Araştırma Makalesi / Research Article

Investigation of the effects of levetiracetam on sympathetic skin response

Levetirasetam'ın sempatik deri yanıtları üzerine etkilerinin araştırılması

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Abstract

Background: It has been aimed to investigate the effects of levetiracetam on sympathetic skin response.

Material and Methods: Thirty-seven patients those admitted to neurology policlinic and electroencephalography laboratory of Harran University Medical Faculty or neurology policlinics of the other area hospitals and using levetiracetam regularly as monotherapy or polytherapy with the diagnosis of epilepsy and 26 non- taking medicine healthy people were involved to the study. Sympathetic skin responses of the patient and healthy groups were measured from the right-hand region by the electromyoneurography device. Nine male and 14 female patients were taking monotherapy. Their ages were between 16 and 63 with a mean of 26.73 ± 10.62. 7 male and 7 female patients were taking polytherapy. Their ages were between 16 and 38 with a mean of 24.21 ± 6.32. Healthy people of the control group were 21 males and 5 females. Their ages were between 20 and 45 with a mean of 29.69 ± 5.77.

Results: Mean of sympathetic skin response latencies in monotherapy taking patient group was shorter compared to the control group and a statistically significant difference was detected ($p \leq 0.05$). There has been no statistically significant difference between monotherapy taking patient group and control group in terms of mean sympathetic skin response amplitude levels. There has been no statistically significant difference between polytherapy taking patient group and control group in terms of mean sympathetic skin response amplitudes and latencies.

Conclusion: These results point out that levetiracetam treatment may partly cause hyperactivity in sympathetic skin reactions.

Keywords: Levetiracetam, Sympathetic skin response, Epilepsy

Öz.

Amaç: Levetirasetamın sempatik deri yanıtları üzerine etkilerinin araştırılması amaçlandı.

Materyal ve Metod: Harran Üniversitesi Tıp Fakültesi nöroloji polikliniğine, elektroensefalografi laboratuvarına, çevre hastanelerin nöroloji polikliniklerine başvuran epilepsi tanısı almış, monoterapi ya da politerapi şeklinde Levetirasetam daha önceden reçete edilmiş ve düzenli kullanan 37 hasta ile, ilaç kullanmayan sağlıklı 26 kişi çalışmaya dahil edildi. Hasta ve sağlıklı gruplara elektomyo-nörografi cihazı ile sağ el bölgesinde sempatik deri yanıtlarına bakıldı. Monoterapi alan hasta grup 14 bayan ve 9 erkekten oluşmaktadır. Yaşları 16-63 arasındaydı ve yaş ortalaması 26,73 ± 10,62 idi. Politerapi alan hasta grup 7 bayan ve 7 erkek hastadan oluşmaktaydı. Yaşları 16-38 arası olup, yaş ortalaması 24,21 ± 6,35 idi. Kontrol grubu olan sağlıklı bireyler 5 bayan ve 21 erkekten oluşmaktaydı. Yaşları 20 - 45 yaş arası olup, yaş ortalaması 29,69 ± 5,77 idi.

Bulgular: Monoterapi alan hasta grubundaki sempatik deri yanıtı latans ortalaması kontrol grubu ile kıyaslandığında kısa olup, istatistiksel olarak anlamlı fark saptandı ($p \leq 0,05$). Monoterapi alan hasta grubundaki sempatik deri yanıtı amplitüd değerleri, kontrol grubu ile kıyaslandığında istatistiksel olarak anlamlı fark saptanmadı. Politerapi alan hasta grubundaki sempatik deri yanıtı latans ve amplitüdlerin ortalamaları, kontrol grubu ile kıyaslandığında istatistiksel olarak anlamlı fark saptanmadı.

Sonuç: Bulgular, levetirasetam tedavisinin sempatik deri yanıtlarında kısmen de olsa hiperaktiviteye sebep olduğunu göstermektedir.

Anahtar kelimeler: Levetirasetam, Sempatik deri yanıtları, Epilepsi

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Introduction

Things said about the frequency and importance of epilepsy in modern society, are not exaggerated. Based upon the epidemiologic study of Hauser et al., it can be estimated that approximately 2 million persons in the United States have epilepsy (i.e. chronic, recurrent cerebral cortical seizures) and 44 new cases per 100000 emerge each year can be predicted (1).

Epilepsy is a clinical condition caused by increased excitability of neuronal cells in the brain (neuronal hyperexcitability). Epileptic seizure results from increased rapid and local electrical discharges in grey matter and manifests itself clinically by a stereotypic disorder related to cognitive, behavioural, emotional, motional, and perceptual functions limited to a time frame (2).

Autonomic nervous system regulates circulatory system, secretory glands, functions of internal organs, and similar unconscious functions. It is classically composed of two main divisions, namely sympathetic and parasympathetic nervous systems. Apart from these systems, a distinct system called noncholinergic - noradrenergic or enteric nervous system has been defined. This system is responsible for maintenance of motor, secretory, and absorption functions of the gastrointestinal system along with gastrointestinal hormones (3).

Sympathetic skin responses (SSR) is known to contain excitatory suprasegmentary inputs and inhibitory inputs from striatum, and to reflect the activity of the posterior hypothalamus and brain stem reticular formation (4).

Similar centers are affected in seizures and interictal paroxysms and they may play role in epilepsy-dependent autonomic symptoms (5).

It has been suggested that SSR represents sympathetic sudomotor flow in central and peripheral nervous system. Although it has been suggested in some studies that abnormal SSR and autonomic dysfunction are nor interrelated, recent studies revealed that such a relationship may actually exist and even significant changes are present in response amplitude and latencies (6-8).

Material and Methods

Material: A total of 63 subjects were enrolled in 2009, 37 of which were patients with epilepsy presenting to the Neurology polyclinic, EEG laboratory at Harran University Faculty of Medicine or neurology clinics of other hospitals, who have prescribed levetiracetam as monotherapy or polytherapy and regularly use this therapy; control group consisted of 26 subjects. SSR was measured at right hand region in patients and healthy controls using Dantec, KeyPoint V5–11 branded EMG-ENG device. The local committee of ethics at Harran University, Faculty of Medicine approved the study and all subjects gave informed consent.

The inclusion criteria were as follows: Having the diagnosis of epilepsy, Older than 15 years, mentally competent, giving consent for inclusion in the study, Using levetiracetam as monotherapy or as a combination with one of the other antiepileptic drugs for at least two weeks, Having no other chronic or metabolic disorder.

The exclusion criteria were as follows: Younger than 15 years, having another chronic or metabolic disorder, Using the drug for less than 2 weeks, Being mentally retarded, Quitting the study at own will.

The control group consisted of healthy sympathetic skin responses from physicians, nurses, laboratory workers, and other hospital staffs, which were healthy, used no drugs, and had no chronic or metabolic diseases.

Method: Sympathetic skin response (SSR) was recorded in all patients and healthy subjects using Dantec EMG device at normal room temperature (24-26 ºC) and hand skin temperature of 30ºC, after rewarming the subject if needed, in supine position following right hand and wrist was cleaned and active electrodes were placed in the palm and surface electrodes on the dorsum of the hand. It is a well-known rule that SSR habituations may develop very rapidly following consecutive electrical stimuli. Thus, the electrical stimulus was given to median nerve for a total 4 times with at least 3-minute inter-stimulus intervals by avoiding habituation. Filter setting of the device was kept at 0.5 Hz-2 kHz, stimulus duration at 0.01 seconds, stimulus amplitude at 25 mA. SRS latency was measured from the beginning point of negative deflection while SRS amplitude from the apical points of negative and positive deflections. Statistical analyses were performed with SPSS 16.0 software package using one-way ANOVA with post hoc test of Tukey.

Results

The study included 63 subjects, 37 of which used levetiracetam and 26 of which were healthy controls who did not use the drug. The group using levetiracetam as monotherapy was composed of 14 females and 9 males. Their age ranged 16-63 years with a mean of 26,73 ± 10,62 years. The group using levetiracetam as polytherapy was composed of 7 females and 7 males, with an age range of 16-38 averaging 24,21 ± 6,35 years. The control group included 5 females and 21 males; their age ranged 20-45 years, with a mean of 29,69 ± 5,77. There were no significant differences between monotherapy, polytherapy, and control groups in terms of mean age and gender distribution (Table 1).

Table 1. Demographic features of patient and control groups

Group	Gender		Mean Age (Mean ± SD)
	Female	Male	
Monotherapy	14	9	26,73 ± 10,62
Polytherapy	7	7	24,21 ± 6,35
Control	5	21	29,69 ± 5,77
Total	26	37	28,61 ± 8,16

SD: Standard Deviation

Mean values of SSR latency and amplitude in the polytherapy group, on the other hand, were not significantly different from control group (mean SSR latency values for polytherapy and control groups were 1,33±0,47 and 1,42±0,33, respectively and amplitude values were 2,39±2,46 and 2,77±2,54, respectively, other latency and amplitude values being similar, p>0.05). Furthermore, Table 2 shows mean latency and amplitude values of monotherapy, polytherapy, and control groups, and figures 1 and 2 presents in detail the separate comparisons of mean SSR latency and amplitude values of monotherapy and polytherapy groups with control groups. Successive 4 SSR samples without habituation belonging to monotherapy and control groups were shown in figures 3 and 4. Also; in figures 1 and 2 mean SSR latencies and amplitudes are shown.

Table 2. Mean SSR values of monotherapy, polytherapy, and control groups

SDY Parameters	Monotherapy	Significance	Polytherapy	Control
Lat1	1,03±0,52	0,008	1,33±0,47	1,42±0,33
Lat2	0,89±0,55	0,001	1,21±0,58	1,45±0,39
Lat3	0,86±0,58	0,001	1,03±0,72	1,46±0,38
Lat4	0,85±0,61	0,001	1,00±0,70	1,47±0,36
Amp1	2,92±2,87		2,39±2,46	2,77±2,54
Amp2	1,46±1,30		1,88±1,91	1,95±1,52
Amp3	1,53±1,62		1,93±2,00	2,10±1,67
Amp4	1,70±2,19		1,16±1,16	2,41±1,68

Discussion

Partial and generalized epilepsies alter autonomic functions during ictal, postictal, and interictal periods. Alterations in autonomic functions may manifest itself as affected sympathetic, parasympathetic, and adrenal medullar systems (9). It has been suggested that symptoms resulting from alteration in autonomic functions are dependent on cortical, limbic, and hypothalamic systems (10,11). Seizures typically increase heart rate and blood pressure by activating the sympathetic nervous system. On the other hand, during partial seizure parasympathetic activation or sympathetic inhibition may also take place (9).

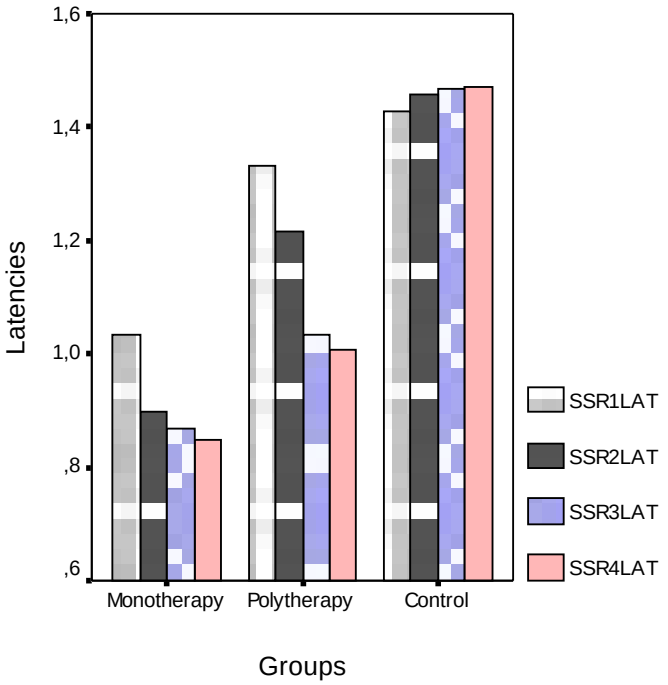

Figure 1. Mean SSR latencies in patient and control groups

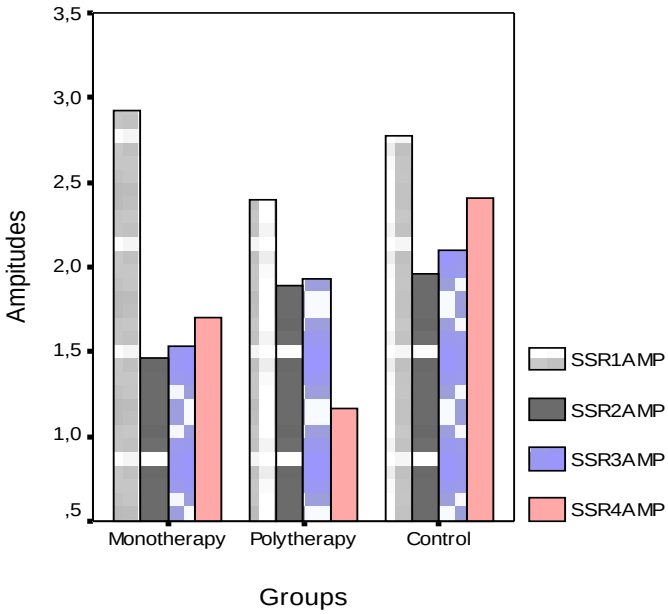

Figure 2. Mean SSR amplitudes in patient and control groups

It has been reported that during the interictal period an autonomic dysfunction develops which is probably related to epileptic discharges (12,13). Faustman et al. reported a parasympathetic dysfunction in people with epileptiform activities and normal EEG (14).

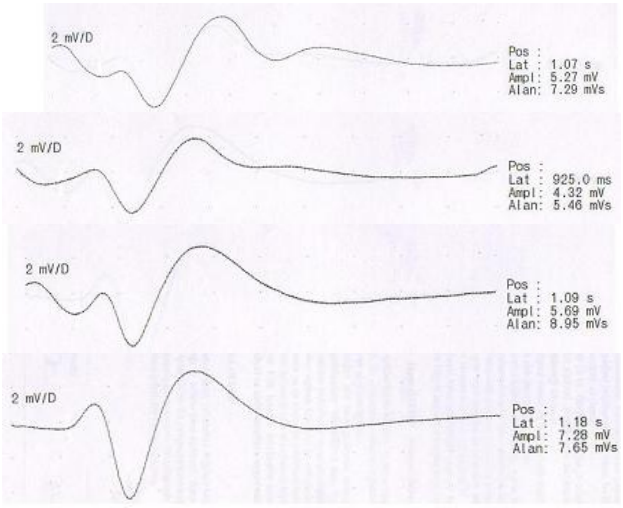

Figure 3. A SSR sample of patients taking monotherapy (consecutive 4 responses without habituation)

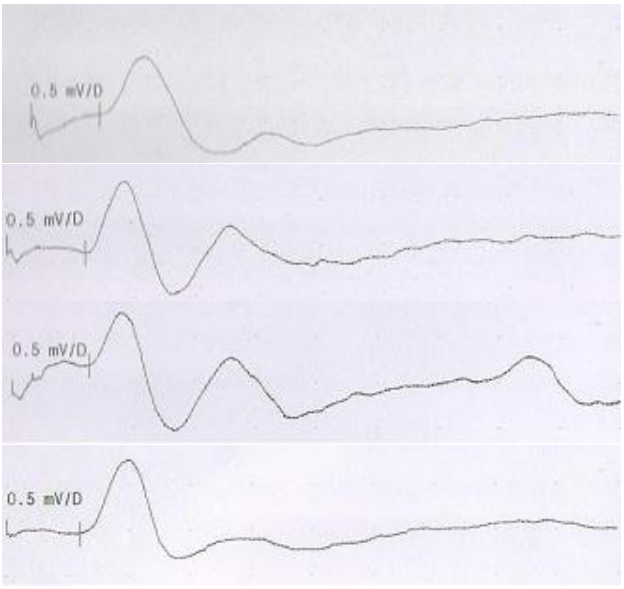

Figure 4. A SSR sample of the control group (consecutive 4 responses without habituation)

Antiepileptic agents may also alter autonomic functions (9). However, another study has suggested that antiepileptic drugs, especially carbamazepine, along with epilepsy per se could change autonomic control of the cardiovascular system and this effect may be difficult to differentiate from the effect of epilepsy (15). Some antiepileptics with anticholinergic properties such as carbamazepine and phenytoin may cause fatal cardiac arrhythmias in excessive doses. Abrupt discontinuation of carbamazepine may increase sympathetic activity in sleep (9).

Under the light of this information, the importance of autonomic dysfunction has been stressed in both epilepsy itself and non-surgical treatments in epilepsy management. Detection of this autonomic dysregulations may involve certain tests, one of which is SSR assessments.

In 1992, Drory et al. grouped 100 healthy subjects according to age in whom SSR was measured and found that latency values prolonged and amplitude values were lowered and even disappeared with again (16). Yet, it is unclear which factors influence amplitude values. Further studies are needed in this field.

We aimed to determine the effects of levetiracetam on autonomic function by assessing the effects of the drugs on SSR in patients with epilepsy. A total of 23 epilepsy patients aged 16-63 years with a mean of 26,73 ± 10,62 years using levetiracetam monotherapy and 14 epilepsy patients aged 16-38 years with a mean of 24,21 ± 6,35 years using polypharmacy with levetiracetam. In addition, 26 healthy controls of 20-45 years with a mean of 29,69 ± 5,77 years were included.

SSR studies in literature assessing autonomic functions in patients taking antiepileptic therapy, are scarce. We aimed to reveal beneficial or detrimental effects of levetiracetam in epileptic therapy by evaluating its autonomic effects apart from possible effects.

We studied SSR latency and amplitude values in the groups of monotherapy, polytherapy, and control groups. Mean values of SSR latency in monotherapy group were significantly shorter compared to control group. Berilgen et al. also found significantly longer SSR latencies of upper extremity before the treatment in partial epileptic patients. However, they noted that SSR latencies in upper extremities significantly lowered following treatment (17). Moreover, SSR amplitude values in monotherapy group were not significantly different from control group. Berilgen et al. reported no significant difference in SSR amplitudes in the upper extremities in partial epilepsy compared to control group both before and after therapy (17). Our results on SSR latency and amplitudes were similar to those reported by Berilgen at al. These authors explained the significant drop in SSR latencies by improved sympathetic function.

They explained the mechanism of sympathetic improvement by a decrease or interruption of abnormal electrical discharges originating from epileptic focus by epileptic therapy. They also compared latencies prior to and following treatment but did not compare post-treatment values with control group. However, careful analysis of their results reveals a shorter mean latency compared to control group. Since they missed this detail, they erroneously interpreted the abbreviation of SSR latencies by antiepileptic therapy as improvement in sympathetic functions. In our study, complete control of seizure activity was achieved by monotherapy, SSR latencies being significantly shorter than the control group. If antiepileptic agents improved sympathetic dysfunction by only suppressing or interrupting abnormal electrical discharges originating from an epileptic focus, we would not expect a significantly shorter latency in patients completely free of seizures compared to

the control group. In other words, lower responses compared to population averages could not be expected by the repair of a disorder. Under the light of the available data, we could explain shorter SSR latencies in monotherapy patients compared to controls in the following manner: As is known, SSR contains excitatory suprasegmentary inputs and inhibitory inputs from striatum and it reflects the activity of the posterior hypothalamus and brain stem reticular formation.4 Thus, levetiracetam evokes excess sympathetic activity by depressing inhibitory inputs in striatum, partly similar to the phenomenon of increased deep tendon reflexes by disappearance of the inhibitory mechanism in upper motor neuron diseases. We feel that other antiepileptic agents, in addition to levetiracetam, will cause the same results since they exert an inhibitory function in many systems of the central nervous system.

In this case, the question emerges why polytherapy did not shorten the latency. We can explain the similarity of SSR latency and amplitude values in polytherapy and control groups by smaller sample sizes in our study. Because, although no significant difference was observed, SSR latency values in the polytherapy group were lower than controls. There might be a significant difference if the sample size in polytherapy group were similar to that of monotherapy group. The main reason of smaller sample sizes was that levetiracetam was not in used as monotherapy at the time of study enrollment.

Devinsky et al. compared 24 patients with partial epilepsy using carbamazepine with healthy controls and reported autonomic dysfunction during interictal period, which was attributed by the authors to the effects of chronic epilepsy or drugs (18).

Miles et al. , in their study assessing SSR latencies and amplitudes in 50 patients with epilepsy having generalized tonic-clonic or complex partial seizure and secondary generalized seizure, found that SSR latencies in these patients were longer and amplitudes greater compared to controls. Based on this finding, they suggested that epilepsy patients develop unknown physiologic alterations at any time, which lead to autonomic dysfunction and it may be related to SUDEP (unexplained sudden deaths related to epilepsy) (5).

All patients in the above-mentioned study of Miles et al. had seizures electrophysiologically, in other words, EEGs of each of them contained epileptiform activities. Furthermore, only 5 patients had no seizures clinically and 40 were receiving antiepileptic therapy. We think that the predominant excitatory rather than inhibitory effects of epileptic activities on cortical, limbic, and hypothalamic system explain the autonomic dysfunction. However, if Miles et al. had enrolled their patient group from epilepsy patients with no active epileptic seizures, they would have results similar to ours.

This study, by revealing the relationship between levetiracetam therapy and SSR, demonstrated that, even for a small part of the autonomic nervous system, levetiracetam shortens the response time. However, further studies are clearly needed as studies in literature assessing autonomic functions in patients taking antiepileptic therapy are scarce and not consistent with each other.

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