#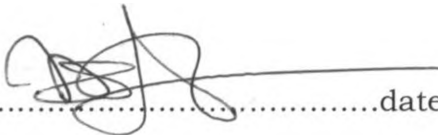 CORRECTED QT INTERVAL IN PATIENTS WITH EPILEPSY ATTENDING KENYATTA NATIONAL HOSPITAL AND THE KENYA ASSOCIATION FOR THE WELFARE OF PEOPLE WITH EPILEPSY CLINICS IN NAIROBI.

A DISSERTATION SUBMITTED IN PART FULFILMENT OF MASTER OF MEDICINE DEGREE IN INTERNAL MEDICINE OF THE UNIVERSITY OF NAIROBI.

BY

DR JOHN KIBET RONO

DECLARATION

I declare that this dissertation in part fulfilment of my M.Med thesis (Internal Medicine) is my original work and has not been presented to any other university or forum

Signed..date.........11|3|2009

SUPERVISORS

This dissertation has been submitted for consideration and with our approval as university supervisors

Signed... Date....16 / 3 / 09.

PROF. A.M. ADAM

Consultant Neurologist and Associate Professor of Medicine

Department of Medicine, University of Nairobi

Signed.......................................Date....13 / 3 / 2009....

DR. M. JOSHI

Consultant Cardiologist and Clinical Epidemiologist

Senior lecturer, Department of Medicine

University of Nairobi.

Signed.......................................Date....17/03/09.

DR. J.O. JOWI

Consultant Neurologist and Physician

Aga Khan University Hospital

Nairobi

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- Other members of the Department of Internal Medicine their support, encouragement and criticism.
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ABBREVIATIONS

AEDS	-	Antiepileptic drugs
CBZ	-	Carbamezapine
CI	-	Confidence interval
Clonaz	-	Clonazepam
ECG	-	Electrocardiogram
EEG	-	Electroencephalogram
Fig	-	Figure
KAWE	-	Kenya Association for the Welfare of people with Epilepsy
Km	-	Kilometres
KNH	-	Kenyatta National Hospital
Min	-	minute
mmHg	-	millimetres of mercury
ms	-	Milliseconds
mV	-	millivolts
Na valp	-	Sodium Valproate
NGO	-	Non-governmental Organization
Phenobarb	-	phenobarbitone
PHT	-	Phenytoin
pp	-	page
s	-	Second
SD	-	Standard deviation
SE	-	Standard error
SUDEP	-	Sudden unexpected death in epileptic patients
Tab	-	Table
USA	-	United States of America
WHO	-	World Health Organization

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ABSTRACT

Background:

Patients with epilepsy have a mortality rate two to three times that of the general population. Sudden unexpected death in epilepsy (SUDEP) is a major cause in studies of mortality in epilepsy. SUDEP is defined as a non accidental death in a patient with epilepsy with or without evidence of a seizure having occurred and excluding status epilepticus, where autopsy reveals no anatomical or toxicological cause. The effects of seizures and antiepileptic drugs on cardiac conduction are known to cause SUDEP. The duration of the QT interval (prolonged or shortened) has been implicated in its pathogenesis.

Objectives

To compare the QT interval in patients with epilepsy with non-epileptic age (to the nearest one year) and sex matched controls.

Study design

Comparative cross-sectional study

Methods

Standard 12-lead ECGs were recorded from 146 patients with epilepsy (62 not on treatment, 84 on antiepileptic drugs) and 146 age and sex matched controls from Kenyatta National Hospital and the Kenya Association for the Welfare of people with Epilepsy (KAWE) clinics in Nairobi. The mean QT - interval corrected for heart rate (QT_c) for the patients with epilepsy and controls were compared. The relationship between mean QTc and seizure frequency, type and number of anti-epileptic drugs was analysed.

Results

The mean QTc for patients with epilepsy (405.7 ±31ms) was significantly shorter than in the control group (414.9±29.6 ms), $p<0.0001$. Untreated patients with epilepsy had a significantly shorter mean QTc of 405.6±33ms compared to the matched controls (415.4±27.8ms), $p=0.0005$. Similarly, patients on anti-epileptic drugs also had a significantly shorter QTc compared to the matched controls (405.9±29.6ms vs. 414.6±31ms, $p=0.0003$).

However, there was no statistical difference in the mean QTc in both groups of epilepsy patients (on anti-epileptic drugs and not on treatment) (405.6±33ms vs. 405.9±29.6ms, p value= 0.91). The mean QTc did not significantly differ between patients in relation to seizure frequency (p=0.253) and type (p=0.225) and number of antiepileptic drugs (p =0.77).

Conclusion

Patients with epilepsy had a significantly shorter QTc than controls and there was no association between anti-epileptic drugs and QT interval.

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Epilepsy is defined as recurrent presentation of two or more unprovoked seizures [1]. The annual incidence of epilepsy is approximately 0.3 to 0.5% in different populations throughout the world and the prevalence has been estimated at 5 to 10 persons per 1000 [2]. The prevalence in Kenya is between 10.2 to 18.2 per 1000 [3] and is the second commonest presenting neurological condition at KNH [4].

Patients with epilepsy have a risk of death that is roughly two to three times greater than expected in a matched population without epilepsy [2]. A significant number die from accidents, status epileptics and a syndrome known as sudden unexpected death in epileptic patients (SUDEP) [2].

SUDEP is a sudden unexpected non-accidental death in a patient with epilepsy with or without evidence of seizure having occurred and excluding status epileptics where autopsy reveals no anatomic or toxicological cause [5].

It usually affects young people (between 20 - 40 years) with convulsive disorders and tends to occur at night. The cause is unknown; it may result from brainstem-mediated effects of seizures on cardiac rhythms or pulmonary function [2]. Ventricular arrhythmias associated with abnormal QT interval have been implicated in the pathogenesis of SUDEP [5].

SUDEP incidence rates of up to 5 per 1000 per year have been reported by studies based on tertiary epilepsy clinic data [6]. Other reports have documented an incidence of 0.5 - 6 per 1000 person years of follow-up and it accounts for 7-18% deaths in people with epilepsy in USA [7]. There is scanty data in Africa on the mortality of epilepsy, however, a small study in Ethiopia [8] gives an estimate of 3.16% (compared with 1.64% in those without epilepsy) with status epilepticus and burns being the modes of death attributed directly to seizures. SUDEP goes unrecognised in our set up [8].

1.1 Pathophysiology of Arrythmias and SUDEP

As per the definition, autopsy fails to reveal the underlying cause of death in SUDEP but pulmonary oedema or other organ congestion e.g. enlarged heart, enlarged liver is commonly found [9]. Different pathophysiological events may contribute to SUDEP in different patients, and the mechanism is probably multifactorial.

Respiratory events, including airway obstruction, central apnoea, and neurogenic pulmonary edema are probable terminal events. Cardiac arrhythmia during both Ictal and interictal periods leading to arrest play a role. Antiepileptic drugs (AEDs) such as carbamezapine may also contribute to SUDEP [7].

Abnormal neuronal electrical activity corresponding to a seizure can involve central areas for regulation of autonomic activity [10].
Endogenous opioids that may be released during seizures have been implicated in the causation of central hypoventilation and could account for the suppression of respiratory drive leading to death [11] Massive sympathetic discharge can be the cause of potentially fatal ictal arrythmias. Damage to the myocardium caused by frequent increase in plasma catecholamines can produce areas of degeneration and fibrosis that can serve as new foci for tachyarrythmias in the interictal state [12]. Fibrosis of the conduction system have been reported in 33% of patients at autopsy[13]. However, quantitative evaluation of fibrosis has demonstrated a trend towards more fibrosis in the deep and subendocardial myocardium of SUDEP cases[14]. Li and co-workers [15] found that during temporal lobe seizures there was evidence of sinus tachycardia and sometimes sinus bradycardia, which might be related to sudden death.

A recent case control study showed that the relative risk of SUDEP increased with the number of seizures per year, appearing substantially higher in patients with more than 50 seizures per year than in patients with two or less seizures per year [16]. The incidence of SUDEP is highest in

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patients with refractory seizures [6].

It has been found that both long and short QT interval is associated with a two-fold increased risk of sudden death[17, 18]. Short QT interval leads to shorter atrial and ventricular refractory period and altered automaticity with increased susceptibility to ventricular fibrillation and atrial fibrillation [19]. Prolonged QT interval leads to the development of a polymorphic ventricular tachycardia called tirade de pointes through the development of early after depolarizations and triggered activity resulting from prolonged repolarizations[20].

Recently, the concept of channelopathy has been introduced to explain the pathophysiology of epilepsy, episodic ataxia, periodic paralysis and cardiac disorders such as short QT syndromes .[2] Malfunctions in ion channels resulting from mutations in the genes encoding channel proteins or the presence of auto antibodies are implicated in causing these conditions [21]. Mutations of the K⁺ current rectifier channels (e.g. Ikr, Iks, Ikl) with gain of function leads to shortening of repolarization and subsequent shortening of QT interval as shown in figure 1 below [22].
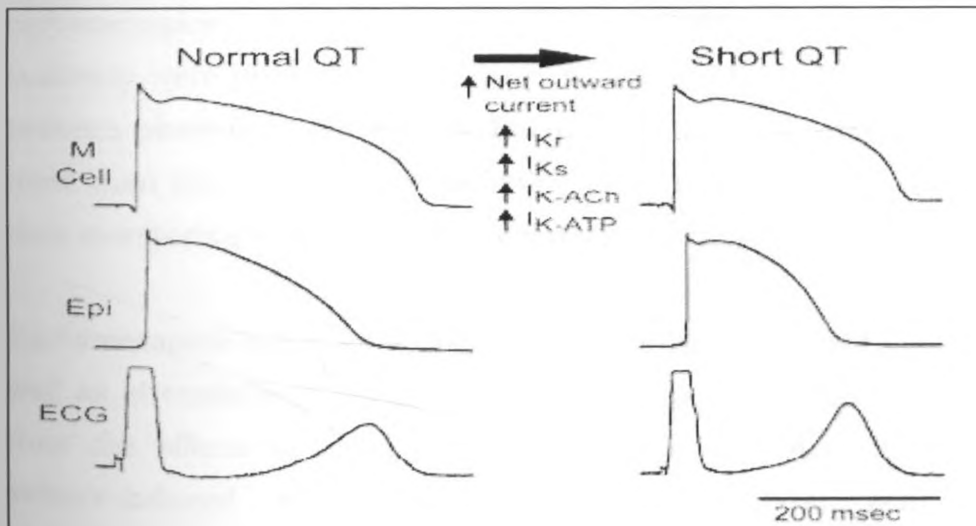

Fig 1. Cellular changes attending shortening of QT interval secondary to an increase in net outward repolarizing current. Epi=epicardium

Many ion channel disorders are co-expressed in the heart and brain. Some individuals may have a coexisting unrelated 'mild' genetic susceptibility, which then manifest because of uncontrolled seizures.[23]

Tan H. et al. [24] demonstrated that epilepsy patients had a significantly shorter QT_c than controls, particularly in the subgroup of patients with cryptogenic epilepsy. They concluded that shortening of the QT_c interval was associated with sudden cardiac death. In a different study, Tavernor and colleagues [25] examined QT interval corrected for rate (QT_c) during at least two interictal epileptiform discharges in patients who later died from SUDEP and from other patients with intractable seizures who were still alive. They found a statistically significant increase for QT_c values during EEG discharges among those who died suddenly.

1.3   Role of Antiepileptic drugs in Arrythmias and SUDEP

The possibility that carbamezapine is involved in sudden death among those with epilepsy has been considered [26, 27] and this may also apply to other antiepileptic drugs. This observation has however not been seen in other studies [16, 28]. Timings [29] found that it was the association with carbamezapine, which was most frequent: 11 of 14 patients who died suddenly were prescribed this drug. A recent study showed no association between phenytoin and SUDEP but demonstrated the risk to be increased more than nine fold if carbamezapine plasma levels at the last therapeutic dose monitoring was above the recommended range[30].

Carbamezapine has been associated with prolongation of the QT interval, as well as alterations in cardiac rhythm, but its role is difficult to dissociate from the effects of epilepsy itself, such as brainstem inhibition due to seizure-induced release of gamma aminobutyric acid and other neuroinhibitory peptides [31].

Also carbamazepine and Oxycarbamezapine may cause inappropriate antiduretic hormone secretion with hyponatraemia leading to sudden death [32]. Nitrazepam has been associated with an increased risk of sudden death

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especially in young children. This may be due to dysphagia, recurrent respiratory tract infections, gastroesophageal reflux and aspiration especially if there is increased salivation: a common side effect of this drug [33].

During a trial of the antiepileptic drug lamotrigine, the rate of SUDEP among those taking it was within the range expected for the population, and did not appear to be affected either by the dose or duration of treatment, and was similar to that reported in a population of patients treated with gabapentin [28]. However, as Lamotrigine has been shown to posses an Ikr (cardiac rapid delayed rectifier potassium ion current) – blocking potential, thus prolonging the QT interval, it is possible that certain patients with epilepsy may be at increased risk of torsade de pointes and Sudep when treated with Lamotrigine [34]. This may be a result of the drug itself, the drug and seizure induced metabolic changes such as acidosis, or the drug and a specific genetic disposition.[35]

Some traditional anti-epileptic drugs such as primidone, phenytoin and magnesium are known to shorten QT interval; however, the mechanism is unclear[36, 37]

SUDEP has been associated with low or undectable levels of antiepileptic drugs, which suggest that a sudden fall in their plasma concentrations might be a critical causative factor [31].

Kenneback and colleagues [38] recorded changes in cardiac rhythm and variability during abrupt withdrawal of carbamezepine and phenytoin in 10 patients with side effects of these drugs. Continuous ECG recordings and daily measurements of drug concentrations were made from the last day of treatment and for the following 4 days. Three patients had a 10-fold increase in ventricular premature beats, and in others, there was a significant reduction in heart rate variability and of sympathetic and parasympathetic tone. These findings may contribute to sudden death even in absence of seizures.

However a recent study of postmortem AED concentration demonstrated no major differences in AED levels of SUDEP cases compared with those of control [39]. It has been found that polytherapy with AEDS and frequent dose adjustments may contribute to SUDEP [16]. Frequent changes of AEDS also play a role [40, 41, 42].

1.4 Other Risk Factors for SUDEP

Nilsson and colleagues [16] found early onset of epilepsy to contribute independently to sudden death. This has been consistent in other studies [43]. Young adulthood is another consistent factor for SUDEP [44, 45]. Other factors, which have been suggested, include male gender [16, 45] black race [44, 46], recent head injury and alcoholism [46].

Prevention of SUDEP includes identifying patients at high risk, educating patients and their families about SUDEP, identifying seizure precipitants and promoting compliance with treatment [47].

Supervision at night (defined as the supervising person sharing the same bedroom, or use of special precautions such a monitoring device) was associated with a decreased risk of SUDEP in a large case control study [48].

Control and prompt treatment of seizures and avoidance of an abrupt withdrawal of AEDs also reduces the risk of SUDEP [9].

2.0   STUDY JUSTIFICATION

While epilepsy is common in our environment [4], no study has been done on SUDEP. QTc abnormalities have been implicated in the pathogenesis of SUDEP and identification of risk factors for QTc abnormalities in our set up will alert clinicians to appropriately advice such patients and institute rigorous follow up programmes for them.

Expected perceived benefit of study results

Corrected QTc interval is one of the highest risk factors of SUDEP studied. QTc measurement may identify a risk group. Based on the findings of the study it will be possible to justify or otherwise the incorporation of ECG as part of the routine work-up and follow-up of patients with epilepsy in our setup.

3.0   STUDY OBJECTIVES

Research Question

Does the duration of QT-interval in patients with epilepsy differ significantly from that of non-epileptic age and sex matched controls?

3.1   Broad Objective

To compare the duration of corrected QT-interval of the ECG in patients with epilepsy and non-epileptic matched controls.

3.2   Specific Objectives

1. To compare QT interval in patients with epilepsy before treatment with non-epileptic matched controls
2. To compare QT interval in patients epilepsy on treatment with AEDs with non-epileptic matched controls
3. To compare the QT interval in patients with epilepsy not on treatment with those on AEDs
4. To determine the relationship between the QT interval and:
    i.   Type of anti-epileptic drugs
    ii. Frequency of seizures

Null Hypothesis

There is no significant difference in QT interval between the patients with epilepsy and non-epileptic matched controls.

4.0 METHODOLOGY

4.1 Study design
Comparative cross-sectional study.

4.2 Study area
The study was carried out at the KNH adult neurology clinic and the KAWE clinics in Nairobi.

KNH
This is a tertiary referral and teaching hospital in Nairobi, Kenya. The neurology clinic runs every Monday morning and is conducted by neurologists and senior house officers. On average 80 patients are reviewed every week of which over 30% have epilepsy.

KAWE
This is a non-profit making NGO established in 1982 and has three clinics in Nairobi catering for patients with epilepsy. These are Karen, Riruta and Huruma clinics. Each clinic is run once a week by a neurologist/paediatrician and clinical officers with the help of the nursing staff trained on epilepsy.

4.3 Study population
The cases were patients with epilepsy seen at KNH adult neurology clinic and the KAWE clinics. Controls were non-epileptic individuals who were escorts of patients, hospital/clinic staff or students from the nearest school matched for age and sex.

4.4 Inclusion criteria
1. Patients with epilepsy who were seen at KNH adult neurology clinic and KAWE Nairobi clinics.
2. Those who were willing and gave consent for the study.
3. Non-epileptic age and sex matched individuals as controls.

4.5 Exclusion criteria
1. Unwillingness to participate in the study
2. Patients/controls with hypertension, cardiac, thyroid and renal diseases, diabetes mellitus, or use of phenothiazines, tricyclic antidepressants, antiarrythmic agents and all other drugs known to affect QT interval

other than AEDs. They were excluded through history, physical examination and checking the patient records from the clinic files.

4.6   Operational definitions

Patient with Epilepsy: A patient diagnosed and documented to have Epilepsy at a KAWE Nairobi clinic or KNH adult neurology clinic

AED naive patient: Newly diagnosed patient with epilepsy not on treatment with AEDs

AED experienced patient: Patient with epilepsy who has been on treatment with antiepileptic drugs for at least one month and followed up at the KNH adult neurology clinic

R-R interval: The duration between two successive R waves of the ECG.

QT – interval: The duration between the beginning of the Q wave and the end of the T wave of the ECG.

QT$_c$:   Rate related ("corrected") QT interval.[49]

$$\text{Calculated as} \quad \sqrt{\dfrac{QT}{R\text{-}R}}$$

Normal range:

      Male =   371ms – 440ms

      Female=   371ms – 460ms

4.7   Sampling Method

Patients

Patients with epilepsy attending KNH adult neurology clinic and KAWE clinics were evaluated for suitability.   Each week a list of all patients with epilepsy booked for each clinic was drawn up. Consecutive sampling method was used for the AED naive and AED experienced patients. Those who met the inclusion criteria had the study explained to them, and if they consented, they were recruited. Those patients who did not give consent were excluded and selection of further patients following consecutive sampling was done until the sample size was achieved.

Controls

Controls were also be recruited weekly. A similar number of controls to match the patients for that week were selected.   Sources of controls were escorts of the patients in the clinics, the hospital/clinic staff and pupils from the nearest school. Once a control subject was identified and met the inclusion criteria, the study was explained to him/her and was recruited if consent was given. Consent for children and pupils who were below eighteen years was obtained from parents/guardians and school administration respectively after proper explanation of the study. They were recruited after getting their assent.

4.8   Sample Size Determination

Using the formula for comparing proportions from two independent groups, a sample size N, was determined as shown below[50].

$$N = \left[Z_{\frac{\alpha}{2}} \sqrt{\frac{(K + 1)\, Pq}{K\,(P_1 - P_2)^2}} + Z_\beta \sqrt{KP_1q_1 + P_2\, q_2} \right]^2$$

Where N = Total number of study subjects

K = Number of controls per case (1:1)

Z = Standard   deviation (1.96)

p_1 = Proportion of cases with abnormal QTC (67%)

P_2 = Proportion of controls with abnormal QT_C (32%)

In a previous study, 67% of cases had abnormal QT_C compared to 32% in   controls [18]

$q_1 = 1 - p_1$

$q_2 = 1 - p_2$

p   = overall proportion $\left[\dfrac{p_1 + kp_2}{K + 1} \right] 2$

q $= 1 - P$

α = Level of significance   = 0.05 at 95% CI 1.96

Z_β = Power of study at 80% (0.842)

N=53

However, in the study there were AED naive and AED experienced patients to be compared with respective controls hence a total of 106 cases (53 AED naive patients and 53 AED experienced patients) and 106 controls. The total number of study individuals was 212.

4.9   Clinical Procedures

After obtaining clearance from the KNH Ethics and research committee, the study tools (questionnaire and ECG) were pre-tested at KNH.

The clinicians and staff of KNH adult neurology clinic and KAWE clinics were informed of the study by the principal investigator to seek their help in patient recruitment. The principal investigator visited each clinic every week to recruit study subjects.

Patients with epilepsy and controls who fulfilled the inclusion criteria and gave informed consent were recruited into the study by the researcher.

Once recruited, patients age, sex, age at onset of seizures, frequency of seizures and use of antiepileptic drug treatments were obtained from history and the clinic files and tabulated into the data sheet shown in appendix I. A detailed history of drugs taken elsewhere was also taken. A newly diagnosed patient not on treatment was recorded as an AED naive while a patient who had been on AEDs for at least one month and being followed up in KNH adult neurology clinic was recorded as AED experienced. Physical examination was done and a standard resting 12 lead ECG was done on each patient and control as they were being recruited. Screening and recruitment procedure is illustrated in figure 2 below.

```
        KNH/KAWE CLINIC              NEAREST SCHOOL
                  │                          │
             ┌────┴────┐                     │
             ▼         ▼                      │
        Patient      Control  ◄───────────────┘
             ╲         ╱
              ╲       ╱
               ▼     ▼
              CONSENT
                 │
                 ▼
     History and physical examination
                 │
                 ▼
              ENROLL
                 │
                 ▼
               ECG
```
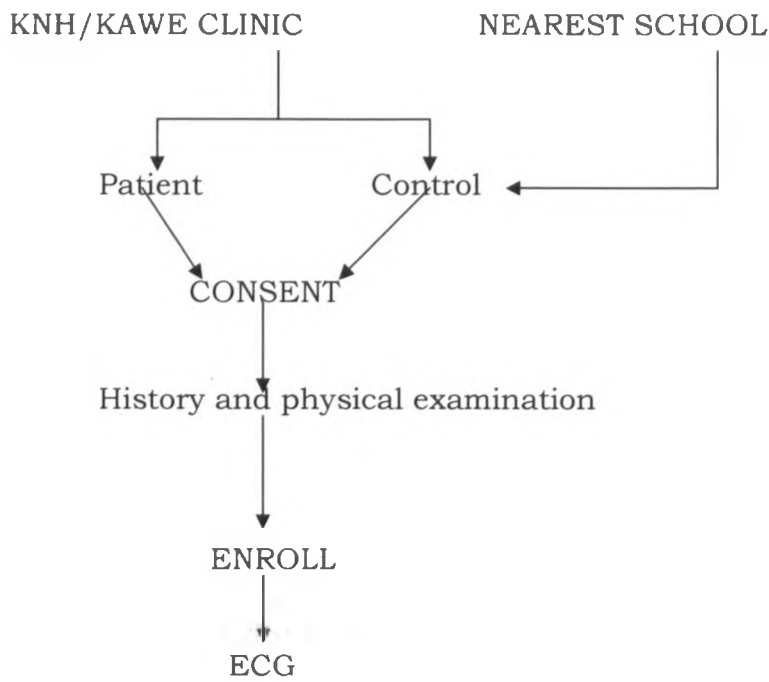
Fig 2: Flow chart showing screening and recruitment of participants

Model MAC®PC automated ECG machine, manufactured by Marquette Electronics, USA was used. Prior to the study, validation of measurement of QT interval was done by comparing the automated QTc and the manually calculated QTc of twenty (20) patients at KNH as shown in table 1 below. Also, two readings were also obtained from each of the twenty patients at intervals of five minutes to evaluate internal consistency of the ECG machine as shown in table 2. A paired t test was done to compare the QTc and correlation obtained between the two readings. The ECG machine was consistent.

Table 1. Manual calculated and automated QTc readings from twenty patients

Patient no.	Manually calculated QTc	Automated QTc
1	397	393
2	407	406
3	400	400
4	423	422
5	426	426
6	395	397
7	411	411
8	471	473
9	406	406
10	417	416
11	425	429
12	429	433
13	370	371
14	380	380
15	470	474
16	372	372
17	425	421
18	466	466
19	397	397
20	401	401
Mean	414.00	414.70
Standard deviation	29.08	29.83
SE of Mean	6.50	6.67

Correlation =0.998

Table 2. Two consecutive automated QTc readings from twenty patients

Patient no.	First reading	Second reading (after 5 minutes)
1	397	397
2	406	405
3	400	400
4	422	422
5	426	426
6	393	393
7	411	411
8	473	473
9	406	406
10	416	416
11	429	426
12	433	433
13	371	371
14	380	381
15	474	472
16	372	374
17	421	421
18	466	467
19	397	397
20	401	401
Mean	414.70	414.25
Standard deviation	29.83	29.51
SE of Mean	6.67	6.60

Correlation =0.999

The calibrations of the ECG paper used in the study were as follows: 10mm represented 1mV while 25mm represented one second.

The same ECG machine was used throughout the study and two ECG readings were done on each study subject and the average QTc obtained. The ECGs were done by the principal investigator and analysed by the researcher who liaised with a cardiologist. The R-R, QT interval and QTc were obtained and entered into the data sheet (Appendix 1). The ECGs were done as stipulated in the ECG manual [51].

The results of the ECG were communicated to the study patient/control. If a patient/control was found to have an abnormal ECG, he or she was referred

to the appropriate clinic/hospital for further evaluation in consultation with the respective clinicians at the clinics.

4.10 Data Management

Data entry and statistical analysis was done using the Statistical Package for Social Sciences (SPSS) version 12. Data was cleaned before analysis.

Continuous data such as age, age at onset of seizures, seizure frequency and QTc was analysed using means, standard deviations, medians, proportions and frequency distribution. Categorical data such as clinic, cases and controls, sex and type of AEDs was analysed using percentages with their corresponding confidence interval.

Univariate and bivariate analysis was done comparing cases and controls as well as the old and the new patients. A t- test was used to compare the mean QTc for cases and controls as well as new and old patients. Analysis of variance (ANOVA) was used to compare the mean QTc among patients in relation to seizure frequency and anti epileptic drugs. A p value of ≤ 0.05 was taken to be statistically significant.

Analysed data was presented in the form of tables, pie charts and graphs.

5.0   ETHICAL CONSIDERATIONS

Approval to carry out the study was obtained from KNH ethics and research committee and the board of directors of KAWE (See APPENDIX II).

Eligible patients /controls were informed of the study in a language they understood best. Expectations of the study participation including performing the ECG as well as the benefits of the study were explained. Confidentiality was assured.

After full explanation (APPENDIX III), a consent form (APPENDXI IV) was offered for signing by the patient/ control or guardian indicating the acceptance to participate in the study. Participation in the study was voluntary. Those patients who did not give consent/accent to participate were excluded and this did not in any way affect their medical care in the clinics.

The results of the ECG were communicated to the study subjects. Those found to have abnormal ECGs were referred to the relevant clinics/ hospital in liaison with primary clinician for further evaluation.

6.0 RESULTS

A total of 321 study participants were screened out of which 292 subjects were enrolled and analysed between June 2007 and October 2007. They comprised of 146 patients with epilepsy and 146 controls matched for age and sex. Twenty nine (29) patients with epilepsy were excluded from the study; six (6) had hypertension, 4 had fever, 5 declined to give consent, 3 had rheumatic heart disease, 2 were diabetic and 1 had rheumatoid arthritis. Six (6) patients were on drugs known to affect QT interval namely: artemether/lumefantrine combination (1), chlorpherinamine (2), chlorpromazine (2) and diazepam (1).

Among the enrolled patients with epilepsy, 62 had not been started on AEDs while 84 were on treatment with AEDs as shown in table 3 below.

6.1 DEMOGRAPHIC PROFILE

Table 3: Demographic characteristics of the study population

|	CASES			CONTROLS
	AED naive	AED experienced	Total N	Total n
Clinic				
KNH	11	84	95	**95**
Riruta	9	0	9	**9**
Karen	22	0	22	**22**
Mathare	20	0	20	**20**
TOTAL	62	84	146	**146**
Sex				
Male	37	39	76	76
Female	25	45	70	70
Total	62	84	146	146
Median age in years	**16.0**	**22.5**	**21.0**	**21.0**
(range)	**(3-41)**	**(12- 61)**	**(3-61)**	**(4-61)**

Eleven of the AED naive patients were recruited from KNH while 51 were from KAWE. The AED experienced patients were all recruited from KNH.

In total there were more male patients (52.1%) with epilepsy than female (47.9%) giving a ratio of 1.1:1
Among the AED naïve patients, 59.7% (37) were males and 40.3% (25) were females with a male to female ratio of 1.5:1.

The median age of patients with epilepsy not started on treatment was 16.0 years whereas that of patients on anti-epileptic drugs was 22.5 year. The difference was statistically significant (p <0.0001) (Table 3)

Figure 3. Number of seizures reported by patients with epilepsy in the study population in the last one month (n=146)
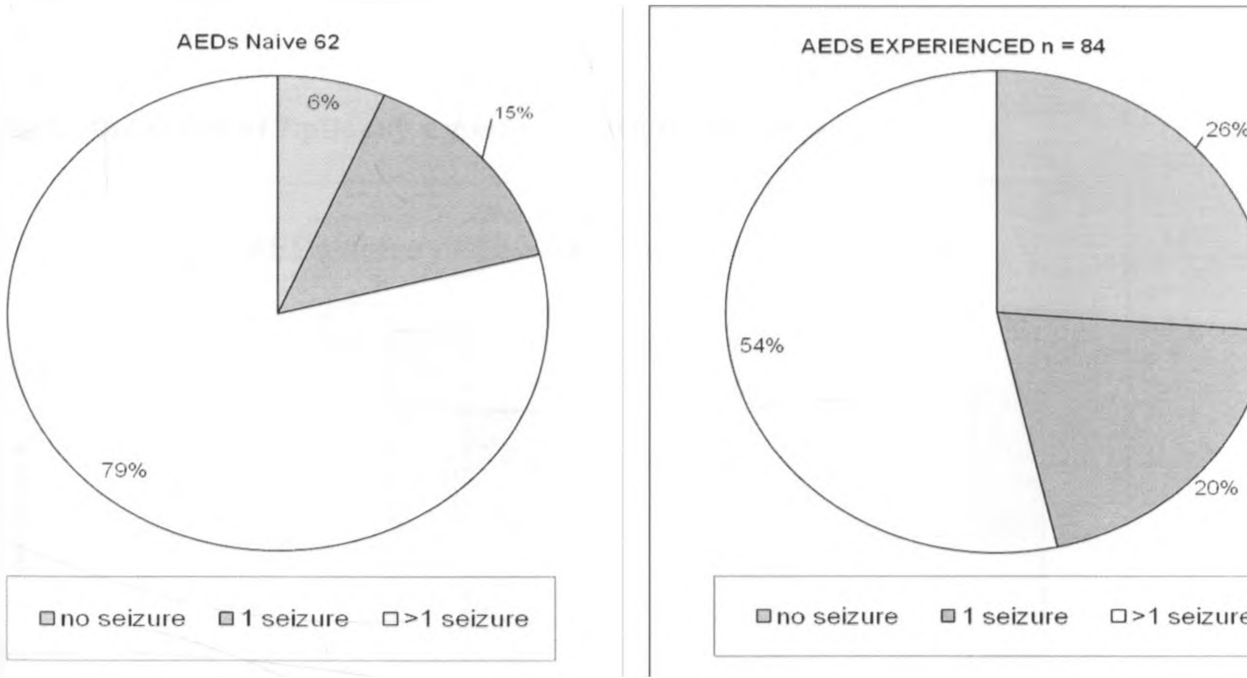
About half (54%) of AED experienced patients had their seizures poorly controlled compared to vast majority (79%) of the AED naive patients. Only 26% of AED experienced patients had well controlled seizures.

Figure 4. Age at onset of seizures among the study patients
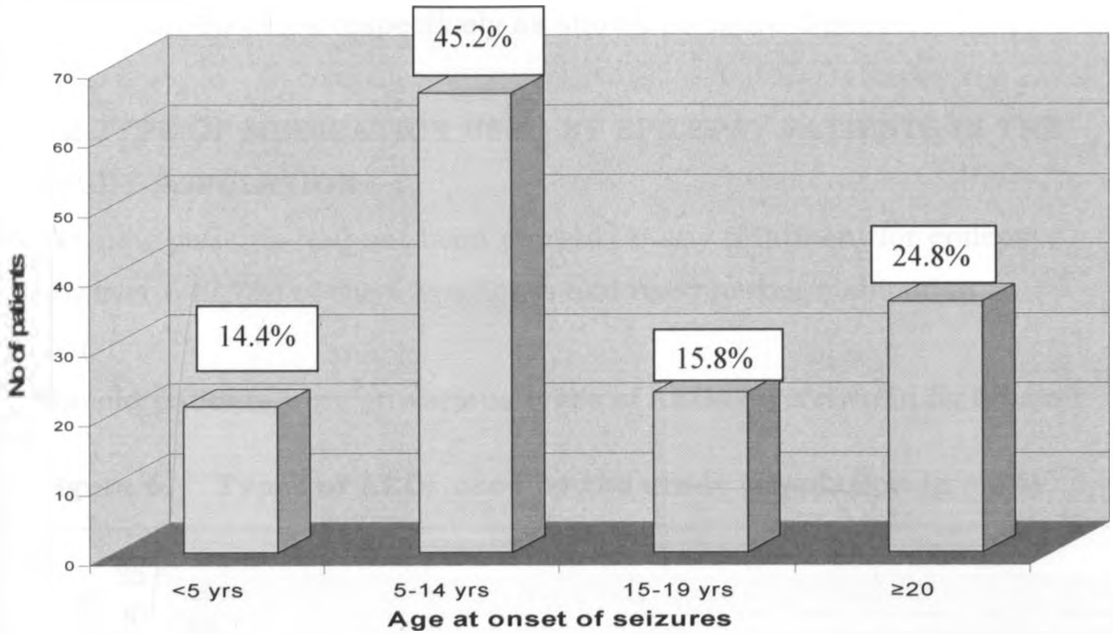
Majority of the patients 66 (45.2%) had an onset of seizures between 5 and 14 years (fig 4)

Fig 5. Duration of Epilepsy among the study patients
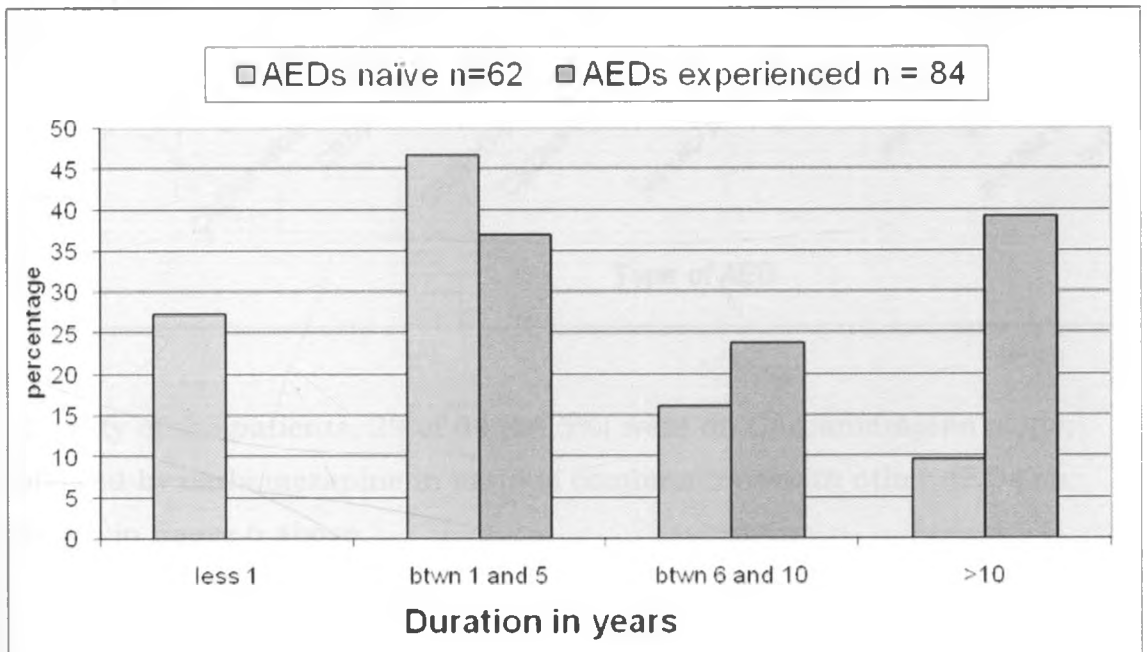
AED experienced patients had had a longer duration of epilepsy than the AED naive patients. However, almost an equal number of the AED

experienced patients (37% and 39%) had their epilepsy for 1-5 years and more than 10 years respectively as shown in figure 5 above.

6.2 TYPE OF MEDICATION USED BY EPILEPSY PATIENTS IN THE STUDY POPULATION

The new patients had not been started on any treatment for epilepsy, however 6 (9.7%) of the 62 patients had used herbal medication.

The old patients were on various types of AEDs as shown in fig 6 below

Figure 6.   Types of AEDs used by the study population (n = 84)
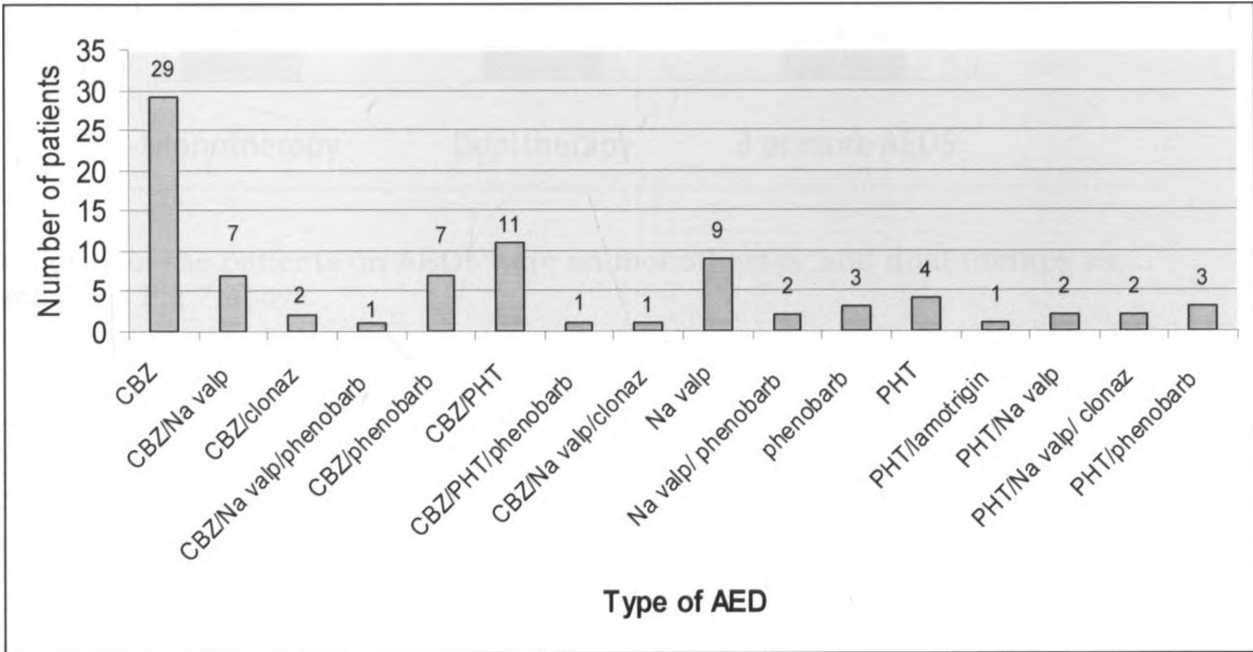
Majority of the patients, 29 of 84 (34.5%) were on Carbamezapine alone, followed by carbamezapine in various combinations with other AEDs as shown in figure 6 above.

Figure 7: Number of Anti-epileptic drugs used by the study patients (N=84)
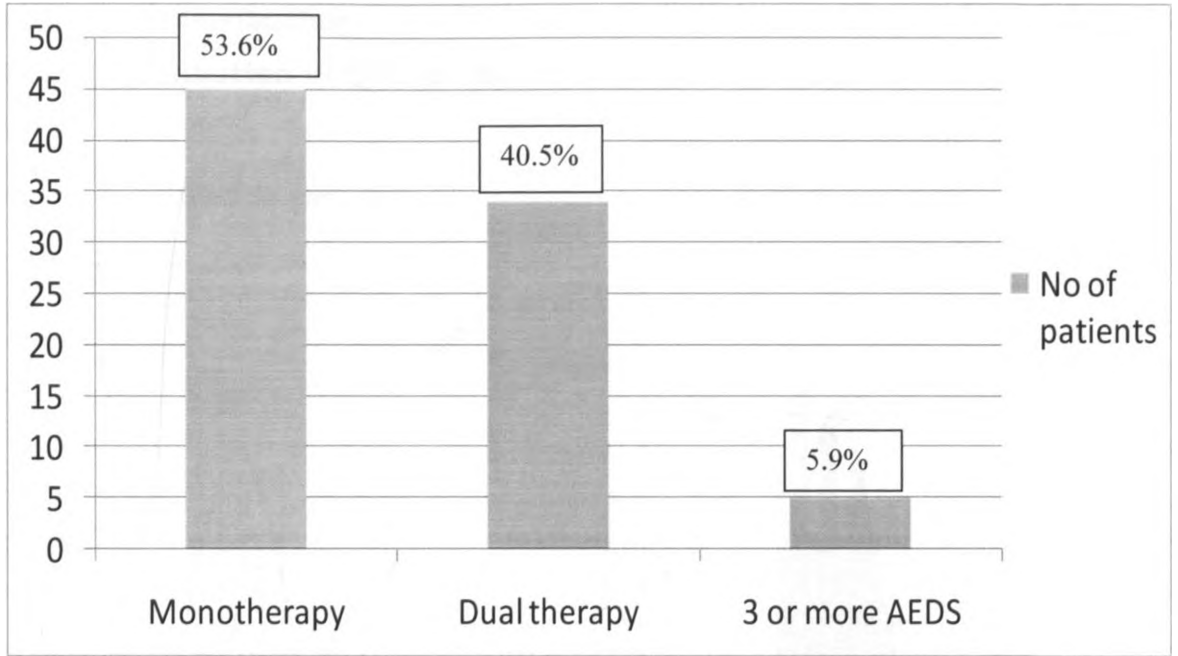
Majority of the patients on AEDs were on monotherapy and dual therapy as shown in Fig 7 above.

6.3.0 THE QT INTERVAL AMONG OF THE STUDY POPULATION

6.3.1 QT distribution

Fig 8. Distribution of QTc in the study population
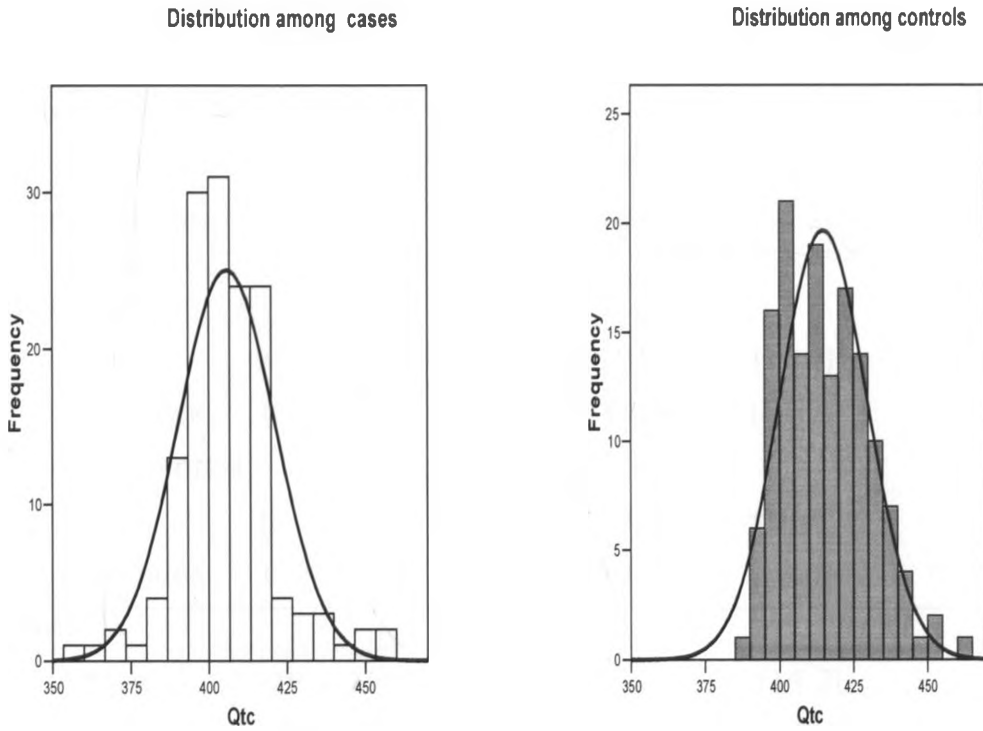
The QTc was normally distributed among patients and controls as shown in figure 8 above. The QTc was longer in controls (mean 414.9ms) than the cases (mean 405.7ms)

6.3.2. Relationship between QTc and sex in the study population.

Females had significantly longer mean QTc than males as shown in table 4 below.

Table 4. Relationship between QTc and sex in the study population

	Mean QTc in ms (SD)		P value
All patients with epilepsy			
o Males (n = 76)	402.0	(15.7)	
o Females (n = 70)	409.9	(14.2)	0.002
AED naïve			
o Males (n = 37)	401.6	(16.3)	
o Females (n = 25)	411.4	(14.2)	0.021
AED experienced			
o Male (n = 39)	402.3	(15.4)	
o Females (n = 45)	409.0	(13.8)	0.037
Controls			
o **Males** **(n = 76)**	412.6	(14.3)	
o **Females** **(n = 70)**	418.1	(14.8)	0.012

6.3.3 Comparison of QTc among patients and controls

The mean QTc of patients with epilepsy and their matched controls was compared using t-test. The mean QTc of patients with epilepsy was 405.7ms (95% CI 374.7-436.7ms) whereas that for controls was 414.9ms (95% CI 385.3-444.5ms). This mean QTc for patients with epilepsy was significantly shorter that that of controls (p < 0.0001).

Shortening of QTc was also observed among the patients with epilepsy who had not been started on treatment as well those who were on treatment with AEDs compared to matched controls (Table 5 below)

Table 5. QTc of patients with epilepsy on AEDs and those not on treatment and their controls

	AED naïve		AED experienced	
	Cases (n=62)	Controls (n=62)	Cases (n=84)	Controls (n=84)
Mean QTc	405.6	415.4	405.9	414.6
95% CI	372.6-438.9	387.6-443.2	376.3-435.5	383.6-445.6
P value	0.0005		0.0003	

The mean QTc for the AED naive and AED experienced patients was significantly shorter than that of their respective controls (p = 0.0005 and 0.0003 respectively) (table 5).

The mean QTc among the AED naive (405.6 ms) and AED experienced (405.9 ms) patients did not differ significantly (p= 0.91)

6.3.4 Relationship between QTc and Anti-epileptic drugs (AEDs)

The mean QTc of patients on monotherapy was 409.9 ms while that of those on polytherapy was 410.4ms. The difference was not statistically significant (p=0.77)

Analysis of variance (ANOVA) was used to determine the relationship between mean QTc and the use of carbamezapine as shown in table 6 below.

Table 6. Relationship between QTc and type of antiepileptic drugs (n = 84)

	Carbamazepine alone (n=29)	Carbamazepine with other AEDs (n=29)	Other AEDs (n=26)
Mean QTc (ms)	409.6	403.4	404.5
95% CI	381.4-437.8	373.4-433.4	373.9-435.1

P value (Anova) = 0.253

The mean QTc of patients using carbamezapine alone was longer than those using carbamezapine in combination or other AEDs. The difference however was not statistically significant (p = 0.225)

6.3.5 Relationship between QTc and seizures

The age of onset for majority (45.2%) of the patients was between 5 and 14 years while 14.3% had onset at less than 5 years of age as shown in table 7 below.

Table 7. The relationship between mean QTc and the age at onset of seizures

Age at onset of seizures (years)	Number (n=146)	Mean QTc in ms (SD)	ANOVA
Less than 5	21	406.3 (18.0)	
5-14	66	406.2 (13.2)	p = 0.95
15-19	23	406.2 (12.9)	
≥ 20	36	404.4 (19.5)	

The mean QTc in relation to age at onset of seizures did not differ significantly among patients with epilepsy (p=0.95)

Table 8: Relationship between QTc and seizure frequency (N=146)

	n	Mean QTc	(SD)
Number of seizures in			
the last 1 month			
0	24	398.5	(15.0)
1	25	407.8	(12.9)
2-5	70	406.2	(15.8)
>5	27	407.5	(14.9)

P value (Anova) = 0.253

There was no significant difference in the mean QTc in relation to seizure frequency as shown in table 8 above (p=0.253).

7.0 DISCUSION

The overall male to female ratio of patients with epilepsy was 1.1:1 and that of the patients who had not been started on treatment was 1.5:1 (Table 3). These findings were comparable to other studies in sub-Saharan Africa where there was male predominance in epilepsy [3, 52]. A study by Mativo et al at KNH found a male to female ratio of 1.3:1 [53]. Patients from KAWE were younger than those from KNH (median age 16 and 21 years respectively) because the KNH group were recruited from the adult neurology clinic while patients of all ages with epilepsy were seen at the KAWE clinics.

Majority (45.2%) of the patients in this study had first occurrence of seizure between 5-14 years of age (fig 4). Most idiopathic seizures accounting for 60% of epilepsy cases begin at this age and the results of this study are similar to other findings obtained from studies in England and Zimbabwe where they found majority of the patients had their first epileptic attacks at 5-14yeas and 6 – 12 years respectively [52, 54].

Most of the patients on AEDs in this study were on monotherapy while 46.4% were on polytherapy. Of those on monotherapy, carbamezapine was the predominant drug, accounting for 64.4%. This result concurs with the study done by Mativo et al, in their study at KNH who found 70% of the patients to be on monotherapy out of which 61% were on carbamezapine [53]. The use of carbamezapine could be preferred because of its availability at the National hospital and the low side effect profile.

Among the patients who had not been started on AEDs in this study, 9.7% had been on traditional herbs. However, Sebit and colleagues in their study in Zimbabwe found that 20 % of epilepsy patients was started with traditional herbs and later shifted to biomedical treatments [52]. This could be due to myths and beliefs associated with epilepsy in various cultures and their influence on the final pathways of treatment [55].

The mean QTc for the study group was within the normal limits. Females are known to have longer QT interval and are at higher risk for torsade de pointes [49]. In this study the mean QTc for females was significantly longer than males. The length of the QT interval is influenced at least in part by sex hormones, mainly testosterone. The short QT interval in males is a reflection of the influence of testosterone on repolarization [55].

The results of this study showed that patients with epilepsy had significantly shorter mean QTc than their matched controls, 405.7 ms Vs 414.9 ms respectively (p <0.0001). Patients with epilepsy on AEDs also had a significantly shorter mean QTc than their matched controls, 405.9ms Vs 414.6 ms respectively (p=0.0003). Similarly, untreated patients with epilepsy had significantly shorter QTc than controls (p =0.0005). The mean QTc did not differ significantly between the patients on treatment with AEDs and those not on treatment (p=0.911). These results demonstrate that epilepsy itself and not AEDs may be responsible for the shortening of QT interval.

Similar findings were observed by Tan H. et al and Kwon S [24, 57]. Tan H.et al in their study of 70 patients with epilepsy in Malaysia found that mean QTc of patients with epilepsy on AEDs was significantly shorter than controls (p<0.0005) [24]. Kwon S. in his study in South Korea also found no significant difference in the mean QTc among patients with epilepsy on AEDs and those not on AEDs [57].

The results of this study differed from those by Drake M.E. et al in USA who found untreated patients with epilepsy to have significantly longer QTc than controls[58]. Their study consisted of 75 epilepsy patients matched to the nearest decade of age with controls. They attributed this to higher incidence of cardiovascular risk factors and concurrent drug use in the older patients with epilepsy. Contrary to that study, we excluded patients with cardiovascular risk factors such as hypertension and diabetes and patients were matched to the nearest one year of age with controls.

It is not clear how epilepsy causes the shortening of QT interval [24]. However, it is also possible that epilepsy may exert long term effects on the heart through effects on hypothalamic and brainstem centres which may gradually shorten QT interval and could lead to sudden cardiac events during seizures. This question may be settled by prospective cardiac studies in newly diagnosed epilepsy patients.

The mean QTc among patients with epilepsy in relation to the seizure frequency in this study did not differ significantly (p = 0.253). Similar findings were seen by Tan H. et al who found that the mean QTc of patients with epilepsy did not differ significantly between patients in duration and frequency of epilepsy.[24]

These findings may be explained by one hypothesis of cardiac mechanisms of SUDEP. Malfunction in ion channels resulting from mutations in the genes encoding channel proteins or the presence of auto antibodies have been implicated in the pathogenesis of epilepsy and cardiac disorders such as the short QT syndrome [21]. Mutations of the K^+ current rectifier channels with gain of function leads to shortening of repolarization and subsequent shortening of QT interval [22]. The ion channel disorders are co-expressed in the heart and brain and are expressed in some individuals through genetic susceptibility which manifest because of uncontrolled seizures[23]. Shortening of QT interval may lead to SUDEP through arrhythmias. Further advances in the studies of complex minor genetic susceptibility may further research into SUDEP.

There is an on going debate on the clinical significance of antiepileptic drug-induced QT prolongation that may be a risk factor for sudden death caused by cardiac arrest.[29, 30] Their effects are likely the result of the inhibition of repolarizing potassium channels especially Ikr, which leads to lengthening of QT interval and the development of an early afterdepolarization [35]. In addition, the increasing

interest in the concept of channelopathy led us to evaluate the potential effect of antiepileptic drugs on QT interval.

The results of this study showed that there was no significant difference in the mean QTc of patients with epilepsy on monotherapy compared to those on polytherapy of AEDs (p=0.771). This concurs with similar studies done elsewhere [24, 57]. The findings of this study also showed that the mean QTc of patients using carbamezapine alone, carbamezapine in combination with other AEDs or those on other AEDs did not differ significantly (p=0.255). Antiepileptic drugs therefore had no effect on QT interval.
These findings agree with the result of a preliminary study in which the effects of carbamezapine on heart conduction were evaluated in young patients with epilepsy.[59]
In a different point of view, no association exists between the use of AEDs and QT prolongation in patients with normal QT interval. Certain drugs such as carbamezapine are metabolized by hepatic P450 isoenzyme CYP3A. When drugs that inhibit CYP3A are administered together, plasma levels of the parent drug increase, thus leading to a further lengthening of QT interval and increasing the risk of torsade de pointes.[57] However, this study suggests that carbamezapine and other antiepileptic drugs or even polytherapy of AEDs may not lengthen QT interval.
Some traditional antiepileptic drugs such as primidone, phenytoin and magnesium are known to shorten the QT interval; [36, 37] however the mechanism is unclear. Considering these facts, sodium channel blockers may be used in an attempt to normalize the QT interval. A better understanding of the arrythmogenic mechanisms of antiepileptic drugs will allow physicians to identify antiepileptic patients at risk and prevent them from developing any cardiac toxicity and ultimately sudden death.

8.0 CONCLUSIONS

- Patients with epilepsy had significantly shorter QTc than matched controls.
- There is no association between anti-epileptic drugs and QT interval. Epilepsy, but not the antiepileptic drugs may be responsible for shortening of QTc in patients with epilepsy.

9.0 STUDY LIMITATIONS

- Recall bias by the patients about their clinical information. Some patients could not remember the number of seizures they have had in the past.
- Lack of medical records for controls for verification.

10.0 RECOMMENDATIONS

1. More studies need to be done to validate the incorporation of ECG as part of routine work up and follow up of patients with epilepsy in our set up.
2. Studies on SUDEP are required in East Africa to chart its prevalence and any associated factors

APPENDIX I: DATA SHEET

Study no _____   Date _____

1. Clinic

    ☐ KNH   ☐ KAWE

    If from KAWE, specify;

    Karen   ☐

    Mathare   ☐

    Riruta   ☐

2. Category

    Case

        New   ☐

        Old   ☐

    Control   ☐

3. Age (years)   ☐

4. Sex: Male ☐   Female ☐

5. Age at onset of seizures_____

6. Number of seizures in the last

    One month   ☐

    Three months   ☐

    Six months   ☐

    One year   ☐

    More than one year ☐

7. History of sudden death in the family (other siblings, father, mother grandparents, cousins)?

    Yes   ☐

    No   ☐

8. History of heart disease in the family

    Yes ☐

    No ☐

9. History of diabetes mellitus in the family

    Yes ☐

    No ☐

10. History of alcohol use

Yes ☐

No ☐

If yes,

(i) Quantity of alcohol in grams in a month_____

(ii) For how long _____

11. On AED?

Yes ☐

No ☐

If yes which ones?

a. Carbamezapine alone ☐

b. Phenytoin alone ☐

c. Sodium valproate alone ☐

d. Ethosuximide alone ☐

e. Clonazepam alone ☐

f. Carbamezapine/phenytoin ☐

g. Phenytoin/phenytoin/phenobarbitone ☐

h. Carbamezapine/sodium valproate ☐

i. Sodium valproate/phenobarbitone ☐

j. Carbamezapine/sodium valproate/phenobarbitone ☐

k. Others (specify) _____

12. How long have you been on AEDs? _____

13. Physical Examination

Pallor   Yes ☐   No ☐

Jaundice   Yes ☐   No ☐

Leg Oedema   Yes ☐   No ☐

Pulse rate (Beats/min) ☐

Blood pressure (mmHg) ☐

Apex beat   ☐

35

Heart sounds

       Normal   ☐

       Abnormal ☐

Cardiac Murmurs

  Yes ☐

  No ☐

14.   ECG   First reading   Second reading   Mean QTc

    R-R interval (s)   _____   _____

    QT – Interval (s)   _____   _____

    QT_C (ms)   _____   _____   _____

APPENDIX II ETHICAL APPROVAL FORM

KENYATTA NATIONAL HOSPITAL
Hospital Rd along, Ngong Rd
P O Box 20723, Nairobi
Tel: 726300-9
Fax 725272
Telegrams MEDSUP*, Nairobi
Email KNHplan@Ken Healthnet org

Ref KNH ERC/ 01/ 4408

13th June 2007

Dept of Clinical Medicine & Therapeutics
School of Medicine
University of Nairobi

RESEARCH PROPOSAL: THE QT INTERVAL IN PATIENTS WITH EPILEPSY SEEN AT THE KENYATTA N HOSPITAL AND THE KENYA ASSOCIATION FOR THE WELFARE OF PEOPLE WITH EPILEPSY CLINICS IN NAIROBI"   (P43/3/2007)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and approved your revised research proposal for the period 13th June 2007

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given   Clearance for export of biological specimen must also be obtained

On behalf of the committee   wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication

Prof. A.N. Guantai
SECRETARY, KNH-ERC

      The Deputy Director CS, KNH
      Prof K M Bhatt, Chairperson, KNH ERC
      The Dean, School of Medicine, UON
      The Chairman Dept of Clinical Med & Therapeutics, UON
      Supervisor   Prof A M Adam, Dept of Medicine UON
            Dr M Joshi Dept of Medicine, UON
            Dr J O Jowi KNH

APPENDIX III: STUDY SUBJECT CONSENT EXPLANATION

Introduction

I am Dr. John K. Rono, a Postgraduate student, currently doing postgraduate studies in internal medicine at University of Nairobi.

As part of my postgraduate studies, I am required to do a research project. I intend to do a study on the QT interval (heart conduction) in patients with epilepsy.

The study requires comparing QT interval of the ECG (electrocardiogram) in patients with epilepsy and those without epilepsy of same age and sex. With your permission, I my need to include you into the study.

About the study

Patients with epilepsy are prone to sudden unexpected and unexplained death than the general population. This condition results from the effects of epilepsy itself and its medication on the heart and specifically the QT-interval.

Early detection and correction of QT interval abnormalities can prevent sudden death. The study will involve taking a medical history from you, checking your medical records, doing a physical examination and an ECG. Performing an ECG is not an invasive procedure; it involves attaching metal electrodes on the chest, upper limbs and left foot. The signals from the electrodes will be recorded on the electrocardiograph, which will show the electrical activity of the heart. The QT interval will be determined from the ECG. I as the principal investigator will perform the ECG. I will discuss results of the ECG with you. If an abnormality will be detected, you will be referred to the appropriate clinic/hospital for further evaluation.

Participation in the study is a matter of choice and it is your right to choose. Whether you choose to participate or not will not affect your medical care. Confidentiality will be maintained at all times. At the end of the study, I will hand over the study findings to the medical department in the University of Nairobi. Any useful information that will improve the quality of care will be shared with the caregiver for appropriate action.

Note: In case of patients less than 18 years, the explanation will be done to the guardian/parent. They will be required to sign the consent on behalf of the patient/study subject.

APPENDIX IV: CONSENT FORM

STUDY No_____   Date_____   Time_____

I have been adequately explained about the study by Dr. Rono. I understand that my rights will be respected and confidentiality maintained at all times.

I also understand that this consent is voluntary and that I can withdraw from the study at any time without any penalties.

I therefore consent to the recruited into the study.

Patient /control subject / Guardian Signature ....Date ....

Signature of investigator .... Date ....

For any further clarifications you may contact Dr. Rono John at Tel: 0722 289 752.

cc:
Subject file
Investigator

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