Short Term Effects of Antiepileptic Drugs on the Heart Using Electrocardiograph as an Assessment Tool of Investigation: A Pilot case Finding Study

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ABSTRACT:

BACKGROUND:

Antiepileptic drugs can induce changes in the electrocardiograph (ECG) records including prolongation of QT interval but there is no evidence to link this effect with the sudden death that reported in epilepsy. The new generations of antiepileptic drugs showed variable effect on the heart. Lamotrigine did not prolonged the QT interval in healthy subjects while levetiracetam prolonged the QT interval in patients cardiac channelopathy presented with congenital long QT syndrome**.**

OBJECTIVE:

This study aimed to investigate effects of antiepileptic drugs that prescribed in a therapeutic regimen to new cases of epilepsy as a part of management on the ECG records at the end of the 1st three months of treatment.

PATIENTS AND METHODS:

A total number of 25 patients, presented for the first time with epilepsy, were recruited from Al-Yarmouk Teaching hospital. Each patient was assessed clinically by consultant neurology prior to enrollment in the study. An electrocardiogram (ECG) was obtained at the time of entry into the study prior to the admission of the study and after three months of treatment with antiepileptic drugs. In addition to the measurements of heart rate and different ECG intervals, a QT-nomogram and cardiac restitution were used in analysis.

RESULTS:

At the time of entry, three patients had a significant short corrected QT interval (QTcB); four patients had a borderline QTcB interval; and one patient had prolonged QTcB interval. QT-nomogram revealed that many patients have abnormal interval and antiepileptic drugs significantly reduced the relaxation phase of cardiac cycle and prolonged the ventricular repolarization.

CONCLUSION:

Antiepileptic drugs carried a harmful effect on the heart and their assessment should be not restricted in the measurement of QT interval before and after treatment or to study their effects on the healthy subject as epilepsy is commonly associated with mutation of sodium and/or potassium channels. Case finding of significant prolonged QT interval in respect to gender and age, assessment of QT nomogram and cardiac restitution are useful tools to identify the patients who are at risk of arrhythmias.

KEY WORDS: epilepsy, ECG, QTcB, restitution.

INTRODUCTION:

Prolongation of QT interval in electrocardiograph (ECG) records is frequently reported with medications like antihistamines, antipsychotics, macrolides, fluoroquinolones, antidepressants and others [1-5]. Antiepeleptic drugs induce changes in the ECG records including prolongation of QT interval but there is no evidence to link this effect with the sudden death that reported in epilepsy [6]. The new generations of antiepileptic drugs showed variable effect on the heart. Lamotrigine did not prolonged the QT interval in healthy subjects [7] while levetiracetam prolonged the QT interval in patients cardiac channelopathy presented with congenital long QT syndrome [8] and in healthy subjects, levetiracetam did not induce prolongation of QT interval [9] On the other hand,

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Feldman and Gidal (2013) [10] attributed the cause of sudden death to the seizure and the antiepileptic drugs are not free from risk in patients who are potentially at risk of prolongation of QT interval. There is evidence that sodium channelopathy is linked with epilepsy as these channels have a low threshold and more likely to produce spontaneous firing and paroxysmal depolarizing of the neurons in the hippocampal region [11]. Moreover, mutation of Nav1.1 channel leads to loss its function and showed a link with febrile convulsion and intractable seizure [12]. The rationale of this study is related to the fact that not all antiseziures exert their effect on the sodium channels and antiepileptic drugs not necessarily induced prolongation of QT interval if we assumed the distribution of types of voltage sodium channels in heart and brain are shared similarity. Therefore, this study aimed to investigate effects of antiepileptic drugs that prescribed in a therapeutic regimen to new cases of epilepsy as a part of management on the ECG records over the 1st three months of treatment

PATIENTS AND METHODS:

This double blind clinical trial reviewed by the Scientific Committee at College of Medicine and approved the Council of Al-Mustansiriya University in Baghdad, Iraq. The patients were recruited from Al-Yarmouk Teaching and Baghdad Hospitals from 1st February to the end of July 2015. A consent form was obtained from each patient prior to the enrollment in this study for the following reasons:

New cases of epilepsy (including primary and secondary epilepsy) who did not receive antiepileptic medications at the time of the entry in the study were enrolled in this study. The eligible patients for this study were both gender of whatever age in order to cover the childhood epilepsy (up to 18 years old), adult epilepsy (19-49 years) and patients with associated risk factors of epilepsy (≥50 years).

The criteria of inclusion are: patients with a clinical diagnosis of epilepsy. The diagnosis of epilepsy is achieved by the consultants of neurology. The patients were newly diagnosed and did not use antiepileptic medications. The clinical diagnosis of epilepsy is supported by electrophysiological study, electro-encephalogram (EEG), and radio-imaging studies. The criteria of exclusion are: patients with cardiovascular or hepatic or renal diseases, psychotic disorders, clinical and laboratory evidence of electrolyte disturbances, current history of medications (e.g. macrolides; antipsychotics, antidepressants; antihistamines antiarrhythmics), and pregnant or lactated mothers.

At the first visit, each patient was examined thoroughly by the consultants of neurology and the data that related to the objective of the study were obtained by the researcher candidate. Then each participant is subjected to the electrocardiography (ECG) investigation on the admission into the study and this record represented as "before treatment record".

Then the patients were treated with antiepileptic drugs according to the prescriptions guided by the consultants of the neurology according to their diagnosis. Then the patients were followed-up for three months after receiving the antiepileptic drugs. At the end of the trial patients were investigated with the second ECG record and this record represented "after treatment record". The specifications of the ECG machine are: 12 standard leads, the sensitivity is 10 mm/mV, the record speed is 25mm/sec. The machine electronically recorded on the ECG trace the heart rate, PR interval, QRS interval, QT interval, QTc, and P-R-T axis for diagnosis.

The ECG records of patients who were in sinus rhythm are obtained. In order get an accurate measurement, the strip ECG record of each patient is divided in respect to the leads, that is, (Lead I,II,III) strip; (Lead aVR, avL, aVF) strip; and (precordial leads V1-V6) strip. Then the ECG record strips were scanned and the scanned picture was magnified by PC windows photo-viewer to zoom. From each ECG record strips, the following data were obtained: Heart rate (beat/min); R-R interval (sec.); P-R interval (sec.);QRS wave duration (sec.); QRS dispersion (sec.); QTm (QT measured) interval (sec.); QTc(QT corrected)interval (sec.); JTm (JT measured) interval (sec.); JTc (JT corrected) interval (sec.); TQ interval (sec.); R wave amplitude V5 (mV); S wave amplitude (mV); and summation of S(v1) and R(v5).

QTc (QT corrected) interval (sec.): It calculated by using the following formulae:

Bazett formula (QTcB) = $QTm/\sqrt{R}R$ [13].

The cut-off point of QTcB value is used according to Goldberg et al (2006) [14] with a modification of children and adolescent age that instead of < 15 years, ≤18 years old is considered:

Table 2.1 Cut-off value of QTcB according to age and gender.

Category	Children and adolescent < 18 years	Adult male	Adult female
Normal	<0.44 sec.	< 0.43 sec.	< 0.45 sec.
Borderline	0.44-0.46 sec.	0.43-0.45 sec.	0.45-0.47 sec.
Prolonged	>0.46 sec.	>0.45 sec.	>0.47 sec.

A QT nomogram plot that developed by Chan et al (2007) used to identify the patients who are vulnerable or at risk of developing cardiac arrhythmias[15]. The QT-nomogram plot represented a plot of heart rate against the QT interval and any point out of the curve indicated that patient is vulnerable to cardiac arrhythmias. QTcB/TQ ratio is simply calculated by dividing the QTcB interval by TQ. This ratio represents the ECG restitution. The term restitution means the ability of heart to recover from the contraction of the one beat to the relaxation phase of the next beat. This ratio represented the relationship between the duration of action potential (represented by QT duration) and the diastolic interval (represented by the TQ duration). Therefore a ratio of ≥ 1.0 is an alarm for cardiac arrhythmias (due to reentry of impulse) and indicates that the patient may at a risk of *torsade de pointes* [16,17].

A total number of 25 patients (9 female and 16 male) with age ranged from 5 to 80 years old were completed the study.

2.4 Statistical analysis

The results are presented as number, percent and whenever possible as mean ± SD. Excel 2007 program was used for the analysis of the data. The data were analyzed using Student's "t" test (two tailed, paired). The probability of ≤ 0.05 is considered as the lowest limit of significance.

RESULTS:

Table 1 shows the characteristics of the patients enrolled in the study. The number of male patients is higher than corresponding number of female gender. In respect to the age group the distribution of patients according to their occupation showed student in patients of ≤18 years old and employee in age group 19-49 years. Most of the patients were resident in the urban areas and all patients were Arab ethnicity. Four out of 25 patients (16%) have family history of epilepsy in patients of age ≤18 years. History of head injury and migraine are reported in 4% and 8% of patients. Table 2 Shows that all the patients were treated with monotherapy and levetiracetam was prescribed to 15 (60%) patients. Supplementary drug therapy including calcium and/or without vitamin D were prescribed only to three patients. Table 3 shows the changes that occurred after three months of treatment with antiepileptic drugs. The statistical analysis revealed non-significant differences in the ECG at the baseline and after three months of treatment. The non significant increase of the mean value of QTcB is 17 milliseconds. The mean value of the ratio of QTcB to TQ does not reach the value of 1. Table 4 shows the three patients (12%) have significant shortening of the QTcB interval and changed to within normal duration of QTcB after treatment with antiepileptic drugs. Borderline value of the duration of QTcB interval is observed in four patients (16%) and remained so after treatment. Only one patient (4%) has significant prolonged QTCB duration and this number increased to 2(8%) patients after treatment. Figure 1 shows the clustering of patients around the nomogram line indicated the prolongation of QT interval after treatment. Also the QT-nomogram shows that number of patients whether before or after treatment are distributed above the QT nomogram, that is, have significant prolonged QTcB interval. Figure 2 shows the restitution steeping of the heart in epilepsy patients. Before the treatment the patients are distributed in an ellipsoid shape indicating that the relaxation phase of the heart is approximately equal to that of depolarization and repolarization of the ventricle. After antiepileptic treatment the restitution steeping takes a triangle shape and shifted to the left side which indicates that the heart undergoes short relaxation period and longer duration of depolarization and repolarization.

Table 1: Characteristics of patients enrolled in the study.

	≤ 18 years	19-49 years	≥ 50 years
Gender (Female: Male)	5:8	3:5	1:3
Age (year)	13.4±4.7	32.1±9.9	66.3±12.0
Occupation Employee Student Housewives Children Retired	 - 12 - 1 -	 5 2 1 - -	 1 - 1 - 2
Residency Urban Rural	 9 4	 7 1	 0 4
Ethnicity Arab Kurd Turkmen	 13 0 0	 8 0 0	 4 0 0
Family history of epilepsy 1st relative 2nd relative Negative	 2 2 9	 0 0 8	 0 0 4
History of head injury	1	0	0
History of migraine	2	1	0

The results are expressed as absolute number.

Table 2: Distribution of patients according to the antiepileptic drug prescription.

Current drug therapy	≤ 18 years	19-49 years	≥ 50 years
Monotherapy Carbamazepine Oxycarbazepine Sodium valoproate Levetiracetam Lamotrigine Polytherapy	 1 3 3 6 0 0	 0 0 1 6 1 0	 1 0 0 3 0 0
Supplementations Calcium Vitamin D *plus* calcium	 0 2	 1 0	 0 0
Drug-adverse reactions	1	0	0

The results are expressed as absolute number

Table 3: Effect of short term antiepileptic drug on the electrocardiograph records.

Electrocardiograph Record	Before treatment	After treatment
Heart rate (beat/min.)	80.7±13.8	80.7±10.1
PR interval (sec.)	0.150±0.025	0.152±0.021
QRS complex (min.)	0.089±0.019	0.094±0.019
QRS dispersion (sec.)	0.044±0.017	0.045±0.017
QTm interval (sec.)	0.358±0.038	0.365±0.035
QTcB interval (sec.)	0.407±0.037	0.420±0.035
TQ interval (sec.)	0.591±0.155	0.558±0.093
QTcB/TQ ratio	0.747±0.244	0.774±0.144
JTm interval (sec.)	0.269±0.036	0.271±0.034
JTc interval (sec.)	0.318±0.038	0.325±0.024
Voltage criteria (Sv1+Rv5)	0.704±0.374	0.759±0.361

The results expressed as mean ±SD. Non- significant differences.

Table 4: Case finding of changes in the duration of QTcB interval in patients treated with antiepileptic drugs.

	Before Treatment	After treatment
Short QTcB interval (≤0.350 sec.)	3	0
Normal QTcB interval (Children and adolescents: < 0.440 sec.) (Adult males: (< 0.430 sec.) (Adult females: (< 0.450 sec.)	17	19
Borderline QTcB interval (Children and adolescent: 0.440-0.460 sec.) (Adult males: (0.430-0.450 sec.) (Adult females: (0.450-0.470 sec.)	4	4
Abnormal (pathological) QTcB interval (Children and adolescent: > 0.460 sec.) (Adult males: (> 0.450 sec.) (Adult females: (> 0.470 sec.)	1	2

The results are expressed as absolute number

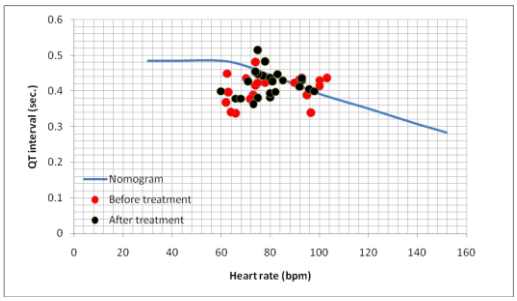

Figure 1: QT nomogram shows the effect of antiepileptic drugs on QT interval.

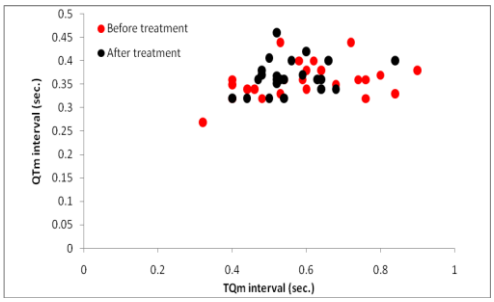

Figure 2: Effect of antiepileptic drugs on the restitution steepness as a function of QTm interval against TQm interval.

DISCUSSION:

The results of this study show that antiepileptic drugs in short term therapy induce significant effect on the heart manifested by prolongation of QT interval and shortening the relaxation phase of the heart. The characteristics of the patients are unlikely influence the results. Family history of epilepsy is reported in 4 patients aged ≤ 18 years and this observation is in agreement with other study which demonstrated eight of 107 patients with pediatric idiopathic epilepsy had a family history of autosomal dominant inheritance in their families [(18)]. In this study, the possibility of drugs interaction is not the cause of cardiac toxicity of antiepileptics because the policy of monotherapy was applied to all patients as a therapeutic regimen. Danielsson et al (2007) found that polytherapy more than monotherapy induced prolonged repolarization of the cardiac cycle and associated with high risk of arrhythmias[(19)]. The antiepileptic drugs that prescribed in this study induced ECG changes as supported by the following evidences. Firstly, three patient had shortening of QTCB which corrected to the within normal value after treatment. Mutation of potassium rectifying inward channel (Kir 2.1) is associated with epilepsy phenotype and short QT syndrome [(20)]. Therefore, antiepileptic drugs are of advantage in management of epilepsy and short QT syndrome. Secondly, the number of patient with significant prolonged QT is one before treatment and becomes two after treatment. As mentioned in introduction, many antiepileptic prolonged QT interval. The QT nomogram shows that there are many patients are distributed above the nomogram line and those are potentially at risk of cardiac arrhythmias. The use of QT nomogram in assessment of QT interval in epilepsy is reported for the first time in this study. Literature review revealed that QT nomogram is a useful tool in assessment of QT in patients treated with antipsychotics overdose [(21, 22)]. And thirdly the plot of heart restitution revealed that the distribution of patients shifted to the left side which indicated the relaxation phase of the heart becomes shorter after using antiepileptic and therefore, the patients are at risk of lethal arrhythmias. Such effect is reported in patients with a mutation in the potassium channels (KCNH2-encoded human Ether-à-go-go) that is commonly associated with epilepsy [(23)] Antiepileptic drugs are useful in termination of seizure in patients presented with potassium channels mutation via their effects on the sodium channels in the brain and therefore their prescriptions may be adversely the cardiac channels [(24)]. One of the limitations of the study is small sample size.

CONCLUSION:

Antiepileptic drugs carried a harmful effect on the heart and their assessment should be not restricted in the measurement of QT interval before and after treatment or to study their effects on the healthy subject as epilepsy is commonly associated with mutation of sodium and/or potassium channels. Case finding of significant prolonged QT interval in respect to gender and age, assessment of QT nomogram and cardiac restitution are useful tools to identify the patients who are at risk of arrhythmias.

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