A VALPROINSAV, A CARBAMAZEPIN ÉS A LEVETIRACETAM HATÁSA A TP-E INTERVALLUMRA, VALAMINT A TP-E/QT ÉS A TP-E/QTC ARányRA

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Cél – A P-hullám-diszperzió értékelése antiepileptikus kezelés (AETH) előtt és után, valamint a ventricularis repolarizáció kockázatának vizsgálata a Tpeak-Tend (Tp-e) intervallum és a Tp-e/QT arány használatával epilepsziás betegek körében.


Eredmények – A Tp-e intervallum hosszabbnak, a Tp-e/QT és a Tp-e/Qtc arányok magasabbnak bizonyultak a betegcsoportban, mint a kontrollok között (p < 0,05, minden esetben), ugyanakkor a QTmax arány szignifikánsan alacsonyabb volt a betegcsoportban. Három hónap AETH után a betegek körében szignifikáns mértékben növekedett a QTmax, a QTcmax és a QTcd érték. A Tp-e/QT és a Tp-e/Qtc arányok variációjaidot különösen a levetiracetam és a valproinsav kezelés után jelentős mértékben megnőtt a patientcsoportban (p < 0,05). A carbamazepinnel kezelt betegekben csökkenő hatást teremtett a Tp-e intervallum és a Tp-e/QT arány a terápiának első és utáni értékei között a terápiának első és utáni értékei között.

Következtetés – Az epilepszia arrhythmogen környezettel társulhat, és az AETH-ban részesülő betegek körében a Tp-e intervallum és a Tp-e/QT arány mértéke semmilyen szignifikáns változást nem mutatott.

Keywords: epilepsy, ECG, arrhythmia, Tp-e interval, Tp-e/QT ratio

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AVALPROINSAV, A CARBAMAZEPIN ÉS A LEVETIRACETAM HATÁSA A TP-E INTERVALUMRA, VALAMINT A TP-E/QT ÉS A TP-E/QTC ARányRA

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Aim – To evaluate P-wave dispersion before and after antiepileptic drug (AED) treatment as well as to investigate the risk of ventricular repolarization using the Tpeak-Tend (Tp-e) interval and Tp-e/QT ratio in patients with epileptiform disorder.

Methods – A total of 63 patients receiving AED therapy and 35 healthy adults were included. ECG recordings were obtained before and 3 months after anti-epileptic treatment among patients with epilepsy. For both groups, Tp-e and Tp-e/QT ratio were measured using a 12-lead ECG device.

Results – Tp-e interval, Tpe/QT and Tpe/QTC ratios were found to be higher in the patient group than in the control group (p<0.05, for all), while QTmax ratio was significantly lower in the patient group. After 3 months of AED therapy, significant increases in QT max, QTc max, QTc,d, Tp-e, Tp-e/QT, and Tp-e/QTC were found among the patients (p<0.05). When the arrhythmic effects of the drugs before and after treatment were compared, especially in the valproic acid group, there were significant increases in Tp-e interval, Tp-e/QT and Tp-e/QTC values after three months of treatment (p<0.05). Carbonazepine and levetiracetam groups were not statistically significant in terms of pre- and post-treatment values.

Conclusions – It was concluded that arrhythmogenic environment may be associated with the disease, and patients who received AED monotherapy may need to be followed up more closely for arrhythmia.

Keywords: epilepsy, ECG, arrhythmia, Tp-e interval, Tp-e/QT ratio

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Globally, epilepsy represents one of the most prevalent and serious neurologic conditions, with a reported prevalence of approximately 1% \(^1\). Various mechanisms have been implicated in the pathogenesis of epilepsy including dysregulation of ion channel function. Since these channels form the basis for the electrophysiological excitability of and communication between neurons, a dysfunction in them induced by mutations may directly affect the excitability of the brain and trigger epileptic seizures \(^2\). For instance, there is now mounting evidence of genetic code mutations in ion channels in epileptic children, who had been previously diagnosed with idiopathic or cryptogenic seizure disorders \(^3\), \(^4\). Moreover, channelopathies play a role in the pathogenesis of cardiac rhythm disorders such as the prolonged QT syndrome \(^5\), \(^6\). Acquired long QT syndrome is characterized by the prolongation of QT interval in electrocardiography (ECG) recordings \(^7\). It is thought that QT dispersion (QTd) does not reflect the spatial heterogeneity of ventricular refractoriness and may be caused by projections of repolarization dipole \(^8\). The difference between the maximum QT (QTmax) and minimal QT (QTmin) intervals in all measurable ECG electrodes, i.e. the QTd is considered a marker of arrhythmia that also provides a non-invasive and quantitative means for identifying non-homogeneous irregularities of the myocardial repolarization \(^9\).

Tpeak-Tend (Tp-e) interval is a practical measure for the transmural repolarization distribution in association with arrhythmogenic process \(^10\). Also, Tp-e/QT and Tp-e/QTc ratios are used as electrocardiographic indices of ventricular arrhythmias \(^11\). QTd alterations reflecting neurological disorders have also been defined \(^12\), \(^13\). Epileptic seizures may lead to severe autonomic and cardiovascular dysfunction \(^14\), \(^15\). Epileptic seizures may trigger untoward autonomic consequences including bradycardia, asystole, and even death \(^16\). Certain AEDs and particularly carbamazepine (CBZ) have an impact on the QT interval, with consequent development of cardiac rhythm disorders \(^17\). Despite numerous studies examining QT interval and QTd in epileptic patients, to the best of our knowledge, no studies have looked at Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio specifically.

In this study, ECG assessments were performed in epileptic patients with no other known disorders and in healthy controls.

**Patients and methods**

Patients with established diagnosis of epilepsy and no other systemic disorder attending to the Epilepsy Outpatient Unit, Department of Neurology, of our hospital before January 2016 and receiving monotherapy with first generation AEDs such as CBZ or valproic acid (VPA) or new generation AED levetiracetam (LEV) at any dose were included. The age at onset of seizures, disease duration, AED used, duration of AED use, seizure type, neurological exam results, and electroencephalography, cerebral imaging, and ECG findings were assessed. The diagnosis of epilepsy was based on ILAE 2017 classification \(^18\). The study protocol was approved by the Ethics Committee of our university (25th May 2016, No: 2016/4-4). Inclusion criteria were age between 18 and 50 years, presence of no conditions other than epilepsy, no regular use of medications other than AEDs, normal physical/neurological exam findings, normal cranial magnetic resonance imaging (MRI) findings, and use of CBZ, VPA, or LEV for a minimum duration of 6 months. Subjects in the patient or control group were excluded from the study if they had any abnormal complete blood and blood biochemistry results. Also excluded were those with diabetes mellitus, hypothyroidism, hyperthyroidism, chronic renal failure, cerebrovascular disease, cardiac valvular disease, pericardial or myocardial disorders, congenital cardiac disease, rhythm or conduction disorders, anti-arrhythmic use, and use of medicines known to affect the QT interval or the activity of the sympathetic nervous system. Examples of medicines with an effect on the QT interval include pridimone, rufinamide, and phenytoin \(^19\), \(^20\), none of which were used by our study participants. Patients receiving treatment with more than one AEDs were also excluded, to eliminate potential confusion regarding the cardiac effects of AEDs. ECG recordings obtained before and 3 months after the treatment were assessed in all patients. Also, ECG recordings in healthy individuals attending to the neurology outpatient unit were obtained using a 12-lead standard ECG device (Cardiofax M model 1350 K, Nihon Kohden, Tokyo, Japan) at a rate of 50 mm/sec and amplitude of 1 mV/cm. ECG interval assessments in both groups were performed by a cardiology specialist (E.Y.). P wave duration, PR and PR intervals, QRS duration, QT interval, and Td interval were measured manually. Tp-e/QT and Tp-e/QTc ratios were calculated from these parameters. Also, the corrected QT dispersion (QTcd) measurements were carried out based on the Bazett’s formula. In short, this involves the QTc based on Bazett’s formula (QT/RR\(^{1/2}\)) to measure the absolute QT interval in the ECG device \(^12\). The normal QTc value for males and females should be < 0.44 and < 0.46 sec., respectively. A QTc of > 0.44 sec and > 0.46 sec for male and female patients
are considered abnormal. For the calculation of dispersion values, the longest and shortest intervals in 12-lead recordings were determined, and the difference was considered as the QTcd for a given ECG recording. The Tp-e interval was measured from the peak to the end of the T wave.

Pre- and post-treatment QT interval, QTd interval, and QTcd were compared within the patient group to determine the risk of dysrhythmia, and also comparisons were made with healthy controls. Furthermore, the alterations in ventricular repolarization parameters (Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio) in patients on AED therapy were investigated.

STATISTICAL ANALYSIS

All analyses were performed using SPSS 21.0 for Windows (SPSS Inc., Chicago, Ill., USA). Continuous variables were calculated as means ± standard deviation; categorical variables were defined as percentages. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate a normal distribution. An independent-samples t-test and Mann-Whitney U tests were used to compare continuous variables between the two groups. Paired t test and Wilcoxon tests were used to compare variables between basal and after treatment values. The c² test was used to compare categorical data. A p-value <0.05 was considered to indicate significance.

Results

A retrospective data analysis was performed in a group of patients who were on AED monotherapy. The overall patient group consisted of 63 patients (mean age 29.9 ± 10.5 years); of these 26 were female (mean age 27.0 ± 10.2 years) and 37 were male (mean age 32.0 ± 10.2 years). A total of 35 subjects (mean age 28.9 ± 8.9 years), 18 female (mean age 28.6 ± 9.8 years) and 17 male (mean age 29.2 ± 8.1 years), attending to the neurology outpatient unit with complaints of headache and somatic conditions. The difference was considered as the QTcd for a given ECG recording. The Tp-e interval was measured from the peak to the end of the T wave.

Pre- and post-treatment QT interval, QTd interval, and QTcd were compared within the patient group to determine the risk of dysrhythmia, and also comparisons were made with healthy controls. Furthermore, the alterations in ventricular repolarization parameters (Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio) in patients on AED therapy were investigated.

As those with epilepsy syndromes due to neurodegenerative conditions.

Of the 63 patients with epilepsy included in the study 21, 18, and 23 were receiving treatment with VPA, CBZ, and LEV, respectively. Table 1 shows the demographic characteristics of the patients. Forty-three patients had partial seizures, and 20 were diagnosed with primary generalized seizures. The daily dosage ranged between 400 and 1200 mg for CBZ, while it was 500 to 1500 mg/day for patients on VPA or LEV treatment.

Patients receiving AED therapy had similar pre-treatment HR, QT, QTc, QTcd, Tp-e/QT and Tp-e/QTc values as compared to control subjects, except for QT max, which was significantly different (p<0.05) (Table 2). After 3 months of AED treatment, significant increases in QT max, QTc max, QTcd, Tp-e, Tp-e/QT, and Tp-e/QTc were found among the patients (p<0.05) (Table 3). The difference between pre- and post-treatment HR and QTd values did not reach statistical significance (p>0.05) (Table 3).

Mean Tp-e interval was significantly longer in the patient group both before and after AED therapy as compared to controls (74.2 ± 7.5, 75.1 ± 12.4, and 80.1 ± 15.2 msec, p<0.05). Also, as compared to pre-treatment values, Tp-e/QT and Tp-e/QTc were significantly higher after 3 months of AED therapy.

**Table 1. Age and gender distribution of patient and control group**

<table>
<thead>
<tr>
<th></th>
<th>Patient (n: 63)</th>
<th>Control (n: 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>31.7±13.6</td>
<td>28.9±8.9</td>
<td>0.221*</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>37 (58.7%)</td>
<td>17 (48.6%)</td>
<td>0.333**</td>
</tr>
</tbody>
</table>

*Independent sample t test, **chi-square test, p < 0.05

**Table 2. Electrocardiographic values of the patient and control group**

<table>
<thead>
<tr>
<th></th>
<th>Patient (n: 63)</th>
<th>Control (n: 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (beats/min)</td>
<td>75.6±9.5</td>
<td>71.2±10.4</td>
<td>0.011*</td>
</tr>
<tr>
<td>QT max (ms)</td>
<td>369.2±30.7</td>
<td>369.1±27.6</td>
<td>0.985**</td>
</tr>
<tr>
<td>QTc max (ms)</td>
<td>416.1±33.7</td>
<td>412.6±30.9</td>
<td>0.036*</td>
</tr>
<tr>
<td>QTd (ms)</td>
<td>33.1±8.6</td>
<td>28.6±10.9</td>
<td>0.028**</td>
</tr>
<tr>
<td>QTcd (ms)</td>
<td>35.8±9.3</td>
<td>32.1±11.9</td>
<td>0.003**</td>
</tr>
<tr>
<td>Tp-e (ms)</td>
<td>75.1±12.4</td>
<td>74.2±7.5</td>
<td>0.036*</td>
</tr>
<tr>
<td>Tp-e/QT</td>
<td>0.20±0.03</td>
<td>0.18±0.02</td>
<td>0.001**</td>
</tr>
<tr>
<td>Tp-e/QTc</td>
<td>0.23±0.04</td>
<td>0.19±0.03</td>
<td>0.001**</td>
</tr>
</tbody>
</table>
therapy (0.20 ± 0.03, 0.22 ± 0.04 and 0.23 ± 0.04, 0.25 ± 0.05; *p<0.05, for all) (Table 3).

When the arrhythmic effects of the drugs before and after treatment were compared, especially in the VPA group, there were significant increases in Tp-e interval, Tp-e/QT and Tp-e/QTc values after three months of treatment (*p<0.05). There was a statistically significant difference in CBZ and LEV groups before and after treatment (Table 4).

### Discussion

Sudden cardiac death is likely to be a cause of sudden unexpected death in epilepsy (SUDEP) in a minority of epilepsy patients. The exact mechanisms of SUDEP remains unknown, although a number of factors have been implicated including cerebral electrical stimulation as well as arrhythmias such as tachycardia, bradycardia, asystole, AV block, or ventricular fibrillation. Certain AEDs are known to have an impact on the cardiac rhythm and conduction. Cardiac side effects represent a relatively rare complication of AED therapy, and most reports involve CBZ use. On the other hand, other AEDs such as diphenyl hydantoin have anti-arrhythmic effects. Published data on the effect of AEDs on QTd is scarce, and QTc represents a useful and non-invasive means for assessing the repolarization heterogeneity of the ventricular myocardi- 

Table 3. Electrocardiographic values at baseline and 3 months after AED treatment in the patient group

<table>
<thead>
<tr>
<th>Patient at</th>
<th>Patient at</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline (n: 63)</td>
<td>3rd month</td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>75.6±9.5</td>
<td>77.1±10.9</td>
</tr>
<tr>
<td>QT max (ms)</td>
<td>369.2±30.7</td>
<td>408.9±18.8</td>
</tr>
<tr>
<td>QTc max (ms)</td>
<td>416.1±33.7</td>
<td>443.7±37.9</td>
</tr>
<tr>
<td>QTd (ms)</td>
<td>33.1±8.6 (8.0)</td>
<td>34.6±9.4</td>
</tr>
<tr>
<td>QTcd (ms)</td>
<td>35.8±9.3 (11.5)</td>
<td>38.9±10.3</td>
</tr>
<tr>
<td>Tp-e (ms)</td>
<td>75.1±12.4</td>
<td>80.0±15.1</td>
</tr>
<tr>
<td>Tp-e/QT</td>
<td>0.20±0.03 (0.04)</td>
<td>0.22±0.04</td>
</tr>
<tr>
<td>Tp-e/QTc</td>
<td>0.23±0.04 (0.06)</td>
<td>0.25±0.05</td>
</tr>
</tbody>
</table>

*paired t test, **Wilcoxon test, *p < 0.05

Abbreviations: HR: heart rate, QTc: corrected QT interval, QTd: QT dispersion, QTcd: QTc dispersion, Tp-e: peak and the end of the T wave

Previously, an association between seizure disorders and longer QTc interval has been reported. In particular, AEDs have been implicated in QT prolongation. Hesdorffer and Tomson also suggested that AEDs such as lamotrigine (LTG) and CBZ may increase the risk of SUDEP. In another study, potential cardiac side effects of AEDs such as CBZ and LTG have also been underscored. Also, alterations in PR and QTc intervals have been reported in epileptic patients treated with multiple AEDs in a study by Krishna and Krishnamurthy, with LEV being associated with marked effects in terms of PR and QTc prolongation. Conversely, Hulhoven, et al. reported a negligible effect of LEV on QT interval in healthy subjects. In a 2003 study by Akalin, et al. the same drug was associated with increased QT and QTcd in epileptic children, while other anti-epileptic agents (VPA, CBZ, phenobarbital) had no effect on QTd. Again, in another study by the same authors, children and infants with breath holding spells did not exhibit any statistical differences with controls in terms of QT and QTc interval. However, significant increase in QTd and QTcd was noted among the patient group, and the authors concluded that QTd may be increased in patients with breath holding spells. In one study, Köndler, et al. found longer QTc in 30 children and infants with childhood epilepsy in comparison with controls. Doğan, et al. reported longer QTc and QTcd that involved the QTc interval. A study by Siniscalchi, et al. comparing post-stroke epilepsy patients receiving AEDs with controls, a longer QTc was found in the former group, in addition to a significantly more marked effect of phenobarbital on prolonging QTc as compared to LEV. Issa, et al. reported prolonged QT interval in a 25-year old patient receiving LEV treatment. Similar to these previous reports, patients in our study were found to have a significant increase in QTd after 3 months of medical treatment as compared to the treatment free period. Also, Tp-e interval was longer in epileptic patients during both pre-treatment and post-treatment periods as compared to controls (74.2 ± 7.5, 75.1 ± 12.4, and 80.1 ± 15.2 milliseconds, *p<0.05). Also, as compared to pre-treatment values, Tp-e/QT and Tp-e/QTc were significantly higher after 3 months of AED therapy (0.22±0.04, 0.20±0.03 and 0.25±0.05, 0.23±0.04; *p<0.05, for all). The increase in QTd in epilepsy patients probably depends on two reasons; (i) auto-
onomic dysfunction\textsuperscript{39}, (ii) genetic mutations that cause disorders in ion channels\textsuperscript{40}. Heart seizures, heart rate variability and blood pressure abnormalities during seizures are indicators of autonomic dysfunction.

In contrast with these findings, in a recent study by Senol, et al.\textsuperscript{41} involving patients with different epilepsy types, no increase in P wave dispersion was reported, although these authors did not describe AEDs used for monotherapy in their study. The authors suggested that the results may be due to the small sample size and due to the possibility that ECG may fail to rule out intermittent episodes of arrhythmia, concluding that microthromboembolic resulting from atrial fibrillation may not be responsible for epileptic seizures. Kwon, et al.\textsuperscript{42} also failed to observe statistically significant differences in a group of patients receiving monotherapy, CBZ/oxcarbazepine (OXC) both within the monotherapy groups, and also when patients receiving multiple AEDs. Based on these observations these authors suggested that prolongation in QT interval may not predict unexpected deaths in patients with seizure disorders, despite underscoring the risk of cardiac arrhythmias in this patient group that may be triggered by a number of different causes. Furthermore, these investigators also emphasized the importance of regular ECG follow-up assessments after the initial epileptic seizure. Similarly, the observation that patients on AED therapy had significant increase in Tp-e/QT and Tp-e/QTc ratio after 3 months shows the importance of regular ECG follow-ups. Conversely, Saetre, et al.\textsuperscript{43} found a low prevalence of clinically significant ECG alterations with a slight increase in QTc interval in a group of elderly patients with epilepsy. In a recent clinical study, monotherapy with either VPA, CBZ, or OXC had no significant effects on QTd\textsuperscript{44}.

These results may contribute to the risk of cardiovascular mortality by specifying the pathophysiological mechanisms of increased prevalence of ventricular arrhythmia and the heterogeneity of increased ventricular repolarization in evaluating clinical status and prognosis before and after medical treatment in epilepsy patients. Also, routine ECG assessments may allow identification of serious cardiovascular disorders and may help prevent adverse cardiovascular outcomes in patients with seizure disorders.

The main limitation of our study is the relatively small number of patients. The future study should include the assessment of inter-ictal and ictal electrophysiological variables in a large population of patients, including specific syndromes, to further develop the pathophysiological mechanisms of SUDEP.
COMPLIANCE WITH ETHICAL STANDARDS
This article does not contain any studies with human participants or animals performed by any of the authors.
Informed consent written informed consent was obtained from patients who participated in this study.

CONFLICT OF INTEREST
The authors declare that they have no conflict of interest.

DISCLOSURE
All authors report no disclosures. The work described is consistent with the journal’s guidelines for ethical publication.

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AUTHOR CONTRIBUTIONS
Y. Altun MD. Study concept and design; acquisition of data; data analysis and interpretation; drafting manuscript; accepts responsibility for conduct of research.
E. Yasar MD. Data analysis and interpretation; editing manuscript; accepts responsibility for conduct of research.

REFERENCES