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Effect of Sodium Valproate on Somatosensory Evoked Potentials in Juvenile Myoclonic Epilepsy

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ABSTRACT

We analysed somatosensory evoked potentials (SEPs) in the patients with juvenile myoclonic epilepsy (JME) in order to find out if sodium valproate (VPA) affects SEP latencies and amplitudes.

SEPs were studied in 23 patients with JME receiving VPA monotherapy, eight patients with JME not receiving VPA, and a control group consisting of 20 healthy subjects.

The N20, P24, and N34 latencies bilaterally were significantly prolonged in the JME group receiving VPA as compared with the control group. In the untreated patients the P24, and N34 latencies bilaterally and the N20–P24 interpeak latency on the right, were significantly prolonged as compared with the control group. In addition, in the patient group without treatment, the N20–P24 amplitudes bilaterally and the P24–N34 amplitudes from left sided median nerve stimulation, were greater as compared with the control group.

In the SEP latencies, no significant differences were observed between the patients treated and untreated with VPA. Regarding SEP amplitudes, in the untreated group, while the N20–P24 amplitudes from right sided median nerve stimulation were significantly enhanced, all the other amplitudes also showed increase, even insignificant, as compared with the patients treated by VPA.

These findings suggest that the SEPs latencies are prolonged, and the amplitudes are enhanced in JME. The changes of the SEPs latency in JME could be due to abnormal synaptic transmission and not influenced by VPA. On the other hand, the increase of the amplitude tends to be lowered by VPA.

INTRODUCTION

Multimodal evoked potentials in human epilepsy have revealed enhanced amplitudes as well as prolonged peak latencies [3, 10, 15]. In certain types of myoclonus and epilepsy, a striking abnormality of the SEP is its pathological enlargement [18]. It is reported that cortical components of SEPs are of remarkably high amplitude in patients with progressive myoclonic epilepsy (PME) [6, 20].

Prolonged evoked potential peak latencies indicating slowed neural conduction are usually due to structural damage (e.g., demyelination). There is increasing evi-

dence that disorders associated with abnormal synaptic transmission also produce evoked potential changes [15].

Although previous studies suggest that evoked potential latency prolongation is primarily due to epilepsy itself, the effects of antiepileptic drugs (AEDs) must be taken into account [15]. Evoked potentials have been used in the assessment of the effects of AEDs on central neural conduction [4, 7, 8, 9].

For these reasons, we analysed SEP in the groups of JME patients treated and untreated with VPA, and in a control group. We aimed to investigate if there was any change in SEPs latencies and amplitudes in the JME patients and if VPA had any influence on SEPs.

MATERIALS AND METHODS

Subjects

This study in case-control type was carried out in 31 patients with JME and in 20 healthy subjects at the Neurology Department, Medical Faculty, Ankara University, from October 1995 to July 1996. There were 23 patients with JME receiving VPA treatment (group 1), eight patients without any antiepileptic drug (group 2) and 20 healthy subjects (group 3). Neurological examination showed no abnormal signs in the research group.

Group 1 consisted of 9 males and 14 females, with a mean age of 23.0 ± 6.9 years (range 15–38) and average treatment duration of 17.4 ± 16.6 months. Group 2 consisted of one male and 7 females, with a mean age of 19.6 ± 3.9 years (range 16–27). Group 3 was composed of 20 healthy subjects, 5 males and 15 females, with a mean age of 22.4 ± 3.6 years (range 18–31). They had no neurological symptoms or findings in order to be included in the control group.

Testing procedure

SEP recordings were performed in a quiet semidarkened room. The subjects were in a supine position. SEPs were acquired with an electromyography machine, Neuromatic DISA 2000. SEPs were elicited by unilateral percutaneous electrical stimulation of the median nerve at both wrists with a current strength just sufficient to produce a threshold muscular twitch of the abductor pollicis brevis muscle. Constant current square wave pulses of 0.2 ms duration were delivered with a stimulus frequency of 2 Hz. SEPs were recorded with platinum needle electrodes placed 2 cm posterior to C3 and C4, respectively, referred to as Fpz. The filter was arranged as 2–1000 Hz, the sensitivity as 10 mV/division and sweep time as 10 ms/division. The averaging process was carried out at least twice in each measurement, and 400 responses were averaged in order to see the reproducibility of the potentials. The N20, P24, and N34 latencies, the N20–P24 interval, and the N20–P24, P24–N34 amplitudes were analysed. Statistical analysis of data was on a PC computer with the SPSS/PC v.5.01 software using the Mann-Whitney U test and the Kruskal-Wallis One Way Anova test.

For comparison, in the three groups, the Kruskal-Wallis One Way Anova test and in two groups the Mann-Whitney U test were used.

RESULTS

The mean values of N20, P24, and N34 peak latencies, N20–P24 interpeak latency, N20–P24, and P24–N34, interpeak amplitudes in the research group are summarised in table 1. In the same table p values are given obtained by the Kruskal-Wallis One Way Anova test in the three groups. Table 2 shows the results of the Mann-Whitney U test comparing two groups. The N20, P24, and N34 latencies bilaterally were significantly prolonged in the JME group on medication as compared with the control group.

The P24, and N34 latencies bilaterally, and the N20–P24 interpeak latency on the right side were significantly prolonged in the untreated JME patients as compared with the controls. In addition, N20–P24 amplitude bilaterally, and the P24–N34 amplitude from left sided median nerve stimulation were greater in this latter group as compared with the control group.

Eight patients with JME (five on VPA and three untreated) had giant SEP amplitudes (one or both of N20–P24, and P24–N34), meaning an amplitude value > 3 SD above the average value of the control group.

In the untreated JME patients, the N20–P24 amplitude obtaining right sided median nerve stimulation was significantly higher than that of the JME patients treated with VPA ($P < 0.008$), and all the other amplitudes were higher in the untreated patients' group than the treated patients' group.

There was no difference in the latency between treated and untreated groups.

Table 1. The Average Latency and Amplitude Values of Research Group and p Values.

Variable	Patients treated with	Patients without treatment	Control	p-values
Latency (ms)	Mean ± SD	Mean ± SD	Mean ± SD	
Right				
N20	17.6 ± 1.2	17.0 ± 1.1	16.4 ± 1.2	0.003*
P24	23.2 ± 2.0	23.8 ± 1.5	20.8 ± 2.7	0.000*
N34	30.5 ± 3.9	31.2 ± 3.7	25.2 ± 4.5	0.001*
N20–P24	5.7 ± 2.1	6.8 ± 1.8	4.4 ± 2.4	0.007*
Left				
N20	17.9 ± 1.7	16.6 ± 0.9	16.1 ± 0.9	0.000*
P24	23.9 ± 3.3	22.8 ± 2.4	21.0 ± 3.0	0.003*
N34	31.6 ± 3.5	31.4 ± 2.7	26.1 ± 4.3	0.000*
N20–P24	6.1 ± 2.7	6.3 ± 2.3	4.9 ± 2.4	0.135
Amplitude (μV)				
Right				
N20–P24	6.9 ± 3.5	10.5 ± 2.5	5.4 ± 1.9	0.001*
P24–N34	4.6 ± 4.6	6.9 ± 5.6	2.9 ± 2.2	0.076
Left				
N20–P24	6.1 ± 3.0	9.6 ± 3.9	5.8 ± 1.9	0.033*
P24–N34	5.5 ± 4.3	8.1 ± 7.3	2.9 ± 2.4	0.024*

* $p < 0.05$: Significant differences in three groups
p values obtained by Kruskal-Wallis One Way Anova test.

DISCUSSION

According to our knowledge, SEP in JME was first studied by Salas-Puig et al. [19] in 1992. They compared patients with JME and patients with idiopathic generalised epilepsy (IGE) with a control group of healthy subjects. The patients with IGE had a prolonged N19–P25 interval as compared with both the control and JME groups [19]. Because the IGE and JME groups belong to primary generalised epilepsy, probably with a common epileptogenic mechanism, the cause of the differences in this interval was explained by the use of AEDs. According to previous studies, VPA does not produce any changes in SEP latency [12, 15, 19], whereas phenytoin (PHT) produces a prolongation of the SEP latencies [4, 19]. It was therefore suggested that the prolonged N19–P25 interval in the IGE patients might be explained by the treatment with PHT.

We found that the N20–P24 interval was significantly prolonged in the untreated JME patients and insignificantly prolonged in the treated JME patients as compared with the control group. This finding suggests that there may be a synaptic delay in the thalamocortical pathways in JME. VPA seemed to have no effect on the N20–P24 interval since there was no difference between treated and untreated patients.

Broughton et al. [1] noted significantly shortened SEP latencies of components N19 and P22, prolonged latencies of later components and enhanced SEP amplitudes in patients with photosensitive seizures. Mervaala et al. [14] on the other hand,

Table 2. p Values in Mann-Whitney U Test.

Variable	Group 1–3 P	Group 1–2 P	Group 2–3 P
Latency (ms)			
Right			
N20	0.001*	0.21	0.09
P24	0.0002*	0.39	0.0001*
N34	0.001*	0.76	0.003*
N20–P24	0.002	0.25	0.003*
Left			
N20	<0.0001*	0.02	0.17
P24	0.002*	0.45	0.012*
N34	0.0001*	0.72	0.004*
N20–P24	0.18	0.87	0.023
Amplitude (μV)			
Right			
N20–P24	0.22	0.008*	0.0001*
P24–N34	0.29	0.13	0.03
Left			
N20–P24	0.84	0.02	0.012*
P24–N34	0.06	0.42	0.01*

* $p < 0.017$: Significant differences in two groups.
p values obtained by Mann-Whitney U test

found the P22 component latency to be significantly prolonged and N19 and N30 components not to differ significantly in the patients with primary generalised seizures from the healthy subjects. The divergent results may be due to differences in methodology. The early component latencies are correlated to the height of the subject, which must be taken into consideration.

In our study, the N20 latency bilaterally was significantly prolonged in patients with JME receiving VPA treatment (group 1), as compared with the control group. Since it is believed that the N20 component reflects short-latency thalamocortical activation of area 3b in the posterior bank of the rolandic fissure, this finding suggested moderate slowing of the impulse conduction in the thalamocortical pathways in JME, as in PME. Although no difference was found between the patients not receiving any AED (group 2) and healthy subjects (group 3) in N20 latency, and since there was no difference between the patients receiving VPA (group 1) and the patients without treatment (group 2), the reason for a prolonged N20 latency is probably not due to any drug effect. In addition the longest N20 latencies were obtained in the group 1 subjects, and group 1 had the largest percentage of male subjects. This finding might also be due to the fact that males tend to have longer arm lengths than females, on average. It might have been better to measure P14 or even N9 latencies and calculate conduction times from these to the cortical peaks. Because all subjects had a normal neurological examination, the measurement of these parameters was excluded.

In this study the P24 latency was significantly prolonged in both patient groups as compared with the healthy subjects. It is known that this component is generated at least in part by motor area 4, which receives direct thalamocortical projections. Therefore, this points out that there is an affection in the thalamocortical pathway in JME. Mervaala et al. [16] demonstrated that the latencies of the SEP N19 and P22 were significantly prolonged in ambulatory PME patients and severely affected PME patients, and the N30 component was prolonged in severely affected PME patients. In PME, the latencies of the SEP components show a mild slowing of the impulse conduction in peripheral and spinal sensory pathways, and a marked slowing in the impulse conduction between the thalamus and the somatosensory cortex. The mean slowing correlated to the clinical stage of PME. Severely affected PME patients showed more slowing of conduction compared to ambulatory PME patients with less severe clinical symptoms [16].

In our study the JME patients had significantly prolonged late latencies beside early latencies as compared with healthy subjects. The N34 latency was prolonged in both treated and untreated JME patients. This was probably due to a slowing of central impulse conduction in patients with JME as in patients with PME as shown by Mervaala et al. [16], because the N30 wave was probably generated in the supplementary motor area. We also found some changes in SEPs amplitudes in the JME patients. The N20–P24 amplitudes bilaterally and the P24–N34 interpeak amplitudes from left sided median nerve stimulation were greater in untreated patients as compared with the control group. Studies of SEP amplitudes have primarily centred around PME, habitually detecting P25 and N33 responses of high amplitude [6, 16, 19]. Mervaala et al. [16] reported that the SEP amplitude grew in the early stages of

the disease, but diminished again, even to a subnormal level, as the disease progressed. These findings suggested a marked affection of the central sensory conduction in PME. The giant SEP was shown to be characteristic of "pyramidal" myoclonus by Halliday [6] and of "cortical reflex" myoclonus by Chadwick et al. [2] and Hallett et al. [5]. It was postulated that the giant SEP was generated, at least in part, by common physiological mechanisms to the myoclonus-related cortical spike, or that the latter may comprise a constituent of the former [11, 20].

In JME the large N20–P25 amplitude was first reported by Salas-Puig et al. In that study SEP was analysed in 35 patients with JME and in 26 patients with IGE; the P25 amplitude of the SEP was significantly higher in JME. In 5 patients with JME (14%), giant SEPs meaning an amplitude value > 3 SD above the average value of the healthy subjects were observed [19]. Our eight patients with JME (five on VPA and three untreated) had giant SEP amplitudes (one or both of the N20–P24 and P24–N34 amplitudes) that was over three times the standard deviation of the average in normal (approximately 10 μV). In the untreated JME patients the N20–P24 amplitude obtaining right sided median nerve stimulation was significantly higher than that of JME patients treated with VPA ($P < 0.008$).Although significant differences in SEP latencies and amplitudes were not observed comparing the treated and untreated patients, except the N20–P24 amplitude on the right side; the amplitudes were higher in the untreated JME patients than those of the treated patients.

The present results are is partially compatible with those of previous reports [12, 13]. Kubota et al. [13] observed that the P25–N33 amplitude in patients on VPA medication tended to be lower than in patients on other drugs, but there was no data on untreated patients [12, 13]. Kanazawa and Nagafuji [12] reported that N20–P25 amplitudes lowered after complete seizure control by valproic acid treatment in two patients.

In JME some changes occurred in latency of SEP, suggesting a delay in the thalamocortical pathway and the central conduction. There were no significant differences in the latency between JME patients receiving VPA and untreated patients. It is therefore suggested that VPA has no effect on SEP latencies.

On the other hand, VPA tend to lower the SEP amplitudes in JME patients. It was suggested that a disturbance at the level of the inhibitory cortical interneurons, or in the inhibitory mechanisms of the subcortical structures was a possible reason of the enhanced amplitudes in JME [17, 18, 19].

VPA probably tends to lower slightly higher cortical excitability before treatment in JME patients [12]. The effect of the valproic acids on the SEP amplitudes in JME patients could reveal new aspects of the disease and its pathophysiology. This may also become an indicator to control the seizures in JME patients.

REFERENCES

1. Broughton, R., Meier-Ewert, K. H. & Ebe, M.: Visual, somatosensory and retinal potentials in photosensitive epilepsy. Electroencephalogr Clin Neurophysiol 27:373–386, 1969.
2. Chadwick, D., Hallett, M., Harris, R., Jenner, P., Reynolds, E. H. & Marsden, C. D.: Clinical, biochemical and physiological features distinguishing myoclonus responsive to 5-hydroxytryptophan, tryptophan, with a monoamine oxidase inhibitor, and clonazepam. Brain 100:455–487, 1977.
3. Chiappa, K. H. & Ropper, A. H.: Evoked potentials in clinical medicine. N Engl J Med 306:1205–1211, 1982.

4. Green, J. B., Walcoff, M. & Lucke, J. F.: Phenytoin prolongs far-field somatosensory and auditory evoked potential interpeak latencies. Neurology 32:85–88, 1982.
5. Hallett, M., Chadwick, D. & Marsden, C. D.: Cortical reflex myoclonus. Neurology 29:1107–1125, 1979.
6. Halliday, A. M.: The electrophysiological study of myoclonus in man. Brain 90:241–284, 1967.
7. Hammond, E. J.& Wilder, B. J.: Effect of gamma-vinyl GABA on human pattern evoked visual potentials. Neurology 35:1801–1803, 1985.
8. Harding, G. F. A., Alford, C. A. & Powell, T. E.: The effect of sodium valproate on sleep, reaction times, and visual evoked potentials in normal subjects. Epilepsia 26:597–601, 1985.
9. Hirose, G., Kitagawa, Y., Chujo T., Oda, R., Kataoka, S. & Takado, M.: Acute effects of phenytoin on brainstem auditory evoked potentials: clinical and experimental study. Neurology 36:1521–1524, 1986.
10. Hughes, J. R.: A review of the auditory system and its evoked potentials. Amer J EEG Technol 25:115–158, 1985.
11. Kakigi, R. & Shibasaki, H.: Generator mechanisms of giant somatosensory evoked potentials in cortical reflex myoclonus. Brain 110:1359–1373, 1987.
12. Kanazawa, O. & Nagafuji, H.: Valproate lowered the amplitude of visual and somatosensory evoked potentials in two cases of untreated juvenile myoclonic epilepsy. Psych Clin Neuroscien 51:425–429, 1997.
13. Kubota, H., Watanabe, H., Fijiwara, T., Yagi, K. & Seino, M.: On the somatosensory evoked potentials in the patient of juvenile myoclonic epilepsy. Jpn J EEG EMG 23:186, 1995.
14. Mervaala, E., Keranen, T., Penttila, M., Partanen, J. V. & Riekkinen, P.: Pattern-reversal VEP and cortical SEP latency prolongations in epilepsy. Epilepsia 26:441–445, 1985.
15. Mervaala, E., Keranen, T., Tiihonen, P. & Riekkinen, P.: The effects of carbamazepine and sodium valproate on SEPs and BAEPs. Electroencephalogr Clin Neurophysiol 68:475–478, 1987.
16. Mervaala, E., Partanen, J. V., Keranen, T., Penttila, M. & Riekkinen P.: Prolonged cortical somatosensory evoked potential latencies in progressive myoclonus epilepsy. J Neurol Sci 64:131–135, 1984.
17. Obeso, J. A., Artieda, J., Luquin, M. R. Vaamonde, J. & Martinez Lage, J.M.: Antimyoclonic action of piracetam. Clin Neuropharmacol 9:58–64, 1986.
18. Rothwell, J. C., Obeso, J. A. & Marsden, C. D.: On the significance of giant somatosensory evoked potentials in cortical myoclonus. J Neurol Neurosurg Psychiatry 47:33–42, 1984.
19. Salas-Puig, J., Tunon, A., Diaz, M. & Lahoz, C. H.: Somatosensory evoked potentials in juvenile myoclonic epilepsy. Epilepsia 33:527–530, 1992.
20. Shibasaki, H., Yamasita, Y., Neshige, R., Tobimatsu, S. & Fukui R.: Pathogenesis of giant somatosensory evoked potentials in progressive myoclonic epilepsy. Brain 108:225–240, 1985.

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