

## ORIGINAL ARTICLES

# Carbamazepine and the QTc interval: any association?

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### Abstract

**Objective:** To determine whether carbamazepine monotherapy in epilepsy patients is or is not associated with prolongation of the QTc interval. **Methods:** This case-control study enrolled 100 consecutive patients with generalized tonic-clonic seizures. Fifty patients were already taking carbamazepine for a variable time, and the rest (n=50) were not on any antiepileptic drug. The QTc interval was calculated after doing a resting 12-lead ECG examination on a single occasion. **Results:** Of the 50 patients who had received carbamazepine, 11 patients displayed prolongation of their QTc interval, while 8 patients out of the 50 in the control group had QTc interval prolongation after correction for gender; *p* value =0.49, OR 1.36, 95% CI 0.54-3.29.

**Conclusion:** This study demonstrated no statistically significant association between carbamazepine monotherapy and prolongation of the QTc interval. Carbamazepine does not seem to prolong the QT interval when used as monotherapy for epilepsy. The presence of prolonged QTc interval in such patients should prompt a search for co-factors that prolong this interval, such as multiple medications, electrolytes disturbances, structural heart disease, and congenital long QT interval syndromes.

### INTRODUCTION

Several antiepileptic drugs have been found to adversely affect the cardiovascular system. Carbamazepine may result in arrhythmias, AV block, bradycardia, chest pain, heart failure, oedema, hyper/hypotension, syncope, thromboembolism, and thrombophlebitis.<sup>1</sup> When compared with the general population, epileptic patients have a greater risk of developing sudden explained death.<sup>2-4</sup> Although the precise mechanism (or mechanisms) behind this observation is still controversial, a drug-induced prolongation of the QT interval has been suggested by many studies, and carbamazepine has been included as one of the culprits of this QT interval prolongation.<sup>5</sup>

### METHODS

In conducting this case-control study, we tried to find an association between the use of the anti-epileptic carbamazepine and prolongation of the QTc interval. The study was conducted at

the Baghdad Teaching Hospital and Sulaimaniya General Teaching Hospital. Patients from the Neurology Outpatients' Clinic as well as Inpatients were enrolled from June 1<sup>st</sup> 2009 to February 1<sup>st</sup>, 2010. Post-graduate neurology trainees did the history taking and clinical examination. All patients underwent a resting 12-lead ECG examination, which was carried out by technicians. These ECGs were interpreted by Physicians. The Hospital Administration, its Medical Ethics Committee, and the caring Neurologists approved the conduction of this study. An informed consent was obtained from the patients/guardians.

### Inclusion criteria and initial work-up

We evaluated 100 individuals with generalized tonic-clonic seizures. Fifty patients with generalized tonic-clonic seizures who were taking carbamazepine (with no other antiepileptics or drugs that prolong the QTc interval) were included in the study. The control group consisted of 50 individuals with newly diagnosed generalized

tonic-clonic seizures, who were otherwise healthy and took no anti-epileptics or other medications. Patients with *any* one of the following were excluded from the study: Pre-existent structural heart disease, cardiac arrhythmia, taking medications that could influence the cardiac conducting system, gross ECG abnormalities (such as prolonged QRS interval and prominent U wave that merges with the T wave), and electrolytes disturbances. However, patients with normal ECG variants, such as persistent juvenile pattern, were included in the study.

All patients (n=100) underwent routine blood tests and resting 12-lead ECG examination. The ECG was done on a single occasion. Patients in the control group had their ECGs done before starting the prescribed antiepileptic medication; the other group of patients were on carbamazepine therapy for a variable period.

We measured the QT interval manually, from the onset of the QRS complex to the point at which the T wave ends, and we measured it for 3 to 5 consecutive beats and averaged.<sup>6</sup> We chose lead II for this purpose as most normal reference ranges are based upon measurements from this limb lead.<sup>7-9</sup> The corrected value (QTc) was calculated using the Bazett formula.<sup>10,11</sup> We did not use automated ECG machines to calculate the QT and QTc intervals, as the accuracy of these automated tools has been shown to be limited.<sup>12</sup>

Trans-thoracic echocardiography was carried out in 38 individuals while brain imaging (CT scan or MRI) was performed in 81 cases. Electroencephalogram was done only in the control group (n=50) at the time of the diagnosis. A QT interval of >0.44 msec in males and >0.46 in females was regarded as prolonged.<sup>13</sup> None of the patients underwent serum carbamazepine assessment.

#### Statistical analysis

The QTc interval findings in patients taking carbamazepine and those who were not taking this antiepileptic were compared. The comparison between these two groups was done using the  $\chi^2$  test and the Student's *t* test. We calculated the *p* value, odds ratio (OR), and 95% confidence interval (95% CI). A *p* value of < 0.05 was considered statistically significant.

## RESULTS

This case control study involved 100 consecutive patients with generalized tonic-clonic seizures.

Fifty-two patients were males while the rest (n=48) were females. The ages of the patients ranged from 2 to 50 years (with a mean of 22.5 years and a standard deviation of 13.7 years). Fifty patients were taking carbamazepine monotherapy (ranging from 3 weeks to 12 years duration and a mean of 5.8 years). The daily doses ranged from 200 to 1200 mg with a mean of 600 mg a day. The control group included 50 patients with newly diagnosed generalized tonic-clonic seizures who were not receiving any anti-epileptic medication. The various patient characteristics are summarized in Table 1.

The majority of the QTc intervals were within the normal limit (when corrected for gender, i.e. <0.44 sec in males and <0.46 sec in females) in patients receiving carbamazepine and in patients who were not on carbamazepine (Table 2). The QTc ranged from 0.29 to 0.59 sec and a mean of 0.42 sec in the carbamazepine-treated group while the control group displayed QTc intervals between 0.32 to 0.51 sec and a mean of 0.40 second. Figure 1 illustrates the maximum, minimum, and average QTc intervals in both groups.

We found no statistically significant association between the two groups (i.e., patients receiving carbamazepine versus patients who were not) in terms of QTc prolongation; *p* value=0.49, OR 1.36, and 95% CI 0.54-3.29. Of the 50 patients who had received carbamazepine, 11 patients demonstrated prolongation in the QTc interval, while 8 patients out of the 50 patients in the control group had prolongation of this interval after correcting these values for the patient's gender.

## DISCUSSION

Prolongation of the QT interval by certain medications and drugs has been well documented by many studies.<sup>14-17</sup> Carbamazepine may result in sinus bradycardia, AV block, cardiac dysrhythmia, and syncope by blocking the sodium channels in the cardiac conducting system. However, these effects were not related to the plasma level of carbamazepine.<sup>1,18-20</sup>

Carbamazepine, which has a tricyclic structure, binds to voltage-dependent sodium channels, mainly during their period of inactivation. Therefore, this binding would extend the inactivated phase and inhibit the generation of action potentials when the cell is still experiencing incoming depolarizing trains; this blocking efficiency of the drug increases with the rate of neuronal firing. The net result will be a negative impact on the heart that is expressed as the

**Table 1: Patient characteristics (n=100)**

Patient characteristics	Cases on carbamazepine n=50	Controls on no treatment n=50
Age (years)		
Mean	19.4	27.2
Median	17.5	22
Gender		
Male	27	25
Female	23	25
Occupation		
Employed	7	19
Unemployed	28	16
Student	9	12
Preschool	6	3
Marital status		
Married	17	21
Single	33	29
Residence		
Baghdad	21	25
Sulaimaniya	20	23
Erbil	5	1
Kirkuk	3	1
Diyala	1	0
Family history of epilepsy		
Positive	22	24
Negative	28	26
Social history		
Smoking	19	23
Alcohol ingestion	2	1
Drugs of abuse	0	0

cardiac side effects of the drug<sup>1,21</sup>, but whether this influence is “clinically” significant or not, it has to be proved or refuted by further analytic studies.

The non-significant “statistical” association between the use of carbamazepine and prolongation of the QTc interval in our study is consistent with the result of a study conducted by Matteoli *et*

**Table 2: Distribution of normal and prolonged QTc intervals among patients treated with carbamazepine (n=50) and patients on no treatment (control group; n=50).**

	Prolonged QTc*	Normal QTc	Total
No. of patients on carbamazepine	11	39	50
No. of patients on no treatment	8	42	50
Total	19	81	100

\* The upper limit of the QTc interval is 0.44 sec in males and 0.46 sec in females.

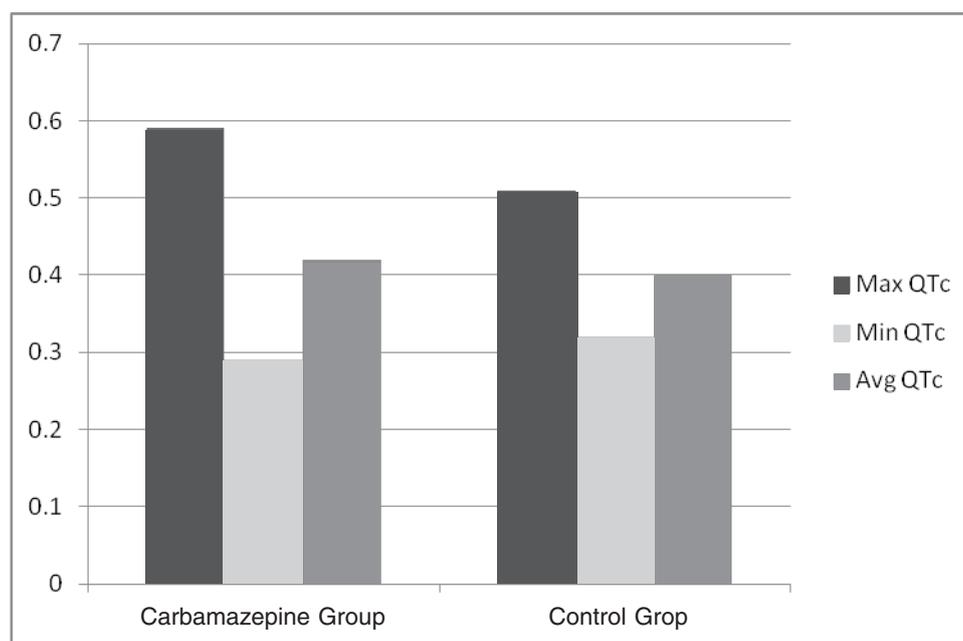


Figure 1: Chart showing maximum, minimum, and average QTc intervals in epileptic patients treated with carbamazepine (n=50) and patients with no treatment (control group; n=50).

*al.*<sup>18</sup> Monotherapy with carbamazepine does not seem to result in QT interval prolongation, unless other factors are also operative; e.g., electrolytes disturbances or preexistent structural cardiac disease. On the other hand, poly-pharmacy with other drugs (including anti-epileptics) can produce QT interval prolongation via multiple mechanisms, including interactions during their hepatic P450 isoenzyme CYP3A metabolism.<sup>22</sup>

In conclusion, this study demonstrated that there is no statistically significant association between carbamazepine monotherapy and prolongation of the QTc interval when this medication is used as monotherapy for epileptic patients. The presence of prolonged QT interval in such patients should prompt a search for other factors that can prolong this interval, such as multiple medications, electrolytes disturbances, structural heart disease, and congenital long QT interval syndromes.

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