Epilepsi 2020;26(2):81-87 DOI: 10.14744/epilepsi.2019.60490

ORIGINAL ARTICLE / KLİNİK ÇALIŞMA

Effects of Levetıracetam Treatment on the Autonomic Nervous System Functions in Epilepsy Patients

Dr. Dilek YILMAZ

Epilepsi Hastalarında Levetirasetam Tedavisinin Otonom Sinir Sistemi Fonksiyonları Üzerine Etkileri

Dilek YILMAZ, Burhanettin ÇİĞDEM

Department of Neurology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

Summary

Objectives: Sudden unexpected death in epilepsy patients is considered to be the most significant epilepsy-related cause of death, and this is associated especially with uncontrolled generalized tonic-clonic seizures, cardiac arrhythmia, decreased heart rate variability, and the use of anti-epileptic drugs. In this study, we aimed to investigate the effects of levetiracetam on the autonomic nervous system by evaluating heart rate variability (HRV) in epilepsy patients using levetiracetam.

Methods: The patients, in whom levetiracetam was started in monotherapy and polytherapy, were divided into two groups in this study. The first group consisted of 29 patients with newly diagnosed epilepsy, in whom levetiracetam was started, and the second group consisted of 11 patients in whom levetiracetam was added to antiepileptic drug treatment. In patients receiving monotherapy and polytherapy, the HRV values measured before levetiracetam was started and the HRV values measured three months after starting levetiracetam in the same patient groups were compared. HRV was measured by a BVP (blood volume pulse) sensor attached to the finger by performing 10-min recordings using the Nexus/BioTrace+ brand device and with frequency-domain spectral analysis.

Results: According to the measurements made before starting the treatment and in the third month of the treatment, no significant difference was obtained between the Total Power (TP), Low-Frequency power (LF), High-Frequency power (HF), Very Low-Frequency power (VLF), and LF/HF values of 29 patients taking levetiracetam in monotherapy and 11 patients taking levetiracetam in polytherapy.

Conclusion: This study demonstrated that the use of levetiracetam in monotherapy and polytherapy had no significant effect on the autonomic nervous system functions.

Keywords: Autonomic nervous system; heart rate variability; levetiracetam.

Özet

Amaç: Epilepsi hastalarında ani beklenmeyen ölüm epilepsi ile ilişkili en önemli ölüm nedeni olarak düşünülmekte ve bu durum özellikle kontrol altına alınamayan generalize tonik klonik nöbetler, kardiyak aritmi, azalmış kalp hızı değişkenliği ve anti-epileptik ilaçların kullanımı gibi nedenlerle ilişkilendirilmektedir. Biz bu çalışmada levetirasetam kullanan epilepsi hastalarında kalp hızı değişkenliğini (HRV) değerlendirilerek levetirasetamın otonom sinir sistemi üzerine etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Monoterapi ve politerapide levetirasetam başlanan hastalar iki gruba ayrıldı. Birinci grup yeni epilepsi tanısı konularak levetirasetam başlanan 29 hasta, ikinci grup ise antiepileptik ilaç tedavisine levetirasetam eklenen 11 hastadan oluşmaktaydı. Monoterapi ve politerapi alan hastalarda levetirasetam başlamadan önce HRV ile aynı hasta gruplarında leveterisetam başlandıktan üç ay sonraki HRV değerlerini karşılaştırıldık. HRV parmağa takılmış bir BVP (blood volume pulse) sensörü ile 10 dakikalık kayıtlar yapılarak NeXus/BioTrace+ marka cihazla frekansa dayalı sistemle elde edilmiştir.

Bulgular: Levetirasetamı monoterapide kullanan 29 ve politerapide kullanan 11 hastanın tedaviye başlamadan önce ve tedavinin üçüncü ayında değerlendirilen Toplam Güç (TP), Düşük frekanslı güç (LF), Yüksek frekanslı güç (HF), Çok düşük frekanslı güç (VLF), LF/HF değerleri arasında anlamlı bir fark elde edilememiştir.

Sonuç: Çalışmamız, levetirasetamın monoterapide ve politerapide kullanımının otonom sinir sistemi fonksiyonları üzerine önemli herhangi bir etkisi olmadığını göstermiştir.

Anahtar sözcükler: Otonom sinir sistemi; levetirasetam; kalp hızı değişkenliği.

Submitted *(Geliş)*: 10.05.2019
Accepted (Kabul) **:** 26.09.2019
***Correspondence (İletişim)*:** Burhanettin ÇİĞDEM, M.D.
***e-mail (e-posta)*:** drbcigdem@gmail.com

Introduction

The risk of death in epilepsy patients is 2–3 times higher than in the normal population. Sudden unexpected death in epilepsy patients (SUDEP) is the most significant epilepsy-related cause of death and is 24-fold higher than in the normal population.[1,2] Cardiac problems are shown among the causes of SUDEP.[3,4] Epileptic seizures are frequently associated with peri-ictal cardiac symptoms, such as sinus tachycardia, or less frequently with rhythm abnormalities, such as bradycardia, asystole or malignant arrhythmia.[5] Heart rate variability (HRV) reflects the balance between parasympathetic and sympathetic activity in the autonomic nervous system (ANS). While low-frequency power (LF) obtained in the evaluation of HRV with frequency domain spectral analysis reflects the sympathetic activity, high frequency power (HF) reflects the parasympathetic (vagal) activity. The LF/HF (Low Frequency/High Frequency) ratio demonstrates the balance between sympathetic and parasympathetic systems.[6]

In general, while increases in HRV reflect a shift towards parasympathetic dominance, decreases in HRV indicate a relative increase in sympathetic activity.[7] A few studies have demonstrated a relationship between SUDEP and decreased HRV.[8,9] Low HRV has been associated with increased cardiac mortality and sudden death.[10] HRV changes in epilepsy patients are probably due to progressive changes in the autonomic nervous system induced by recurrent seizures.[11] The potential proarrhythmogenic effect of seizures and/or antiepileptic drugs (AED) may be responsible for SUDEP.[12] AEDs may not only increase the QT interval on the electrocardiogram but may also reduce the responses of heart rate and blood pressure to physiological stressors and thus make patients prone to SUDEP.[4,13] It has been reported that among AEDs, carbamazepine increases the ANS sympathetic tone[14] and the risk of arrhythmia,[15] and phenytoin depresses hyperactivation of cardiac sympathetic nerves.[16] Levetiracetam, which is considered to be a well-tolerated drug, is a new generation effective antiepileptic drug that binds to the synaptic vesicle protein SV2A distributed everywhere in the central nervous system. It is used in monotherapy and polytherapy in adult and pediatric epilepsy patients with focal and secondary generalized seizures, primary generalized tonic-clonic seizures, and myoclonic seizures.[17] In the literature, there are few studies evaluating the effects of levetiracetam on the ANS. In this study, we aimed to investigate the effects of levetiracetam on the ANS in monotherapy and polytherapy by evaluating HRV using the frequency domain spectral analysis method in epilepsy patients.

Materials and Methods

This study was conducted on 40 patients admitted to the Department of Neurology, Cumhuriyet University Faculty of Medicine Hospital between June 2016 and June 2018, who were diagnosed with epilepsy according to the ILAE classification, and who received levetiracetam treatment. Before this study, ethical approval was obtained from Cumhuriyet University Faculty of Medicine Ethics Committee Presidency with the decision numbered 2016-05/03 and dated 17.05.2016. This study was supported with the project no T-727 by Cumhuriyet University Scientific Research Projects Commission Presidency. Individuals with a disease that would affect the ANS (diabetes and rheumatoid arthritis), taking drugs (anticholinergic, antiarrhythmic and beta blocker) with an impact on the ANS, and having atrial fibrillation, all cardiac arrhythmias, severe renal, liver, and heart failure, and physical or mental disabilities at a level which would prevent understanding and responding to the scales to be applied were not included in this study.

The patients were divided into two groups, as patients in whom levetiracetam was started in monotherapy and polytherapy. The first group consisted of 29 patients with newly diagnosed epilepsy, in whom levetiracetam was started, and the second group consisted of 11 patients in whom levetiracetam was added to AED treatment. In patients receiving monotherapy and polytherapy, the HRV values measured before levetiracetam was started and the HRV values measured three months after starting levetiracetam in the same patient groups were compared.

Heart rate variability analysis

For electrophysiological recording, 10-minute recordings were performed by a BVP (blood volume pulse) sensor attached to the finger after a 20-minute rest period in the Autonomous Laboratory of the Neurology Department of Cumhuriyet University Faculty of Medicine, and HRV values were measured by the Nexus/BioTrace + brand device and the frequency domain spectral analysis method as Total power (TP), Low frequency power (LF), High frequency power (HF), Very low frequency power (VLF), and LF/HF values.

Statistical analysis

In this study, data were evaluated using the SPSS program (Ver: 22. 0). Whether the data met the parametric test assumptions were evaluated by the Kolmogorov-Smirnov test. The chi-square test was used in the evaluation of categorical variables, Student's t-test was used in the evaluation of normally distributed data, and the Mann-Whitney U test was used in the evaluation of non-normally distributed data. The ANOVA test was used in the evaluation of repeated measurements. The data were expressed as mean ± standard deviation, median (interquartile range), number of subjects, and percentage (%).

Results

The age of the 40 patients enrolled in this study was minimum 18 and maximum 84 years, and the patients were divided into two groups. In the first group, there were 29 patients in whom levetiracetam was started as monotherapy, and in the second group, there were 11 patients in whom levetiracetam was added in polytherapy. In this study, the age of the patients in the monotherapy group was 39.62±19 years, and the age of the patients in the polytherapy group was 30.45±12.34 years. Of the individuals in the monotherapy group, 18 (62.1%) were female, 11 (39.9%) were male, and of the individuals in the polytherapy group, eight (72.7%) were female, and three (27.3%) were male. Upon evaluating the types of seizures in the patients receiving monotherapy, there were generalized tonic-clonic seizures in 25 (86.2%) patients, simple partial seizures in two (6.9%) patients, myoclonic seizures in one (3.4%) patient, and tonic seizures in one (3.4%) patient. In the group receiving polytherapy, there were generalized tonic-clonic seizures in four patients (36.4%), complex partial seizures in one (9.1%) patient, secondary generalized tonic-clonic seizures in two (18.2%) patients, and myoclonic seizures in four (18.4%) patients.

No significant difference was observed between the groups concerning the TP, VLF, LF, HF, LF/HF values measured in all patients before starting levetiracetam treatment and in the third month of the treatment (Table 1).

When the TP, VLF, LF, HF, LF/HF values measured before starting levetiracetam treatment in the monotherapy and polytherapy groups were compared, the difference between the groups was found to be insignificant (Table 2).

When the TP, VLF, LF, HF, LF/HF values measured three months after starting levetiracetam treatment in the monotherapy and polytherapy groups were compared, the difference between the groups was found to be insignificant (Table 3).

When the TP, VLF, LF, HF, L /HF values measured before starting levetiracetam treatment and in the third month of the treatment in the monotherapy group were compared, the difference between the groups was found to be insignificant (Table 4).

When the TP, VLF, LF, HF, LF/HF values measured before starting levetiracetam treatment and in the third month of the treatment in the polytherapy group were compared, the difference between the groups was found to be insignificant (Table 5).

Table 1. Comparison of the TP, VLF, LF, HF, LF/HF values measured in all patients before starting levetiracetam treatment and in the 3rd month of the treatment

Treatment groups	Median	Interquartile range	p
TP (ms^2)-1	1552.00	851.00–3908.50	0.316
TP (ms^2)-2	2174.00	1005.00–6389.00	
VLF (ms^2)-1	430.50	197.50–635.50	0.454
VLF (ms^2)-2	580.00	190.00–1257.00	
LF (ms^2)-1	871.50	384.50–2352.00	0.256
LF (ms^2)-2	1112.00	323.00–2919.00	
HF (ms^2)-1	347.50	173.50–1096.00	0.633
HF (ms^2)-2	582.00	277.00–1779.00	
LF/HF-1	2.00	0.95–3.45	0.181
LF/HF-2	1.90	1.2–2.6	

(1: HRV values measured before starting levetiracetam treatment; 2: HRV values measured in the third month of levetiracetam treatment). TP: Total Power; VLF: Very Low-Frequency power; LF: Low-Frequency power; HF: High-Frequency power.

Table 2. Comparison of the TP, VLF, LF, HF, LF/HF values measured before starting levetiracetam treatment in the monotherapy and polytherapy groups

		n	Median	Interquartile range	p
TP (ms^2)	Monotherapy	29	1606.00	847.00–3562.00	0.765
	Polytherapy	11	1498.00	1384.00–4691.00	
VLF (ms^2)	Monotherapy	29	467.00	198.00–825.00	0.402
	Polytherapy	11	348.00	161.00–561.00	
LF (ms^2)	Monotherapy	29	753.00	370.00–2466.00	0.369
	Polytherapy	11	1041.00	624.00–1474.00	
HF (ms^2)	Monotherapy	29	394.00	178.00–1020	0.929
	Polytherapy	11	298.00	160.00–1354.00	
LF/HF	Monotherapy	29	1.90	0.90–3.20	0.385
	Polytherapy	11	2.50	1.10–4.50	

TP: Total Power; VLF: Very Low-Frequency power; LF: Low-Frequency power; HF: High-Frequency power.

Table 3. Comparison of the TP, VLF, LF, HF, LF/HF values measured in the third month of levetiracetam treatment in the monotherapy and polytherapy groups

		n	Median	Interquartile range	p
TP(ms^2)	Monotherapy	29	2283.00	1088.00–6565.00	0.656
	Polytherapy	11	1954.00	677.00–6070.00	
VLF(ms^2)	Monotherapy	29	694.00	271.00–1292.50	0.363
	Polytherapy	11	471.00	149.00–927.00	
LF(ms^2)	Monotherapy	29	1006.50	332.00–2813.00	0.939
	Polytherapy	11	1112.00	313.00–2999.00	
HF(ms^2)	Monotherapy	29	595.00	347.50–1870.00	0.414
	Polytherapy	11	483.00	152.00–1281.00	
LF/HF	Monotherapy	29	1.70	1.20–2.55	0.914
	Polytherapy	11	1.70	1.30–3.10	

TP: Total Power; VLF: Very Low-Frequency power; LF: Low-Frequency power; HF: High-Frequency power.

Table 4. Comparison of the TP, VLF, LF, HF, LF/HF values measured before starting levetiracetam treatment and in the third month of the treatment in the monotherapy group

Monotherapy	Median	Interquartile range	p
TP (ms^2)- 1	1606.00	847.00–3562.00	0.546
TP (ms^2)-2	2283.00	1088.00–6565.00	
VLF (ms^2)-1	467.00	198.00–825.00	0.657
VLF (ms^2)-2	694.00	271.00–1292.50	
LF (ms^2)-1	753.00	370.00–2466.00	0.432
LF (ms^2)-2	1006.50	332.00–2813.00	
HF (ms^2)-1	394.00	178.00–1020.00	0.795
HF (ms^2)-2	595.00	347.50–1870.50	
LF/HF-1	1.90	0.90–3.20	0.433
LF/HF-2	1.70	1.20–2.55	

(1: HRV values measured before starting levetiracetam treatment; 2: HRV values measured in the third month of levetiracetam treatment). TP: Total Power; VLF: Very Low-Frequency power; LF: Low-Frequency power; HF: High-Frequency power.

Table 5. Comparison of the TP, VLF, LF, HF, LF/HF values measured before starting levetiracetam treatment and in the third month of the treatment in the polytherapy group

Polytherapy	Median	Interquartile range	p
TP (ms^2)-1	1498.00	1384.00–4691.00	0.281
TP (ms^2)-2	1954.00	677.00–6070.00	
VLF (ms^2)-1	348.00	161.00–561.00	0.194
VLF (ms^2)-2	471.00	149.00–927.00	
LF (ms^2)-1	1041.00	624.00–1474.00	0.427
LF (ms^2)-2	1112.00	313.00–2999.00	
HF (ms^2)-1	298.00	160.00–1354.00	0.506
H F(ms^2)-2	483.00	152.00–1281.00	
LF/HF-1	2.50	1.10–4.50	0.294
LF/HF-2	1.70	1.30–3.10	

(1: HRV values measured before starting levetiracetam treatment; 2: HRV values measured in the third month of levetiracetam treatment). TP: Total Power; VLF: Very Low-Frequency power; LF: Low-Frequency power; HF: High-Frequency power.

Discussion

Epilepsy patients have a higher risk of death compared to the general population, and SUDEP is one of the leading causes of epilepsy-related deaths.[1,2] Studies have demonstrated that HRV has a high predictive value for SUDEP.[18] There are many mechanisms and triggering factors responsible for the etiology of SUDEP. Among these, autonomic dysfunction and ictal bradyarrhythmia are quite significant.[19] The imbalance between the postictal sympathetic and parasympathetic systems and the impairment of the autonomic regulation of the brain stem are thought to increase the risk of SUDEP.[20] In the MORTEMUS study, 11 SUDEP cases were recorded in patients followed up in the epilepsy unit. In most of these patients, cardiorespiratory failure, which manifested itself with bradycardia and cardiac asystole that followed postictal short-term tachypnea and tachycardia, developed.[21] Delamont et al.[22] reported that cardiac parasympathetic activity increased during the seizure and returned to normal after the seizure in patients with secondary generalized tonic-clonic seizures. The researchers did not observe any change in the cardiac parasympathetic activity before and after seizures in patients with complex partial seizures.

Upon reviewing the current literature, it is observed that the effects of AEDs on the ANS are variable. While bradycardia is frequently observed at therapeutic doses of carbamazepine, sinus tachycardia may be usually observed at toxic doses.[16] Isojärvi et al.[23] determined a dysfunction in the sympathetic and parasympathetic systems in patients taking AEDs in the long term and decreased HRV in patients taking carbamazepine. Changes in autonomic cardiovascular regulation in the interictal period may be observed in patients with epilepsy. However, it is still unclear whether a decrease in cardiovascular responses is due to epilepsy and interictal discharge or treatment with AEDs.[24] Stefani et al.[25] evaluated HRV in patients receiving polytherapy as awake or while sleeping, while undergoing treatment and after discontinuation of the treatment, and they did not observe any variability. However, in the subgroup analysis they performed, the researchers concluded that Na + channel blockers might have a more significant effect on the cardiac function, but they had no similar impact on HRV. The study carried out by Kennebäck et al.[26] demonstrated a decrease in the TP, VLF, and LF values after the discontinuation of carbamazepine and phenytoin treatment. Persson et al.[27] determined that while there was not any change in the LF/HF ratio measured one month after starting carbamazepine treatment in 15 patients newly diagnosed with epilepsy, it reduced the TP, VLF, LF, and HF parameters. With these results, the researchers demonstrated that carbamazepine could suppress both parasympathetic and sympathetic functions. In the study which was carried out by Tomson et al. on patients with epilepsy and in which HRV in the interictal period was compared with that of healthy controls by a 24-hour recording method, a decrease was observed in the TP and LF parameters of patients receiving carbamazepine treatment, but no change was observed in these parameters in patients receiving valproate treatment.[6] Contrary to these findings, Sathyaprabha et al.[28] demonstrated that

chronic use of carbamazepine as monotherapy does not have any significant effect on ECG time intervals or measures of short- and long-term variability. The results of our study revealed that the use of levetiracetam in monotherapy and polytherapy had no significant effect on HRV. There are also studies reporting that AEDs contribute positively to the ANS by providing seizure control. Lossius et al.[29] evaluated the HRV of patients while receiving AED therapy and after discontinuation of the treatment and demonstrated an increase in parameters displaying both parasympathetic and sympathetic functions after discontinuation of AED treatment. The study conducted by Hallioglu et al.[18] demonstrated that seizure control with AEDs reduced cardiac autonomic dysfunctions in with patients epilepsy. Ryvlin et al.[30] indicated in their study that when patients receiving antiepileptic treatment at active doses were compared with patients having uncontrolled seizures and with the placebo group, the incidence of definite or probable SUDEP could be reduced by more than seven times in patients receiving treatment and with controlled seizures. Epileptic seizures may cause the stimulation of the ANS and impairment of the sympathetic and parasympathetic nervous system regulation. Furthermore, AEDs may impair cardiovascular regulation and have an adverse effect on the ANS.[20] Being seizure-free and especially taking generalized tonic-clonic seizures under control in epilepsy patients are known to be strongly associated with the reduced risk of SUDEP.[31] Therefore, it is essential both to control seizures effectively and to select an antiepileptic treatment that does not have an adverse effect on the ANS. Levetiracetam is one of the most effective new generation antiepileptic drugs frequently used in the treatment of epilepsy nowadays, but there are few studies in the literature on its effects on autonomic functions after starting to use levetiracetam in monotherapy and polytherapy. Since HRV was evaluated before starting levetiracetam treatment and in the third month of levetiracetam treatment in the present study, the results of the study suggest that levetiracetam did not affect the ANS functions.

In conclusion, being able to demonstrate the effect of epileptic seizures and AEDs on the ANS is vital for understanding and preventing the mechanisms of SUDEP, which is the leading cause of epilepsy related-deaths. The findings obtained in this study demonstrated that levetiracetam treatment did not affect the TP, HF, LF, LF/HF values reflecting the sympathetic and parasympathetic nervous system. However, because the present study could be performed with a limited number of patients and because the number of patients, especially in the polytherapy group, was quite low, in order to be able to demonstrate it more clearly whether levetiracetam treatment has an effect on the ANS, there is a need for further studies in which the sample size is larger and in which patients who take drugs in a longer term are evaluated.

Ethics Committee Approval
Ethics committee approved.

Peer-review
Externally peer-reviewed.

Conflict of interest
The authors declare that they have no conflict of interest.

Authorship Contributions
Concept: B.Ç., D.Y.; Design: B.Ç., D.Y.; Supervision: B.Ç.; Materials: B.Ç., D.Y.; Data collection &/or processing: B.Ç., D.Y.; Analysis and/or interpretation: B.Ç.; Literature search: D.Y.; Writing: B.Ç., D.Y.; Critical review: B.Ç.

References

1. Shackleton DP, Westendorp RG, Kasteleijn-Nolst Trenité DG, de Craen AJ, Vandenbroucke JP. Survival of patients with epilepsy: an estimate of the mortality risk. Epilepsia 2002;43(4):445–50.
2. Forsgren L, Hauser WA, Olafsson E, Sander JW, Sillanpää M, Tomson T. Mortality of epilepsy in developed countries: a review. Epilepsia 2005;46 Suppl 11:18–27. [CrossRef]
3. Devinsky O. Effects of Seizures on Autonomic and Cardiovascular Function. Epilepsy Curr 2004;4(2):43–6. [CrossRef]
4. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. Lancet Neurol 2008;7(11):1021–31. [CrossRef]
5. Jeppesen J, Fuglsang-Frederiksen A, Brugada R, Pedersen B, Rubboli G, Johansen P, et al. Heart rate variability analysis indicates preictal parasympathetic overdrive preceding seizure-induced cardiac dysrhythmias leading to sudden unexpected death in a patient with epilepsy. Epilepsia 2014;55(7):e67–71.
6. Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. Epilepsia 2012;53(2):272–82. [CrossRef]
7. Myers KA, Sivathamboo S, Perucca P. Heart rate variability measurement in epilepsy: How can we move from research to clinical practice? Epilepsia 2018;59(12):2169–78. [CrossRef]
8. Rauscher G, DeGiorgio AC, Miller PR, DeGiorgio CM. Sudden unexpected death in epilepsy associated with progressive deterioration in heart rate variability. Epilepsy Behav 2011;21:103–5.
9. Novak JL, Miller PR, Markovic D, Meymandi SK, DeGiorgio CM. Risk Assessment for Sudden Death in Epilepsy: The SUDEP-7 Inventory. Front Neurol 2015;6:252. [CrossRef]
10. Stein PK, Domitrovich PP, Huikuri HV, Kleiger RE; Cast Investiga-

tors. Traditional and nonlinear heart rate variability are each independently associated with mortality after myocardial infarction. J Cardiovasc Electrophysiol 2005;16(1):13–20. [CrossRef]

11. Baysal-Kirac L, Serbest NG, Şahin E, Dede HÖ, Gürses C, Gökyiğit A, et al. Analysis of heart rate variability and risk factors for SUDEP in patients with drug-resistant epilepsy. Epilepsy Behav 2017;71(Pt A):60–4. [CrossRef]
12. Lamberts RJ, Blom MT, Novy J, Belluzzo M, Seldenrijk A, Penninx BW, et al Increased prevalence of ECG markers for sudden cardiac arrest in refractory epilepsy. J Neurol Neurosurg Psychiatry 2015;86(3):309–13. [CrossRef]
13. Hesdorffer DC, Tomson T. Sudden unexpected death in epilepsy. Potential role of antiepileptic drugs. CNS Drugs 2013;27(2):113–9. [CrossRef]
14. Takayanagi K, Hisauchi I, Watanabe J, Maekawa Y, Fujito T, Sakai Y, et al. Carbamazepine-induced sinus node dysfunction and atrioventricular block in elderly women. Jpn Heart J 1998;39(4):469–79. [CrossRef]
15. Pedley TA, Hauser WA. Sudden death in epilepsy: a wake-up call for management. Lancet 2002;359(9320):1790–1. [CrossRef]
16. Tomson T, Kennebäck G. Arrhythmia, heart rate variability, and antiepileptic drugs. Epilepsia 1997;38(11 Suppl):S48–51.
17. Lyseng-Williamson KA. Spotlight on levetiracetam in epilepsy. CNS Drugs. 2011;25(10):901–5. [CrossRef]
18. Hallioglu O, Okuyaz C, Mert E, Makharoblidze K. Effects of antiepileptic drug therapy on heart rate variability in children with epilepsy. Epilepsy Res 2008;79(1):49–54. [CrossRef]
19. Leung H, Kwan P, Elger CE. Finding the missing link between ictal bradyarrhythmia, ictal asystole, and sudden unexpected death in epilepsy. Epilepsy Behav 2006;9(1):19–30. [CrossRef]
20. Ruthirago D, Julayanont P, Karukote A, Shehabeldin M, Nugent K. Sudden unexpected death in epilepsy: ongoing challenges in finding mechanisms and prevention. Int J Neurosci 2018;128(11):1052–60. [CrossRef]
21. Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol 2013;12(10):966–77. [CrossRef]
22. Delamont RS, Julu POO, Jamal GA. Changes in a measure of cardiac vagal activity before and after epileptic seizures. Epilepsy Res. 1999;35(2):87–94. [CrossRef]
23. Isojärvi JI, Ansakorpi H, Suominen K, Tolonen U, Repo M, Myllylä VV. Interictal cardiovascular autonomic responses in patients with epilepsy. Epilepsia 1998;39(4):420–6. [CrossRef]
24. Tomson T, Ericson M, Ihrman C, Lindblad LE. Heart rate variability in patients with epilepsy. Epilepsy Res 1998;30(1):77–83.
25. Stefani M, Arima H, Mohamed A. Withdrawal of anti-epileptic medications during video EEG monitoring does not alter ECG parameters or HRV. Epilepsy Res 2013;106(1-2):222–9. [CrossRef]
26. Kennebäck G, Ericson M, Tomson T, Bergfeldt L. Changes in arrhythmia profile and heart rate variability during abrupt withdrawal of antiepileptic drugs. Implications for sudden death. Seizure 1997;6(5):369–75. [CrossRef]
27. Persson H, Ericson M, Tomson T. Carbamazepine affects autonomic cardiac control in patients with newly diagnosed epilepsy. Epilepsy Res 2003;57(1):69–75. [CrossRef]
28. Sathyaprabha TN, Koot LAM, Hermans BHM, Adoor M, Sinha S, Kramer BW, et al. Effects of Chronic Carbamazepine Treatment on the ECG in Patients with Focal Seizures. Clin Drug Investig 2018;38(9):845–51. [CrossRef]
29. Lossius MI, Erikssen JE, Mowinckel P, Gulbrandsen P, Gjerstad L. Changes in autonomic cardiac control in patients with epilepsy after discontinuation of antiepileptic drugs: a randomized controlled withdrawal study. Eur J Neurol 2007;14(9):1022–8.
30. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol 2011;10(11):961–8. [CrossRef]
31. DeGiorgio CM, Curtis A, Hertling D, Moseley BD. Sudden unexpected death in epilepsy: Risk factors, biomarkers, and prevention. Acta Neurol Scand 2019;139(3):220–30. [CrossRef]