The effects of valproic acid and carbamazepine on strength-duration properties of peripheral nerve

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ABSTRACT

الأهداف: دراسة خصائص القوة والمدة للمحاور الحسية والحركية وتقييم فيما إن كان هنالك تغير في الوقت الحالي من خلال قنوات الصوديوم المستمرة للمحاور الحسية والحركية في الأعصاب المحيطية لمرضى الصرع قبل وبعد استخدام حمض فالبرويك وعلاج كاربامازيبين وذلك لوجود قنوات مماثلة في الجهاز العصبي المركزي والمحيطي.

الطريقة: أجريت هذه الدراسة في جامعة باسكنت، كلية الطب، أضنة، تركيا خلال الفترة من يناير 2011م حتى فبراير 2012م، اشتملت الدراسة على 10 مرضى بصرع جزئي و 10 مرضى بصرع معمم ابتدائي لم يتم وصف علاج مضاد لهم حالياً و 10 مرضى من مجموعة الشاهد. استخدمت الدراسة الجهاز الكهربائي. أجري اختبار كثافة التحفيز لإنتاج الهدف (40% حد أقصى) من امكانات عمل العضلات الحركية و الحسية. تحتاج الحالية إلى انتاج مدة تأثير مختلفة 0.05، و0.1، و0.2، و0.3 و0.5 و 1 متر/ دقيقة. تم عمل منحنيات التحفيز والإستجابة من هذه البيانات وعمل وقت مدة القوة الثابتة باستخدام معادلة ويسيس.

النتائج: أشارت نتائج الدراسة إلى انخفاض الاستثارة المحورية في الجهاز العصبي المحيطي في مجموعة الشاهد أكثر من مرضى الصرع وانخفاضه كذلك بعد استخدام عقار فالبرويك و كاربامازيبين.

خاتمة: حذرت نتائج الدراسة إلى احتمالية فحص دور القناة الأيونية في الجسم الحي عن طريق تقييم خصائص الوقت والقوة المحورية في عدة مسارات أو العلاج الدوائي.

Objective: To study strength-duration properties of motor and sensory axons to evaluate whether there is a change in current through the persistent sodium (Na+) channels of sensory and motor axons in peripheral nerves of epileptic patients before and after valproic acid (VPA) and carbamazepine (CBZ) treatment due to the presence of similar channels in the CNS and peripheral nervous system (PNS).

Methods: This study, conducted in Baskent University Faculty of Medicine, Adana, Turkey from January 2011 to February 2012, involved 10 patients with partial epilepsy, 10 patients with primary generalized epilepsy who were not currently prescribed anticonvulsant therapy, and 10 control subjects. Using an electromyography machine, stimulus intensity was performed to produce the target (40% of maximum) compound muscle action potentials and compound sensory action potentials. The currents required for different stimulus durations, 0.05, 0.1, 0.2, 0.3, 0.5, and 1 ms, were produced. Stimulus-response curves were then constructed, and the strength-duration time constants were estimated using Weiss's formula.

Results: The rheobase of motor and sensory fibres was lower in the control group than the values of patients before and after CBZ and VPA therapy.

Conclusions: In the PNS of epileptic patients, CBZ and VPA therapy results in decreased axonal excitability. This method may be used in investigating the underlying pathology of peripheral nerve diseases in vivo.

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Nerve excitability measurements are carried out to investigate biophysical properties and disturbances of impulse conduction in peripheral axons in human subjects.[1,2] A classic measure of neural excitability is the strength-duration curve, which is the variation in stimulus intensity needed to achieve the same evoked response at various stimulus durations. The strength-duration properties of an axon are the rheobase and

the strength-duration time constant (SDTC). The rheobase is defined as the minimum current intensity needed to obtain excitation with a stimulus of infinite duration. The SDTC, defined as the stimulus duration needed to obtain excitation with a current intensity twice the rheobase, is a measure of the rate at which the threshold current for a target potential decline as stimulus duration is increased. In the formulation of Weiss, it equates to chronaxie, and essentially reflects the capacitive membrane properties.[3,4] Both variables functionally reflect the nodal membrane, and are influenced by changes in membrane potential, impedance, capacitance, and area of axonal membrane devoid of myelin.[5,6] Although, theoretically, several factors can affect the time constant of the strength-duration curve, its measurement provides an indirect estimate of the persistent Na+ conductances of the axonal membrane at the node.[7,8] A broad range of antiepileptic drugs can block the persistent Na+ current at therapeutically relevant doses. Valproic acid (VPA) has been shown to reduce the persistent Na+ currents in neocortical neurons.[9] The results of studies in HEK293 cells suggest that one of the antiepileptic properties of carbamazepine (CBZ) is the blocking of persistent Na+ currents.[10] In this study, we aimed to study the strength-duration properties of motor and sensory axons to evaluate whether there is a change in the current through the persistent Na+ channels of sensory and motor axons in peripheral nerves of epileptic patients before and after VPA and CBZ treatment due to the presence of similar channels in the peripheral nervous system (PNS).

Methods. This study was conducted in Baskent University Faculty of Medicine, Adana, Turkey from January 2011 to February 2012. We obtained a letter from our institute indicating no objection to conduct the study, which was carried out according to the principles of the Helsinki Declaration. The study involved 10 patients (5 women and 5 men with a mean age of 22±11.9 years) with primary generalized epilepsy, and 10 patients (4 women and 6 men with a mean age of 27.2±10.6 years) with partial epilepsy. Epilepsy type was determined according to the guidelines of the International League Against Epilepsy, and based on detailed histories obtained from the patients and/or witnesses, physical and neurological examinations, electroencephalographies, and neuroradiological findings.[11] In the primary generalized epilepsy group, in 6 of the patients, the duration of seizures was 4.3±3 years and the frequency was 2 per month; in 4 of them, the seizures had newly started. In the partial epilepsy group, in 7 of the patients, the duration of seizures was 9.3 ± 9.4 years and the frequency was 3 per week; in 3 of them, the duration of seizures was 7 ± 7.8 weeks and the total seizures they had experienced were 1-2 seizures. Patients who were currently prescribed anticonvulsant therapy (which could have confounding effects on axonal excitability) were excluded. Eighteen of the patients had not been treated with anticonvulsant drugs before, and 2 of them had been prescribed anticonvulsant therapy previously, but had not taken these drugs for at least 2 years. The reasons for the patients' delayed presentation to a physician were documented as low socioeconomic status, and the patients' and their families' dissaffirmation of the disease due to sociocultural factors. One patient had a history of febrile convulsion, and the rest of the patients had no history as an etiological factor. The neurological examination was normal in all subjects, and none had intellectual disability. All patients and controls had normal values in routine laboratory serum testing, which included hematocrit, glucose, vitamin B12, and folic acid levels, mean corpuscular volume, and renal, hepatic, and thyroid function tests. One patient had hippocampal sclerosis on cerebral MRI; the others had normal findings. All patients were studied during a seizure-free period for at least 24 hours before the recordings, and none of them reported seizures during the recording periods. Medical history and physical and neurological examinations were performed by the same neurologist. The control group included 10 healthy volunteers (5 women and 5 men with a mean age of 25.5 ± 9.4 years). The groups were well matched with respect to age and gender. There were no statistical differences in respect to age and gender among control and patients groups. Patients and controls with other systemic or metabolic diseases (diabetes mellitus, nephropathy, dysparaproteinemia, cancer, AIDS, entrapment syndromes, and other neuropathies and causes known to damage to the peripheral nerves) were excluded.

The study used an electromyography machine with the filter settings for the low frequency at 10 hertz (Hz) and for the high frequency at 3 kilohertz (kHz). Sampling time was set to 100 microseconds (μs), and channel sensitivity was set at 1 to 5 millivolt (mV) division for

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motor nerve conduction study. For the sensory nerve conduction study, filter settings for the low frequency were set to 20 Hz and for the high frequency they were set to 3 kHz. In all subjects, left ulnar motor and sensory conduction studies were carried out. Compound muscle action potentials (CMAPs) were recorded from the left hypothenar muscles using bipolar surface electrodes over the abductor digiti minimus by stimulating the ulnar nerve at the wrist. The antidromic compound sensory action potentials (CSAPs) were recorded from the fifth finger by ring electrodes set 3 cm apart around the proximal phalanx by stimulating the ulnar nerve at the wrist. Skin temperature was monitored close to the stimulation site, and kept at >32^{0}C by placing a blanket over the palm and using radiant heat if necessary. The amplitude of the CMAP was measured from peak to peak; CSAP baseline to peak, and the target CMAP and CSAP were set to 40% of the maximal response. The 0.2-ms peak response was used to set the target submaximal response (40% of maximum) and the current required to produce the target response was determined for different stimulus durations, 0.05, 0.1, 0.2, 0.3, 0.5, and 1 ms. The adjustment of stimulus intensity to produce the target CMAP and CSAP were performed manually. This generally took 4-5 stimuli before the target CMAP and CSAP (40% of maximum) were recorded. Stimulus-response curves were then constructed (**Figure 1A**) and the SDTCs were estimated using Weiss's formula.[4] The relation between stimulus duration and stimulus charge (obtained by multiplying stimulus strength by stimulus duration) was linear (**Figure 1B**). From the regression equation for this linear relation, the SDTC was calculated.[12] The SDTC of motor and sensory fibers of the ulnar nerve is given by the intercept of the regression line on the X-axis. The rheobasic threshold for axons contributing to the 40% CMAP and CSAP is given by the slope of the regression line.

All procedures were repeated in patients who were prescribed VPA (Gerot Pharmazeutika GmbH, Vienna, Austria) after 7.4±1.3 months of therapy, and in patients who were prescribed CBZ (Novartis Pharma AG, Basel, Switzerland) after 7.7±1.1 months of therapy. The values of healthy subjects were compared with the values of patients before and after therapy. Also, the patients' values were compared before and after therapy. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 17.0. Categoric variables were summarized as number and percent, continuous variables as mean and standard deviation (if necessary, median and minimum - maximum). Chi-square test was used to compare categoric variables between groups. When continuous variables provided parametric test hypothesis, T-test (Student's t-test) was used to compare patient and control groups. T-test (Paired t-test) was used to compare patients' values before and after therapy in dependent groups, one way ANOVA was used to compare more than 2 groups. After variance analysis, in comparing binary groups, Bonferroni test was used. When continuous variables did not provide a parametric test hypothesis, Mann-Whitney test was used to compare patient and control groups, Wilcoxon Signed-Rank test was used to compare patients' values before and after therapy, and Kruskal-Wallis test was used to compare more than 2 groups. After Kruskal-Wallis test, in comparing binary groups, Mann-Whitney test was used with Bonferroni correction. Quantitative data were presented as means ± standard deviation (± SD). *P*-values less than 0.05 were considered statistically significant.

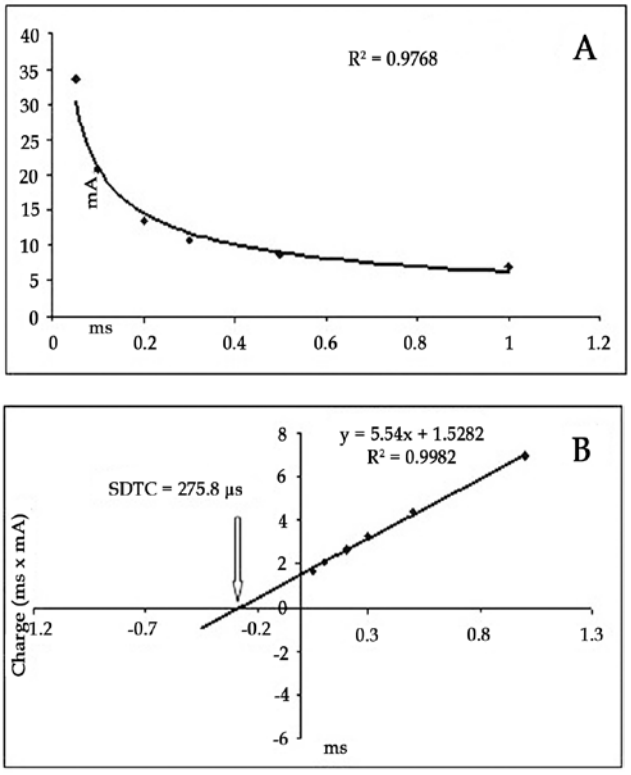

Figure 1 - For a single control subject, the measurement of the strength-duration time constant of motor fibers in 2 panels; **A**) The relationship between stimulus strength (milliampere) and stimulus duration (millisecond) in an example control subject. "R²" refers to the coefficient determined for the motor fibers. **B**) The relationship between stimulus duration and the value achieved by multiplying stimulus duration (charge) for motor fibers. The strength-duration time constant is calculated as follows in this example: When y is accepted as zero, x is found by dividing 1.5282 to 5.54.

Results. Patients were given 777.8±263.5 mg/day VPA for 7.4±1.3 months, and the blood level was 64.5±12 mg/dl on the day of clinical examination. In the VPA group; motor and sensory ulnar nerve conduction velocity studies were normal. There was no statistical difference between the control and patient group before and after therapy, and between values of patients before and after therapy in terms of ulnar nerve conduction velocity studies. The rheobase of motor fibers was lower in the control group than the values of patients before and after VPA therapy (p=0.035, p=0.035). Stimulus strength at 0.1ms of motor fibers was lower in the control group than the values of patients before therapy (p=0.019). Stimulus strength at 1ms of motor fibers was lower in the control group than the values of patients before and after therapy (p=0.029, p=0.052). The SDTCs of sensory fibers were relatively higher, and the rheobase, stimulus strength at 0.1 ms and 1 ms of sensory fibers were relatively lower in the control group than the patient group before and after therapy; however, there was no significant difference. There were no statistical differences in SDTC values of patients before and after therapy (**Table 1**).

Patients were given 700±170 mg/day CBZ for 7.7±1.1 months, and the blood level was 8.3±2.3 mg/dl on the day of clinical examination. In the CBZ group, there was no statistical difference between the control and patient group before therapy in terms of ulnar nerve conduction velocity studies. Motor and sensory distal latencies of the ulnar nerve were lengthened after CBZ therapy (p=0.03, p=0.022), and sensory conduction velocity of the ulnar nerve was slowed (p=0.005). The rheobase of sensory fibers was lower in the control group than the values of patients before and after therapy (p=0.023, p=0.029). Stimulus strength at 0.1 ms and 1 ms of sensory fibers were lower in the control group than the values of patients before therapy (p=0.019, p=0.011). The SDTCs of motor and sensory fibers were relatively higher, and the rheobase, stimulus strength at 0.1 ms and 1 ms of motor fibers were relatively lower in the control group than patient group; however, there was no significant difference. There were no statistical differences in the SDTC values of patients before and after therapy (**Table 2**). Before and after drug therapy, patients underwent a detailed interview including a set

Table 1 - The values of control group, patients before and after Valproic acid (VPA) therapy, and statistical differences.

Variable	Control	Patients before VPA therapy	*P*-value	Control	Patients after VPA therapy	*P*-value
SDTC-M	320±84	323±85	0.853	320±84	322±83	0.971
SDTC-S	418±106	379±106	0.280	418±106	390±97	0.481
Rheobase-M	2.2±0.8	5.4±3.5	0.035	2.2±0.8	3.6±1.7	0.035
Rheobase-S	1.5±0.4	2.7±2	0.218	1.5±0.4	2.7±2.1	0.218
SS at 0.1ms-M	8.9±3.3	20.8±11.7	0.019	8.9±3.3	14±6.7	0.089
SS at 0.1ms-S	7.6±3	12.7±6.9	0.143	7.6±3	9.6±3.5	0.247
SS at 1ms-M	2.8±1	6.9±4.3	0.029	2.8±1	4.6±2.2	0.052
SS at 1ms-S	2.1±0.6	3.7±2.5	0.165	2.1±0.6	2.9±1.3	0.247

SDTC - strength-duration time constant (ms), M - motor, S - sensory, SS at 0.1ms-M - stimulus strength at 0.1 ms of motor fibres, SS at 0.1ms-S - stimulus strength at 0.1 ms of sensory fibres, SS at 1ms-M - stimulus strength at 1 ms of motor fibres, SS at 1ms-S - stimulus strength at 1 ms of sensory fibres (mA)

Table 2 - The values of control group, and patients before and after carbamazepine (CBZ) therapy, and statistical differences.

Variable	Control	Patients before CBZ therapy	*P*-value	Control	Patients after CBZ therapy	*P*-value
SDTC-M	326±83	310±57	0.631	326±83	297±55	0.247
SDTC-S	400±110	358±109	0.315	400±110	371.5±92	0.529
Rheobase-M	2.7±1.5	3.8±1.6	0.105	2.7±1.5	3.8±1.6	0.105
Rheobase-S	1.7±0.7	3.3±2.3	0.023	1.7±0.7	2.4±0.6	0.029
SS at 0.1ms-M	11.4±6.2	15.1±6.6	0.105	11.4±6.2	15.3±8.6	0.218
SS at 0.1ms-S	8.7±3.9	14.2±6.2	0.019	8.7±3.9	11.2±3	0.063
SS at 1ms-M	3.6±2	4.9±2.1	0.075	3.6±2	4.9±2.3	0.105
SS at 1ms-S	2.4±1	4.6±2.6	0.011	2.4±1	3.3±0.7	0.075

SDTC - strength-duration time constant (ms), M - motor, S - sensory, SS at 0.1ms-M - stimulus strength at 0.1 ms of motor fibres, SS at 0.1ms-S - stimulus strength at 0.1 ms of sensory fibres, SS at 1ms-M - stimulus strength at 1 ms of motor fibres, SS at 1ms-S - stimulus strength at 1 ms of sensory fibres (mA)

of screening questions for symptoms of polyneuropathy (muscle cramps, burning feet, muscle pain, limb paresthesia) and neurological examination. They did not have any symptoms or signs of polyneuropathy.

Discussion. Peripheral neuropathy has long been believed to be a complication of antiepileptic drug (AED) treatment, and there are 2 different methods of peripheral nerve impairment associated with AEDs. The first, and best known, is a functional and transient disturbance of nerve function, and the second is a structural lesion of the peripheral nerve, as in chronic peripheral neuropathy.[13] Several retrospective clinical investigations of peripheral neuropathy among patients receiving AEDs documented electrophysiological abnormalities suggesting polyneuropathy in ≤89% of patients.[14] In most of the studies, as most of the patients were receiving polytherapy, multiple AEDs may have been involved. The AED dosage and plasma level did not appear to affect the risk of polyneuropathy in reported studies. Among AEDs, phenytoin is commonly believed to cause peripheral nervous system injury.[13]

The pathophysiology of AED neuropathy is not yet fully understood; however, we may take an account of the mechanism of their anticonvulsant effectiveness. The voltage-gated and ligand-gated ion channels play a fundamental role in the physiology of all forms of epilepsy, so several of these channels represent the critical sites of action for AEDs. There are suggestions such as functional disturbance, and structural lesions of peripheral nerves. It is proposed that electrophysiological abnormalities in patients receiving VPA may reflect a functional impairment, whereas patients receiving CBZ, phenytoin, or phenobarbital may have structural lesions according to the laboratory findings supported by the results of the pathologic investigations.[13]

Both CBZ and VPA have a mechanism of action in common: they modulate the voltage-dependent inactivation of the sodium current.[15] Voltage-gated ion channels not only control excitability in the CNS, but also in the PNS. The Na+ channels have a primary role for the initiation and propagation of action potentials, making them critical determinants of neuronal excitability in both CNS and PNS. Many neurons have 2 types of sodium current: the fast transient Na+ current, and the persistent voltage-dependent Na+ current.[16] The persistent Na+ current plays a role in repetitive firing of action potentials caused by prolonged depolarization.[17] The persistent Na+ current could thus play a role in epilepsy. Furthermore, (aberrant) persistent Na+ currents are demonstrated to be present during epileptic activity.[18] It has also been shown that in subicular neurons of epilepsy patients, the persistent Na+ current is dramatically increased.[19]

In a study by Bono et al,[13] in patients on monotherapy receiving VPA, only peroneal distal latency values were found significantly different from those of controls. The anticonvulsant effectiveness of VPA was suggested to be mainly due to its effect on persistent Na+ current as a result of voltage clamp recordings in acutely dissociated neocortical neurons. Hence, we wondered whether there are axonal excitability changes in the PNS of patients who were prescribed VPA due to the presence of persistent Na+ channels both in the CNS and PNS.

Our results on a small group of patients taking VPA did not show any statistical changes in nerve conduction studies and strength-duration properties of the axonal membrane in the PNS. However, the recorded statistical differences or relative changes in the rheobase and stimulus strength, which are parameters of SDTC, suggested a decrease in axonal excitability in patients before VPA therapy or before and after therapy.

Carbamazepine is a first-line drug in the treatment of most forms of epilepsy. It produces a voltage and frequency-dependent block of Na+ channels, because it binds to the inactivated channels with higher affinity than to channels in the open or resting state.[20] In a study by Danner et al,[21] epileptic outpatients were studied to assess possible effects of the first 6 months of treatment with CBZ using peripheral nerve conduction measurements. Slowed motor conduction value of the median nerve was observed after 6 months of treatment with CBZ, and the effect was correlated with the fasting serum concentration of the drug. In another study by Baldini et al,[22] the hot and cold thresholds were measured at the ankle and wrist, and the thresholds of 12 patients using CBZ were found higher than control subjects.

In our CBZ group, motor, and sensory distal latencies of the ulnar nerve were lengthened after CBZ therapy, and the sensory conduction velocity of the ulnar nerve was slowed. Also, the recorded statistical differences or relative changes in the rheobase and stimulus strength, which are parameters of SDTC suggested a decrease in axonal excitability in patients before CBZ therapy or before and after therapy.

An interesting result of this study is the statistical differences in rheobase and stimulus strength, which are the parameters of SDTC and the relative differences in SDTC when the basal values of patients before

drug therapy and controls were compared suggesting a decreased axonal excitability in the PNS of epileptic patients without any other disease or drug therapy that could affect nerve function. Our results resembled the study by Kiernan et al,[23] who studied the excitability of sensory and motor axons in 5 adult generalized epilepsy with febrile seizures plus (GEFS+) patients with established mutations in the beta1 subunit of Na+ channels (SCN1B). In that study, multiple nerve excitability measurements (SDTC, refractoriness, relative refractory period, superexcitability) were recorded using threshold tracking, and they found a higher threshold in patients than in control subjects. The dominant effects of the mutation underlying GEFS+ were a reduction in functioning Na+ channels in peripheral nerve axons. The same beta subunit mutation seemed to have a dual effect with hyperexcitability of central neurons, but reduced peripheral nerve excitability.[23]

In this study, we measured the parameters that are dependent on persistent Na+ channels. Our limited findings suggested a decreased axonal excitability in the PNS of epileptic patients, and a decreased axonal excitability after CBZ and VPA therapy. Compared with CBZ, VPA had much less effect on nerve conduction, similar to the study by Bono et al.[13] Our results also indicate that electrophysiological abnormalities in patients receiving VPA may reflect a functional impairment, whereas patients receiving CBZ may have structural lesions as well. The positive aspect of this study includes the lack of antiepileptic treatment in the patient group, which could affect the results. As sourcing patients not on antiepileptic treatment is difficult, our sample size was small. The small sample size, the short duration of drug usage of the patients, and being able to measure only a few parameters of axonal excitability were limitations of our study.

In conclusion, we believe we may find more definite changes in the PNS of epileptic patients by applying both genetic studies on channel pathologies and by measuring multiple parameters of axonal excitability dependent on different types of voltage-gated ion channels in larger study groups. Studies with larger patient groups, taking greater dosage of these antiepileptic drugs or taking them for a longer duration would give us more decisive results. Our results also suggest the possibility of investigating ion channel functions in vivo by evaluating the strength-duration properties of an axon in many channelopathies or drug therapies.

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