ORIGINAL ARTICLE

A Pilot Study Comparing the Dose and Serum Drug Levels with Seizure Control in Patients on Carbamazepine Monotherapy

Adedunni W **OLUSANYA**[1], Mustapha **DANESI**[2,3]

AFFILIATIONS
[1]*Department of Pharmacology Therapeutics and Toxicology College of Medicine,University of Lagos, NGERIA*
[2]*Department of Medicine College of Medicine, University of Lagos, NIGERIA*
[3]*Lagos University Teaching Hospital, Idi-Araba, Lagos NIGERIA*

CORRESPONDING AUTHOR
*Adedunni W **OLUSANYA***
Department of Pharmacology Therapeutics and Toxicology College of Medicine,University of Lagos, NIGERIA

E-mail: dedunolusanya@gmail.com
Phone: +234 812 664 8460

DISCLOSURE: None

Received: 18th January, 2017
Accepted: 4th April, 2017

ABSTRACT
Background: The management of epilepsy involves titrating the dose of an antiepileptic drug to a maximum dose before switching over to a second agent. Measurement of serum levels of antiepileptic medications is indicated to determine drug levels in patients with uncontrolled seizure. Carbamazepine is one of the commonly used antiepileptic drugs in this environment. Studies have shown individual variations in drug dose and serum levels at which seizures are controlled.
Objectives: The aims of this study are to compare seizure control rates in patients on a high dose to low dose carbamazepine and to relate serum drug levels of carbamazepine to seizure control.
Methodology: This study consisted of 77 patients on carbamazepine monotherapy (for at least 9 months) for the treatment of epilepsy. Seizures were described as being fully controlled when there was seizure freedom for the preceding 6 months or more. The dose of carbamazepine was documented and serum level of carbamazepine was determined using high-performance liquid chromatography.
Results: Patient who were on a dose of 400mg per day were more likely to be controlled compared to those on higher doses ($p = 0.011$). The mean serum level of carbamazepine in patients who were controlled was lower (9.20±6.28mg/l) compared to 11.50±5.52mg/l in uncontrolled patients ($p = 0.178$).
Conclusions: Higher doses of carbamazepine was not associated with an increase in seizure control rates. Seizure control was achieved at widely varying levels of carbamazepine. This suggests that seizure controlled is not solely dependent on serum drug levels.

***Keywords**: Epilepsy, antiepileptic drugs, therapeutic drug monitoring*

INTRODUCTION

Epilepsy is a chronic neurological disorder affecting about 70 million people worldwide with about 80% living in developing countries.[1,2] The burden of epilepsy is significant in terms of its impact on the health and quality of life.[2]

The primary goals of antiepileptic drug (AED) treatment are to achieve complete seizure freedom using the minimum number of medications without causing adverse events, thereby reducing morbidity, mortality, and improving the quality of life of sufferers.[3]

The drugs used in the treating epilepsy in this environment include carbamazepine, valproate, phenytoin, and phenobarbitone. Of these, carbamazepine is one of the most commonly used. It is indicated as the first-line agent for the treatment of focal and generalized tonic-clonic seizures.[4]

In managing epilepsy, drug dose is adjusted arbitrarily until seizure control is achieved. A second agent is introduced if the first agent fails at the maximal tolerable dose. Polytherapy is introduced after two failed monotherapies.[5] Therapeutic drug monitoring is indicated to determine drug levels when there is therapeutic failure.[6,7,8]

Therapeutic drug monitoring was developed because the dose of antiepileptic drugs was poorly predictive of serum drug levels, adverse effects and seizure control.[6,7,8] A single dose was found to give a widely varying serum levels in patients. An overlap in the dose at which seizures are controlled and doses at which unbearable adverse effects occur was also observed. Similarly, the effect of increasing the dose of AEDs on seizure control is not predictable. Since antiepileptic drugs are given prophylactically, efficacy is only confirmed when a patient becomes seizure free. This may be may take several months especially in patients with infrequent seizures.[6,7,8]

As a result of the unpredictable relationship of the dose and therapeutic endpoints, reference range was developed based on the theory that the serum levels of AEDs will better reflect efficacy and toxicity than the dose of AEDs.[7] The therapeutic range defines the serum levels at which patients are expected to be seizure free and at the same time manifest the maximum tolerable adverse effects. A value below the range was expected not to give any therapeutic effect, while values above the range were expected to be associated with intolerable adverse effects.[6,7] The therapeutic range for carbamazepine is 4-12mg/l.[7]

Some studies have reported a similar therapeutic range in patients with epilepsy, while others showed no relationship between seizure freedom and serum drug levels of carbamazepine.[9,10,11,12, 13, 14, 15] As a result of the conflicting reports, the international league against epilepsy suggested that the term therapeutic range should be replaced with reference range and that levels at which seizure freedom is achieved should be individualized.[7]

Various explanations for these differences in serum drug levels and therapeutic responses include seizure severity, epilepsy syndrome and genetic variations in drug targets.[16,17,18,19] Currently there is a paucity of data on the relationship between dose, serum levels of carbamazepine and seizure control in this environment. Our preliminary study is looking at the how the dose and serum levels of carbamazepine affect seizure control in Nigerian patients on carbamazepine monotherapy.

METHODOLOGY

This study was a cross-sectional study conducted at the Neurology outpatient clinic of the Lagos University Teaching Hospital, Idi-Araba, Lagos (LUTH). Ethical approval was obtained from the Health Research and Ethics committee of LUTH. A written informed consent was also obtained from all study participants prior to inclusion in the study.

Seventy-seven patients diagnosed with epilepsy attending the clinic were recruited for this study. Inclusion criteria are a diagnosis of epilepsy which is defined as the occurrence of at least two unprovoked seizures occurring at an interval of more than 24hours and the use of carbamazepine monotherapy for a minimum of nine months.[20] Exclusion criteria are the use of anticonvulsant polytherapy, seizures occurring less than twice in six months, patients on drugs that could interact with serum levels of carbamazepine i.e. erythromycin, cimetidine, isoniazid, verapamil, pregnancy and non-consent.

A standard questionnaire was administered to all participants to document the

demographic and clinical data. The total dose of carbamazepine in 24hours was documented. Date of last seizure was obtained historically and corroborated by documentation from case records. The seizures were classified according to ILAE (International League against Epilepsy) criteria using clinical and EEG findings.[21]

Seizure control was classified as controlled for an individual who were seizure free for the preceding six months or more on a stable dose of carbamazepine and uncontrolled for patients who were not seizure free.

Five ml of venous blood was taken in the trough phase. The trough phase of the drug is the point of minimum drug concentration which is just prior to a maintenance dose. Serum drug levels were measured using high-performance liquid chromatography.

High-performance Liquid Chromatography

High performance liquid chromatography was carried out at the Central Research Laboratory, LUTH, Idi-araba using the method described by Fadare et al and Yoshida, *et al*.[12,22] Hypersil octadecylsilane (ODS) (C18, 250x 4.6mm, 5 micron) reversed phased column was used for separation of carbamazepine. Mobile phase was a mixture of acetonitrile: potassium hydrogen diphosphate at (50:50, v/v). The internal standard was also prepared at 20µg/ml. The ultra-violet detector wavelength was 236nm for carbamazepine. Validity was determined using six different calibration concentration of carbarmazepine in methanol. Calibration curves were linear and the correlation coefficient was 0.994.

Statistical Analysis

Data generated from the study was analysed using Statistical Package for Social Sciences (SPSS) software version 21. The demographic and clinical characteristics were analysed using descriptive statistics like mean, standard deviation (SD), median, range and proportions. Chi-square was used to compare seizure control and categorical variables while Mann Witney U-test was used to compare seizure control and continuous variables. P value less than or equal to 0.05 was considered statistically significant.

RESULTS

Characteristics of the Study Participants

A total of 77 patients were recruited during the study period. All the patients were on the same brand of carbamazepine. The study participants were made up of 43(55.8%) males and 34(44.2%) with a male to female ratio of 1.3:1.

The age range for this study was between 14-71 years. The mean age of the study subject was 35.5 ±16.2 years. Fifty-three (68.8%) patients had focal seizures while 24 (31.2%) had generalized tonic clonic seizure. Based on aetiology, 12(15.6%) had a positive family history of epilepsy, 24(31.2%) had a possible symptomatic epilepsy while there was no identifiable cause in 41(53.2%) of the participants.

The duration of seizures ranged from 1-26years with the mean duration being 7.8±6.8 years. Duration of treatment ranged from 9 months -25years with a mean of 5.8±5.8years.

Dose and Serum Levels of Carbamazepine

The dose range of carbamazepine in the participants in this study was 200-1000mg/day. The mean was 537.66 ±203.28mg in 24 hours. One (1.3%) patient was on 200mg, 47 (61.0%) the patients were on 400mg while the remainder 29(37.7%) were on doses of 600, 800 and 1000mg per day.The mean serum carbamazepine concentration is 10.13± 6.05 mg/l. The range was from 0 - 22.43mg/l.

Seizure Control

Out of the study participants, 46(59.7%) participants were controlled while 31(40.3%) were not controlled.

Relationship Between the Dose of Carbamazepine and Seizure Control

The seizure freedom rates gradually declined with higher doses of carbamazepine. Seizure control rates on 400mg was 70.8% while the cumulative seizure control was 59.7% on a dose of 1000mg per day (*Table 1*). Patient who

were on a dose of 400mg per day were more likely to be controlled compared to those on higher doses; *p-value* was 0.011 (*Table 2*).

Table 1. Cumulative seizure freedom rates on increasing doses of carbamazepine

Daily dose in mg	n	Controlled n (%)	Cum. controlled n (%)
200-400	48	34 (70.8)	-
600	9	2(22.2)	36(63.2)
800	15	8(53.3)	44(61.1)
1000	5	2(40)	46(59.7)

Table 2. Relationship between low and high dose of carbamazepine on seizure control

Dose	Controlled	Not Controlled	Total	X^2	p value
200-400	34 (66.7%)	17(33.3%)	51	6.521	0.011
600-1000	14(53.9%)	12(46.1%)	26		

**Dose in mg*

Relationship Between the Serum Levels of Carbamazepine and Seizure Control

Although the mean serum level of carbamazepine in patients who were seizure free was lower (9.20±6.28mg/l) compared to those with partial control (11.50±5.52mg/l) it was not statistically significant (p=0.178). The standard deviation was higher in controlled compared to uncontrolled seizures (*Figure 1*).

Figure 1. Relationship between seizure control and serum levels of carbamazepine levels (mg/l)

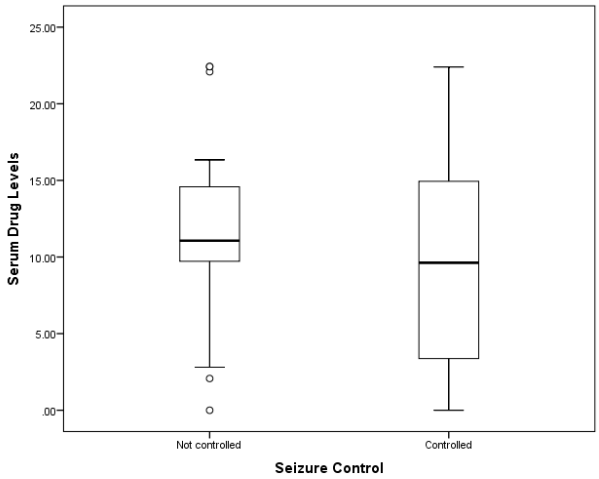

Table 3. Relationship between dose and serum drug level of carbamazepine

Dose (mg)	N	Mean	Range
200-400	48(61)	8.04+/6.13	0-22.40
600	9(11.7)	10.67+ 2.27	6.81-14.94
800	15(19.5)	13.98+ 3.41	9.72-22.09
1000	5(6.5)	17.65+ 4.82	11.11-22.43

Table 4. Analysis of other determinants of seizure control

Variable	Mean (SD)	U*	p-value
Age (yrs)	35.5 ±16.2	683.0	0.755
Seizure duration (yrs)	7.8±6.8	694.0	0.843
Duration of treatment	5.8±5.8	646.0	0.481

Variable	Not controlled n(%)	Controlled n(%)	**X2	p-value
Sex				
Female	13(38.2)	21(61.8)	0.104	0.747
Male	18(41.9)	25(58.1)		
Seizure classification				
Focal	22(41.5)	31(58.5)	0.110	0.740
Generalized	9(37.5)	15(62.5)		
Probably genetic				
Yes	5(41.7)	7(58.3)	0.012	0.914
No	26(40.0)	39(60.0)		
Probably symptomatic				
Yes	9 (37.5)	15(62.5)	0.110	0.740
No	22(41.5)	31(58.5)		
Drug adherence				
Adherent	14(45.2)	17(54.8)	0.518	0.472
Not adherent	17(37.0)	29(63.0)		

** Mann-Whitney U Test*
***Chi-Square Test*

Dose and Serum Levels of Carbamazepine

The dose of carbamazepine is moderately correlated with drug levels (rs=0.445, p=0.000). Although patient on a higher dose tended to have a higher level of carbamazepine, there was a wide range of serum drug levels on a similar dose of controlled release carbamazepine.

Other determinants of seizure control

Univariate analysis was used to identify other factors that could contribute to seizure control in the study participant. There was no statistically significant difference in seizure control in patients with focal vs generalized

seizure, adherent vs nonadherent patients (*Table 4*).

DISCUSSIONS

This study shows that patients on a dose of 400mg were more likely to be seizure free compared to those on higher doses. Brodie et al, observed that 85.4% of the patients who were one year seizure free on carbamazepine were on 400mg per day of controlled release formulation, while the remaining 14.6% needed higher doses.[23] An earlier study also showed that patients on lower doses 400-600mg per day were more likely to remain seizure free compared to higher doses.[24] Comparing the cumulative seizure control percentage in this study, the percentage of patients controlled reduced from 70.8 % to 59.7%. These findings suggests that increasing the dose of carbamazepine to maximal dose may not significantly improve seizure control rates.

Some studies have shown that genetic polymorphism involving sodium channels, which is the site of action of carbamazepine is a determinant of response to carbamazepine.[17,25] Tate, *et al*, first reported that higher doses of carbamazepine were required to control seizures in patients who had a mutation of the voltage-gated sodium channel gene. The mutant strain has been associated with reduced sensitivity of the voltage-gated sodium channels to carbamazepine, hence seizure control is achieved at a higher dose.[17] The mutation has also been associated with carbamazepine resistance.[25] Pharmacoresponse to a low dose of carbamazepine may serve as a tool in the prediction of pharmacoresistance to carbamazepine and drug-resistant epilepsy.[17,25,26]

Genetic variation with the wild type predominance may explain the findings in our study, however this will need to be confirmed in subsequent studies.

In comparing the serum levels of carbamazepine to seizure control, this study shows that patients had a widely varying level of carbamazepine at which seizures were controlled. This conflicts with earlier studies that suggested that patients are likely to be controlled within a therapeutic range of 4-12mg/l.[9,10,11.] Several studies from other parts of the world and a Nigerian study reported findings similar to our study.[12, 13 14,15] Fadare et al reported a wide inter-individual variability in serum levels at which patients on carbamazepine therapy had seizure control and this includes patients on both monotherapy and polytherapy.[12] A recent study had similar reports but was able to establish a relationship between carbamazepine: carbamazepine epoxide ratio and seizure control.[15]

These findings suggest that pharmacoresponse to carbamazepine is not solely dependent on the serum levels of carbamazepine.

The conflicting reports have been attributed to differences in the characteristics of the population studied. Epilepsy has been regarded as a heterogeneous disorder and has been classified based on aetiology, manifestations and as syndromes. This classification has prognostic implications and it has been suggested that patients with less severe seizures will require lower serum levels of carbamazepine compared to people with severe ones.[7] It was argued that the initial study used to define therapeutic range was carried out in a relatively uniform population of patients who had intrinsically severe seizures, hence they needed higher levels of carbamazepine to achieve seizure control.[7] The heterogeneity of the population in our study in terms of aetiology, duration of seizure, treatment duration and epileptic seizure types may contribute to the variable levels of at which seizures were controlled.

In the position paper on best practice for the monitoring of antiepileptic drugs, which was based on an extensive review of studies done on antiepileptic medications, it was recommended that therapeutic drug levels should be individualized. And adjustment in drug dosing should be based on clinical response and not solely on serum drug levels.[7]

While therapeutic drug monitoring may be useful in determining a therapeutic serum drug levels in patients who have been controlled, the utility of this in patients who have never attained seizure freedom can only be useful in assessing compliance since it has been shown that patients attain seizure freedom at levels above the therapeutic range.

The higher doses and relatively higher serum drug levels in patients who were not controlled may be explained by the need to increase the drug dose in non-responders, leading to higher serum levels in patients with poor seizure control. This has been duplicated in other studies.[12,15]

The study showed a moderate correlation between the drug dose and serum carbamazepine levels, although patients on a higher dose had a relatively higher drug level, each dose gave a wide range of serum levels of carbamazepine (*Table 3*).

The rates of seizure freedom in this study were not affected by drug compliance, epileptic seizure type, or aetiology (*Table 4*).

This study assessed short-term seizure over a period of six months. Although a six month period is enough to assess the efficacy of an antiepileptic drug, one year period would have been ideal in order to compare retentions rates. To the best of our knowledge, our study is the first to compare the relationship between dose, serum drug levels and seizure control in patients on carbamazepine monotherapy in Nigerian patients with epilepsy.

This is a pilot study and the findings from the study suggests that patients on a lower dose of carbamazepine are more likely to be controlled than those on higher doses. It appears that increasing the dose of antiepileptic drugs till seizure control is attained or intolerable levels of adverse effect occur may not be reasonable, since the proportion of patients controlled on a higher dose is not significant.

In addition, the varying levels at which seizure freedom is obtained suggests that absolute serum levels of carbamazepine may not be solely responsible for therapeutic efficacy. A single drug level measurement may not contribute significantly to clinical decision when relating to seizure control since levels above the reference range has been shown to control seizures. Determinants of pharmacoresponse to carbamazepine is a potential area for further research.

Although this is a pilot study, the findings here suggests a need to consider changing to a second line agent early since it appears that a smaller proportion of patients respond to higher doses in our study. Further studies need to be carried to identify those who will eventually respond to high doses or patient that will require an early change to a second agent for seizure control.

REFERENCES

1. Ngugi AK Bottomley C, Kleinschmidt I, *et al* . Estimation of the burden of active and life-time epilepsy: A meta-analytic approach. *Epilepsia* 2010; 51:883–890.
2. World Health Organisation. Epilepsy Fact Sheet [Internet]. Geneva: WHO Media centre; 2014 [updated 2016 February; cited 2016 December 18]. Available from http://www.who.int/mediacentre/factsheets/fs999/en/index.htm.
3. Sander JW. The Use of Antiepileptic Drugs—Principles and Practice. *Epilepsia* 2004; 45(6):28–34.
4. Glauser T, Ben-Menachem E, Bourgeois B, *et al*. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2013; 54:1-13.
5. St louis EK, Gidal BE, Henry TR, et al. Conversion between monotherapies in epilepsy: expert consensus. *Epilepsy Behav* 2007; 11:222–234.
6. Suthakaran C and Aditha C. Therapeutic drug monitoring – Concepts, Methodology, Clinical Applications and Limitations. *Health Administrator* 2006; XIX (1):22-26.
7. Patsalos PN, Berry DJ, Bourgeois BF, *et al*. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the sub commission on therapeutic

drug monitoring, ILAE Commission on Therapeutic Strategies. *Epilepsia* 2008; 49(7):1239–1276.
8. Patsalos PN and Berry DJ. Therapeutic drug monitoring of antiepileptic drugs by use of saliva. *Therapeutic drug monitoring* 2013; 35:4-29.
9. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. *Lancet* 1995; 345:476–479.
10. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomized comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res* 1999; 37:81–87.
11. Moreno J, Belmont A, Jaimes O, *et al*. Pharmacokinetic study of carbamazepine and its metabolite carbamazepine 10,11-epoxide in a group of female epileptic patients under chronic treatment. *Archives of medical research* 2004; 35(2):168-171.
12. Fadare J, Falade C, Bolaji O, *et al*. Correlation of the Serum Level of Carbamazepine with Seizure Control and Adverse Drug Reactions among Epileptics in Ibadan, Nigeria. *Int J Drug Dev & Res* 2010; 2(4):690-697.
13. Strandjord RE, Johannessen SI. Single-drug therapy with carbamazepine in patients with epilepsy: serum levels and clinical effect. *Epilepsia* 1980; 21(6):655-652.
14. Vasudev A, Tripathi KD and Puri V. Association of drug levels & pharmacokinetics of carbamazepine with seizure control. *Indian J Med Res* 2000; 112:218-223.
15. Chbili C, Hassine A, Ben Amor S, *et al*. The relationship between pharmacokinetic parameters of carbamazepine and therapeutic response in epileptic patients. *Arch Med Sci* 2015.
16. Martínez-Juárez IE , Hernández-Vanegas, LE, Rodriguez y Rodríguez N, *et al*. Genes involved in pharmacoresistant epilepsy. ***In***: Rocha L and Cavalheiro E.A .Pharmacoresistance in Epilepsy: From Genes and Molecules to Promising Therapies [Internet]. 1st ed. New York: Springer-Verlag 2013. [cited 2016 Dec 18]. Chapter 1. Available from DOI 10.1007/978-1-4614-6464-8_2.
17. Tate SK, Depondt C, Sisodiya SM, *et al*. Genetic predictors of the maximum doses patients receive during clinical use of the anti-epileptic drugs carbamazepine and phenytoin. *Proc Natl Acad Sci* 2005; 102(15):5507–5512.
18. Sánchez MB, Herranz JL, Leno C, *et al*. Genetic factors associated with drug-resistance of epilepsy: relevance of stratification by patient age and aetiology of epilepsy. *Seizure* 2010; 19(2): 93-101.
19. Remy S, Beck H. Molecular and cellular mechanisms of pharmacoresistance in epilepsy. *Brain* 2006; 129(Pt 1):18–35.
20. Fisher RS, Boas WVE, Blume W, *et al*. Epileptic seizures and epilepsy: definitions proposed by the International League against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia* 2005; 46:470–472.
21. Berg AT, Berkovic SF, Brodie MJ, *et al*. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005 – 2009. *Epilepsia* 2010; 51(4):676–685.
22. Yoshida T, Imai K, Motohashi S, *et al*. Simultaneous determination of zonisamide carbamazepine and carbamazepine-10,11-epoxide in infant serum using high-performance liquid chromatography. *J Pharm Biomed Anal* 2006; 23.
23. Brodie MJ, Perucca E, Ryvlin P, *et al*. Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. *Neurology* 2007; 68:402–408.
24. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001; 42:1255–1260.
25. Abe T, Seo T, Ishitsu T, *et al*. Association between SCN1A polymorphism and carbamazepine-resistant epilepsy. *Br J Clin Pharmacol* 2008; 66(2): 304-307.
26. Brodie M, Barry SJE, Bamagous GA, *et al*. Effect of dosage failed of first antiepileptic drug on subsequent outcome. *Epilepsia* 2013: 54(1) 194-198.