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Therapeutic drug monitoring in epilepsy: Can drug levels reliably measure drug adherence?

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ABSTRACT

Background: Drug adherence is often assessed from patients' reports and confirmed with therapeutic drug monitoring. The study investigated the relationship between reports of drug adherence and drug levels of carbamazepine among adult patients on carbamazepine monotherapy. **Methods:** 84 consecutively consenting patients who had been on carbamazepine monotherapy for seizure control were recruited from the Neurology Clinic, LUTH, Idi-Araba, Lagos for the study. Adherence in the past month was assessed using a standard proforma. Drug levels were taken in the trough phase (just before the next dose of carbamazepine) and analyzed using high performance liquid chromatography.
Results: Among the population studied, full adherence was reported in 45.2% of the participants while the remainder had missed one or more doses in the past month. Serum drug levels were found to be significantly higher in patient who reported full adherence compared to non-adherent patients ($p< 0.05$). When levels were compared to the reference range of carbamazepine, 15.8% of the patient who reported good adherence had blood levels in the subtherapeutic range, while 21.7% who reported poor adherence had blood levels in the subtherapeutic range ($p>0.05$).
Conclusion: Adherence is associated with higher drug levels, but both adherent and nonadherent patients had a similar likelihood of having serum drug blood levels in the subtherapeutic range. This calls for caution in the interpretation of drug levels as it relates to adherence. Further studies on standardization of therapeutic drug measurement to develop predictive tools for adherence are recommended.

1. Introduction

Therapeutic drug monitoring involves the measurement of drugs and their metabolites in body fluids and compartments to optimize drug treatment [1]. It is a valuable tool employed in different areas of drug research and medicine to guide treatment for specific drugs that have been known to have marked pharmacokinetic variability, high potentials for drug toxicity, and some conditions associated with reduced drug clearance like chronic kidney disease [2]. Antiepileptic drugs (AEDs) belong to the group of drugs that require therapeutic drug monitoring because of pharmacokinetic variations [3].

In epilepsy, therapeutic drug monitoring is indicated mainly to assess for therapeutic range in patients with poor seizure control and to determine drug adherence in suspected cases of non-adherence to therapy. It is also employed to exclude drug toxicity in patients with adverse drug effects, to guide dosage adjustment in conditions characterized by pharmacokinetic changes and in drugs with dose-

dependent pharmacokinetics [4-5].

Adherence to medical therapy is a major determinant of outcome measures and poor adherence to treatment have been implicated in breakthrough seizures, poor seizure control, poor quality of life and increased mortality [6-9]. A multicentre study among people living with epilepsy in the USA reported a threefold mortality in non-adherent patients compared to those who were adherent to therapy [6]. The negative impact of poor adherence emphasises the importance of taking medications as prescribed, unfortunately, studies have reported poor adherence to antiepileptic drug therapy with prevalence ranging from 26 to 79% as obtained from various studies [10]. Only a few studies have investigated adherence to antiepileptic medications in Nigeria, one of such studies reported that only 17% of the population studied had a high adherence to antiepileptic drugs [11].

Apart from patients' report of poor adherence, therapeutic response has been used subconsciously to judge adherence, especially in the clinics when non-adherences are usually explored in the setting of poor therapeutic response. It is well known that non-adherent patient may experience therapeutic response, for instance in epilepsy care, it has been shown that non-adherent patients may be seizure free [12]. Therapeutic response despite poor adherence has also been document for other disease conditions like infectious diseases, a study which compared adherence to therapy among people living with HIV and viral suppression over a year period reported that an adherence level of about 82% achieved a viral suppression in 90% of subjects, further supporting the evidence that non-adherent patients may experience therapeutic response [13].

Other measures used to assess adherence include patients' report, pill count, electronic drug containers, secondary database analysis such as refill from pharmacies and measurement of drug levels in body compartments [14]. The measurement of drug levels in body compartments involve the use of blood, saliva, hair and nails [15]. Use of dried blood spot has also been demonstrated to provide a cheaper alternative to measuring plasma drug levels, and it has been found to have a strong correlation with the plasma levels of some AEDs [16].

Even though adherence could be assessed using various means, no single method is the gold standard for diagnosing drug adherence. This is because of the significant limitations associated with the various methods, for instance, patients' report is the first step and most readily available method of measuring adherence, but response to questions on adherence has been shown to be subject to both overreporting and underreporting. Recall bias or an intentional action, especially when benefits or consequences are associated with specific responses are some of the factors contributing to over or under reporting of drug adherence [17]. Other methods like the use of pill count, electronic containers and pharmacy refills more accurately describe drug uptake by patients but does not prove that drugs were ingested. Measurement of drug levels in body compartment appears to be a relatively more objective method of assessment of drug intake but like other methods, it has its own limitation [18-19].

Most studies evaluating adherence have been based on patients' report with only a few using other markers of adherence like pill counts, pharmacy refill records and drug levels. Clinical response has also been used as a marker for adherence but patients with poor adherence may also be seizure free and vice versa [12]. Therefore, clinical response may not be a good marker especially in those with drug resistant seizures where a patient continues to have seizures despite good adherence. It appears that combining different measures of adherence may provide a more objective means of assessing adherence, therefore this was carried out to see if there is any concordance between two different methods for assessing drug adherence [20].

This study investigated the relationship between adherence reports and serum drug levels in patients taking carbamazepine monotherapy for seizure control. The study was carried out in patients on monotherapy for seizure control to eliminate possible drug interactions with other antiepileptic drugs that may influence serum drug levels of carbamazepine. Patient on carbamazepine (CBZ) were chosen because CBZ is one of the most used AEDs. Generally, drug levels are reported by comparing to a reference range, and drug reference range are classified into subtherapeutic, therapeutic and toxic levels. Lower level of drugs which corresponds to the subtherapeutic range is expected in poor adherence, we therefore evaluated the relationship between adherence in the population and the likelihood of having drug levels in the subtherapeutic range.

2. Methods

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. This study was granted ethical approval with number ADM/DCST/HREC/268. The study was explained to the participants and a signed informed consent was also obtained from all study participants before inclusion in the study.

Eighty-four patients diagnosed with epilepsy attending the clinic were recruited for this study.

The sample size was calculated using the formula for descriptive studies $n=Z^2 pq/d^2$ where n was the minimum sample size for a population ≥10,000; Z was the standard normal deviate corresponding to 95 % confidence level (standard value of 1.96). The p, prevalence was from the highest prevalence of epilepsy in south-west Nigeria, which was 0.037, while d, the margin of error was set at 0.05 [21]. With the above specifications, the minimum sample size determined for the study was 55, the sample size was increased to 84 to correct for attrition.

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 24 hours and the use of carbamazepine monotherapy for the treatment of epilepsy. Exclusion criteria are the use of anticonvulsant polytherapy, and the concomitant or recent use of enzyme inducing or inhibiting drugs i.e. erythromycin, cimetidine, and isoniazid. Anticonvulsant polytherapy and use of enzyme inducing/inhibiting may affect the drug levels of carbamazepine.

A standard questionnaire was administered to all participants to document the demographic and clinical data and the dose of carbamazepine. Full adherence was defined by the regular use of prescribed dose of carbamazepine over the previous month while non-adherence was the described as missing a dose or more in the preceding month.

Five mL of venous blood was taken in the trough phase for all patient to create uniformity in sampling time using plain sample collection bottles. 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 (HPLC) as previously described [22].

HPLC was a modification of that described by Yoshida and colleagues [23]. Hypersil octadecylsilane (ODS) (C18, 250x 4.6mm, 5 micron) reversed phased column was used for the separation of carbamazepine. Mobile phase was a mixture of acetonitrile: potassium hydrogen diphosphate at (50:50) %. The ultra-violet detector wavelength was 236nm for carbamazepine. Stock standard solution of carbamazepine was prepared by dissolving 10 mg /ml methanol and stored at -4ºC. Other concentrations of carbamazepine were made by diluting stock standard solutions with methanol to achieve calibration concentrations of 1.25, 2.5, 5, 10, 20, 40µg/ml respectively. Glibenclamide was used as the internal standard. It was prepared at 20µg/ml and packed into the serum (standard and samples) for calibration at a concentration 20µg/ml (100µl).

Deproteinization was done adding acetonitrile to plasma at a ratio of 1:2. The mixture was vortex mixed for about 30 seconds and then centrifuged at a rate of 4000 revolutions per minute for 10 minutes. The supernatant was then injected into the HPLC machine for analysis. Flow rate of mobile phase was 1 mL/min through column at the room temperature. All analysis were carried out at the Central Research Laboratory, LUTH, Idi-araba.

Linearity was tested through analysis of serum calibration standards containing known amounts of six different concentrations of carbamazepine. Calibration curves were linear, and the correlation coefficient was 0.994. The intra-day and inter-day coefficient of variation were 0.85% and 1.05% respectively.

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 e.g., mean, standard deviation (SD), median, range and proportions**.** Normality testing for the levels of CBZ was done using Shapiro wick to determine appropriate statistical method. Independent student t-test was used to compare serum drug levels and reported adherence. Chi-square was used to compare adherence and other variables to the different categories of drug level based on the reference range of carbamazepine. ($P < 0.05$) was considered statistically significant.

3. Results

3.1 Demography and clinical characteristics of study participants

The demography and clinical characteristics of study participants are as shown in Table 1. The study participants included 47 (56%) males and 37 (44%) females. The age range was 14–71 years with a mean 34.5 ± 16.5 years.

The duration of seizures ranged from 1 to 26 years, with the mean duration being 7.26 ± 6.49 years. Duration of treatment ranged from 9 months to 25 years, with a mean of 5.92 ± 5.74 years. Doses of carbamazepine used in the study

ranged from 200 to 1000 mg per day, with a mean of 528.57 ± 21.59 mg per day.
The other drugs co-medicated with antiepileptic drugs included antihypertensive drugs in 8 (9.5%), amitriptyline 7(8.3%), aspirin 7 (8.3%) and multivitamins in 3 (3.6%). Herbal drugs were used in 14 (16.7%) of the patients.

Table 1: Demographic and clinical characteristics of study participants

Variable	Frequency	Percentage
Gender		
Male	47	56
Female	37	44
Age in years		
20-39	57	67.8
40-59	16	19.1
>59	11	13.1
Aetiology		
Presumed genetic/idiopathic	12	14.3
Secondary/symptomatic	27	32.1
Unknown/cryptogenic	45	53.6
Comorbidities		
Present	22	24.2
Absent	62	75.8
Seizure Type		
Focal	57	67.9
Generalized	27	32.1
Seizure Control		
Seizure free	49	58.3
Not seizure free	35	41.7
Drug dose		
400	54	64.29
600	10	11.90
800	15	17.86
1000	5	5.95

3.2 Drug adherence among participants

A total of 38 participants (45.2%) reported full adherence to treatment while 46 (54.8%) reported poor drug adherence (Figure 1). Poor adherence in the population was attributed to forgetting to take their medications 39.3%, unaffordability 13.1%, non-availability for purchase 4.8% and adverse effect experienced from taking the medication 1.2%.

3.3 Drug adherence and drug levels

The result showed that patient who reported adherence had significantly higher levels of carbamazepine in the serum compared to non-adherent patients (p = 0.018) as seen in Table 2. The relationship between drug adherence and classification of drug levels based on reference range is shown Table 3. There was no association between adherence and having drug levels in the therapeutic/toxic or subtherapeutic range (p = 0.489). Bivariate analysis however suggested that

the drug dose was correlated with serum drug levels. We further determined the effect of concomitant use of herbal drugs on serum drug levels in the population, the result showed no significant difference in drug levels between users and non-users of herbal drugs. The use of herbal drugs did not significantly affect the serum drug levels in this population.

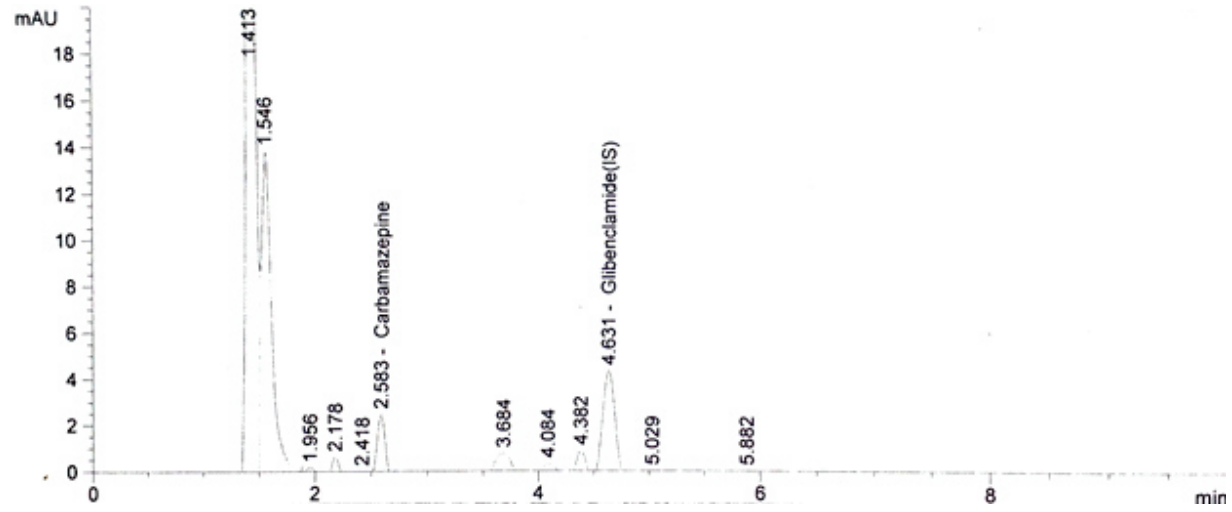

Figure 1: HPLC chromatogram of carbamazepine

Table 2. Relationship between drug adherence and carbamazepine levels in mg/dL

Adherence	n	Mean ± SD	Median	Range	p-value
Adherent	38	11.66±6.35	14.5	0.0-22.4	0.018*
Not adherent	46	8.61± 5.27	9.1	0.0-18.3	

Table 3. Relationship between drug adherence and reference range of carbamazepine

Reported Adherence	Sub-therapeutic	Therapeutic and toxic	p-value
Adherent	6 (15.8%)	32 (84.2%)	0.489
Non-adherent	10 (21.7%)	36 (78.3%)	

Table 4. Relationship between other variables and serum drug levels of carbamazepine

Variable	Spearman's Correlation coefficient	p-value*
Age	-0.182	0.098
Drug dose	0.445	<0.001
Variable	**Mean ± SD**	**p-value****
Sex		
Female	9.11+_5.2	0.231
Male	10.7 ± 6.4	
Herbal drug use		
Yes		
No	8.28±5.4	0.216
	10.33±6.0	

*** Spearman's correlation coefficient, ** independent sample t-test**

4. Discussion

The study showed that the rate of adherence to AED therapy using self-report as a guide, was poor among the participants. Only 45.2% of the respondents used their drugs regularly and as prescribed. The report of adherence is comparable to other studies that have reported non-adherence rates between 26-79 %, but relatively higher than other studies in Nigeria although these studies were carried out in patients on antiepileptic drug polytherapy and monotherapy [10,11,24]. A study in Northern Nigeria reported an adherence rate of 32.6% among patients with epilepsy attending a tertiary health care institution [24]. Another recent study which assessed adherence using four-item Morisky Medication Adherence Scale reported full adherence in only 17% of patients recruited for the study [11]. The relatively higher rate in our study may be because the population studied were on monotherapy whereas other studies included both monotherapy and polytherapy, higher drug burden has been associated with poor drug adherence [25].

Comparing reports of adherence to drug levels, our study showed that patients who reported full adherence had a significantly higher serum levels of carbamazepine compared to those who reported nonadherence (Table 2). The higher levels found in this study was not related to the age and sex of the participants, but higher drug dose was associated with higher drug levels (Table 4). Other studies investigating the relationship between reported adherences and drug levels have given conflicting reports [26-29]. Shah and colleagues had earlier shown that self-reported adherence among a paediatric population was in tandem with the blood levels of AED and pharmacy refills [26]. These findings give credence to patients' reported measures of drug adherence and suggest that self-reported adherence may be believable. Another study however, found relatively lower levels of drugs compared to that predicted for the dose, weight, and other variables [29]. Both studies which were done in paediatric population compared measured value to a reference value of AED which was based on calculations from population pharmacokinetics.

Although our study showed that poor adherence was associated with relatively lower levels of carbamazepine compared to adherent patients, both adherent and non-adherent patients were more likely to have their drug level in therapeutic or toxic range rather than sub-therapeutic levels (Table 3). The reference range for carbamazepine is 4-11mg /dL, values below 4mg are regarded as sub-therapeutic levels and values above 11mg/dL as toxic levels [4]. Different studies have used the presence of undetectable serum drug levels and levels below the standard reference range (sub-therapeutic) to measure drug adherence [28, 30]. This is based on the presumption that patients who are not adherent are more likely to have undetectable drug levels or sub-therapeutic drug levels. This may not always be the case as seen in this study and other reports [31-32]. Majority (78.3 %) of the non-adherent patients had serum levels in the therapeutic range (Table 3), a similar trend was observed in the adherent patients with 84.2 % of them being in the therapeutic range. There was no significant difference in drug levels between adherent and non-adherent patients when the reference range of carbamazepine was used as a determinant of adherence. This is in consonance with previous studies [31-32].

A study carried out by Lunardi and colleagues on patients with suspected drug refractory epilepsy also found no significant difference in the plasma levels of AEDs among adherent versus non-adherent patients when the reference range was used as a defining factor. The study measured the serum drug levels at presentation and to provide an objective assessment of adherence, a second measurement was taken after supervised drug administration The outcome showed that 76.2% of non-adherent patient had drug levels in the therapeutic range and this is similar to that obtained in our study [32]. The measurement of adherence by comparing drug levels to standard reference range may be misleading due to individual variations in pharmacological response to drugs. Studies have documented seizure freedom at drug levels below the therapeutic range and this is the basis for recommending individualization of therapeutic drug levels in epilepsy care [4, 5, 22]. The same apply to drug levels and adherence, bringing to the fore the need to consider individual differences before using drug levels to judge adherence.

Individual factor like age, gender, weight, ethnicity, food, disease state and intestinal microbiome interact to affect the pharmacokinetics of drugs which determines the final concentration of drugs in body compartment [33-37]. Pharmacogenomic variations are also major players in determining drug concentration [38]. Drug factors have also been shown to affect drug levels and these include dose, dosing, timing of samples, brands and physicochemical properties of drugs and drug-drug interaction [32, 39-42]. Unfortunately, these factors are not considered when interpreting the results of drug levels for the determination of drug adherence, leading to over or underestimation of drug adherence.

Therapeutic drug monitoring has been used in other medical specialties to investigate drug adherence and like its use in antiepileptic drug, there are challenges with the cut off value for determining drug adherence. A meta-analysis which compared plasma trough concentrations of amlodipine, hydrochlorothiazide, and valsartan, using HPLC found non-uniformity in the criteria for the determination of poor adherence and concluded that the using trough concentration as a cutoff in the biochemical assessment of adherence can result in inaccurate diagnosis and therefore not recommended [43].

A study recognized some of these limitations and advocated the use of indexed trough analysis (in which the dose of medications is matched to the trough levels in blood) to avoid dose related bias in measuring adherence [44]. This is relatively new, further studies need to be carried out to determine the clinical utility of this. Other studies investigated a combination of direct observation of drug intake and timed measurement of drug levels at multiple times to establish drug adherence [32, 41, 45]. These studies have been able to establish drug adherence even in the presence of sub-therapeutic drug levels but their utility in real world setting is doubtful because of the time and human power involved especially in regions with resource constraint like ours.

Several treatment regimens for chronic diseases like epilepsy, hypertension, diabetes mellitus etc require the commencement of drugs at lower doses and titrating upwards or changing drugs if clinical response is inadequate. An objective assessment of adherence is therefore paramount to avoid unnecessary change in drug treatment. This study highlights the relationship between reported adherence and serum drug level and calls for caution when drug levels are used to judge adherence. It is one of the few studies that have used two measures to determine adherence.

One of the strengths of our study is that measurement of drug levels was carried out in patients on monotherapy therefore eliminating the effect of antiepileptic drug-drug interaction which may interfere with drug levels of carbamazepine. Antiepileptic drugs are known to have high potentials for drug interactions. One of the limitations of our study is that adherence was evaluated using two measures, a third measure of adherence such as pill count, pharmacy refill etc. would have given a stronger validity to our result.

5. Conclusion

The measurement drug level of drug to ascertain adherence may support reports of adherence in patients, however the utility in real-life is questionable because of lack of a specific defining levels for drug adherence. With current advances in artificial intelligence, pharmacokinetic models can be developed which will consider variables such as age, gender, genetic differences, and drug dose in predicting drug concentration. We therefore recommend further studies on standardization of therapeutic drug measurement with strong consideration on individual variations that may affect blood levels of drugs.

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