1. P300 component of auditory event-related potentials in patients with cerebrovascular disease ("grand averaging" of all the patients' results): (a) before and (b) after treatment with AS

Ryc. 1. Składowa P300 słuchowych endogennych potencjałów wywołanych u chorych z naczyniopochodnym uszkodzeniem mózgu (uśrednienie wyników całej grupy pacjentów): (a) przed podaniem AS, (b) po podaniu AS

and the visuo-spatial aspects of working memory. Prolonged latency of the P300 component corresponds to a slowing of information processing, while a decrease in P300 amplitude is usually associated with deficits in attention. On the other hand, amplitude is regarded as the more unstable and less reliable parameter of P300 [13, 14]. Previous ERP studies [15–18] suggest that in patients with multiple brain infarcts, P300 latency is mainly prolonged, and decreases in amplitude are found much less frequently. However, abnormalities in P300 parameters are rather related to the degree of cognitive deficit and not specific to its particular background.

Gehlen et al. [9] and Jorg [7] reported positive effects of treatment with AS in patients with psychoorganic syndrome and mild dementia of various origin. Arciniegas et al. and Barret et al. [10, 11] described a specific benefit from AS treatment for patients with aphasia. Apart from psychometric scales, electrophysiological methods were also used to assess the effect of AS. Following treatment with AS, increased alpha activity and its better synchronization were noted in electroencephalograms [5, 6]. Using transcranial magnetic stimulation, Reis et al. [19] reported that a single dose of AS modulates the excitability of the motor cortex. AS, as well as another NMDA antagonist, memantine, was found to cause increases in the amplitudes of ERP components [8, 20]. In the patients of the present study, TMT-B performance improved in 2/3 of the patients and mean P300 latency decreased significantly after five days of treatment with i.v. AS. These results suggest a positive effect of AS on attention level and speed of information processing. The trend towards decreased P300 amplitude after AS infusion seems surprising, especially as the initial amplitudes did not differ significantly between the patients and controls. Semlitsch et al. [8] and Steube et al. [6] found quite opposite relationships: an increase in P300 amplitude after AS in patients with mild

dementia and better synchronization of EEG after AS in patients with initial normal background EEG activity.

The learning effect has to be considered when assessing changes in TMT-B and ERP performance, especially as the tests were repeated after a short period of time. However, the positive effect of AS described by the majority of the mentioned studies [10, 11, 19, 20] was achieved after a single dose or short-term treatment. Arciniegas et al. [11] suggested that improvement in cognitive parameters persisted only during treatment with AS, with their worsening while the medication was tapered. A scheme of short-term administration of intravenous AS followed by long-term use of the oral agent should perhaps be considered to maintain the beneficial effects of treatment.

In patients with multifocal cerebral vascular lesions, the level of attention assessed by TMT-B improved after a short period of treatment with intravenous AS. In the majority of patients, treatment with AS also resulted in decreased latency of the P300 component of ERPs, suggesting improved speed of information processing. The potentially positive effects of AS in patients with cerebrovascular disease deserve attention and encourage further studies in this field.

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