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Toxicological Profile of Carbamazepine and Levetiracetam on Some Biochemical and Haematological Parameters in Rats

Theophine Chinwuba Akunne[1], Sunday N. Okafor[2*], Zellinjo Igweze[3], Chiamaka N. Njoku[3], Oluwatoyin O. Ojapinwa[3]

[1]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Nigeria, 410001 Nsukka, Enugu State, Nigeria
[2]Department of Pharmaceutical and Medicinal, Faculty of Pharmaceutical Sciences, University of Nigeria, 410001 Nsukka, Enugu State, Nigeria
[3]Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, Madonna University, 510242 Elele, Rivers State, Nigeria

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Corresponding Author:
E-mail : sunday.okafor@unn.edu.ng
Mob.: +2348036556699

Abstract

The prolonged usage of antiepileptic drugs has necessitated the need to study their toxicological profiles using in experimental animals. The toxicological effects of carbamazepine (CBZ) and levetiracetam (LEV) on some biochemical and haematological parameters were evaluated in rats. Haematological parameters evaluated include packed cell volume (PCV), Haemoglobin (Hb) and white blood cell (WBC), while some biochemical parameters studied were liver enzyme tests such as alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and lipid profiles tests such as total cholesterol (TC), triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL). In addition, the body weight and morphological assessment of the vital body organs were determined. Results showed that CBZ and LEV did not significantly affect the haematological parameters. Animals treated with CBZ showed a significant increase in TC and HDL levels at 400 and 1000 mg/kg doses. There was no significant increase in the TC, HDL, LDL and TG in rats treated with LEV. CBZ and LEV treated animals at the doses of 400 and 1000 mg/kg showed a significant increase in body weights from the 6th day after commencement of treatment. There was also a significant increase in the weights of the liver, kidney and heart of the animals treated with CBZ and LEV. The colour and texture of the organs did not change. However, no appreciable weight increase was observed with the lung.

1 Introduction

Epilepsy has continued to be a chronic neurological diseases estimated to affect about 50 million people in the world, of which about 2.5 million people are in United States of America alone[1]. It is managed with standard antiepileptic or antiseizure drugs (AEDs) which often provide symptomatic relief of seizure without a complete cure, thus rendering their usage for life. The chronic use or long term therapy of AEDs might pose a systemic toxicity problem to epileptic patients thus there is need to study their toxicological profiles using experimental animals. In toxicology, there are acute, sub chronic and chronic toxicological studies based on the period of exposure or treatment.

Two standard AEDs, carbamazepine and levetiracetam each belonging to the conventional and recently developed antiepileptic drugs, respectively, were randomly selected for the study. Conventional or first-line AEDs such as phenytoin, phenobarbitone and carbamazepine (CBZ) are commonly used for their efficacy, availability and cost effectiveness[2]. Moreover,

newer or recently introduced AEDs like levetiracetam (LEV), lamotrigine and topiramate have also been used in the treatment of epilepsy though with less availability in the developing nations.

Levetiracetam (LEV**)** an (-)-(S)-alpha-ethyl-2-oxo-1-pyrolidine acetamide, is a pyrrolidone derivative. It is a recently introduced or second-generation antiepileptic drug. It has been found to be very useful therapy in the management of partial-onset seizures in adults and children for primary generalized tonic-clonic seizures and for myoclonic seizures of juvenile myoclonic epilepsy[3].

Safety profile of LEV is highly important because of its chronic use and other clinical indications. Lukyaneztz et al (2002)[4] has shown that levetiracetam has been shown to reduce L-Dopa induced dyskinesias (LID) in a dose-dependent manner. Carbamazepine, 5H-dibenzo[b,f]azepine-5-carboxamide, is an iminostilbene derivative structurally similar to tricyclic antidepressants. Carbamazepine is a first drug of choice in tonic clonic and partial seizures and may be of benefit in all other types of seizures except generalized absence seizures and myoclonic seizures. Carbamazepine is known to exhibit some toxic effects such as causing alterations in haematological parameters[5]. It was therefore, important to study and ascertain the toxicological effects of carbamazepine (CBZ) and levetiracetam (LEV) on some biochemical and haematological parameters using rats.

2 Materials and Methods

2.1 Experimental animals

Twenty four adult albino rats of both sexes weighing between 100 - 200 g were obtained from the animal house of the Department of Pharmacology and Toxicology, Madonna University Elele. The animals were housed in cages and were allowed to acclimatize for a period of one week before commencement of experiment.

2.2 Collection of drug

Carbamazepam (NOVARTIS, Switzerland) and Levetiracetam (UCB Inc. USA) were sourced in a local Nigerian Pharmacy.

2.3 Experimental procedure

The animals were grouped into seven (A-G) groups of six animals each. The animals in groups A, B and C received 100, 400 and 1000 mg/kg of CBZ, respectively while those in groups D, E and F received 100, 400 and 1000 mg/kg of LEV, respectively, lastly group G received 2.5 ml/kg of the vehicle and was used as the untreated control. All treatments were administered orally daily for a period of three weeks. At the end of the 21 days, the animals were anaesthetized with chloroform first and then cardiac puncture technique was used to collect blood samples from the rats. The blood from rat was put in two different bottles - a plain bottle and an anticoagulant (EDTA) bottle. The rat was later sacrificed and the organs harvested, cleaned and weighed. The blood samples were transferred in plain tubes without any additives and were allowed to coagulate. The coagulated blood was centrifuged and the serum separated from the cells with a micropipette. The serum was stored in a freezer at 20 ˚C and the EDTA blood was stored in a fridge at 4 ˚C before they were subjected to haematological and biochemical analysis.

2.4 Liver function analysis

2.4.1 Alkaline phosphatase

Two test tubes were labelled sample and standard and 1.0 ml of distilled water was added to each test tube. One drop of ALP substrate was added to each test tube and incubated at 37°C for 5 minutes. 0.1 ml of sample and standard solution was added into the test tubes respectively. The content of the test tube was mixed thoroughly and read spectrophotometrically at 550 nm against water blank

Concentration of test = $\frac{absobance\ of\ test}{absorbance\ of\ standard} \times concentration$

2.4.2 Serum aspartate aminotransferases (AST)

Two test tubes were labeled test and blank. Into each test tube was added 0.5 ml of buffer solution containing aspartate and alpha-oxoglutarate. 0.1 ml of the sample was added into the test tube labeled test. It was mixed and incubated for 30 minutes at 37° C. 0.1 ml of 2, 4-dinitrophenylhydrazine was added into each test tubes. Another 0.1ml of the sample was added to the test tube labelled test, it was mixed thoroughly and allowed to stand at room temperature for 20 minutes. 5.0 ml of 0.4 N sodium hydroxide solution was then added to each of the test tubes. The content of the test tubes were thoroughly mixed ad read with the UV spectrometer at 540 nm against a blank sample. The concentration of the test was exacted from a prepared standard curve provided in the kit.

2.4.3 Alanine aminotransferase (ALT)

Method: same as AST

2.5 Haematological parameters.

2.5.1 Haemoglobin estimation

Cyanomethaemoglobin method as described by (Chessbrough 2004)[6].

Two test tubes labeled test and standard were placed on the rack, 0.4ml of Drabkin's solution and 0.02ml of blood were added to the test tube labeled test, 4.0ml of Drabkin's solution was added to the test tube labeled blank. The colorimeter was zeroed with Drabkin's solution. The absorbance of the test sample was read at 540nm wavelength and the reading was taken.

It was then calculated using this formula: $\frac{absobance\ of\ test}{absorbance\ of\ standard} \times concentration$

2.5.2 Packed cell volume (PCV)

Microhaematocrit method as described by (Chessbrough 2004)[6]

A plain capillary tube was three quarter filled with well mixed anti coagulated blood and one end was sealed with plastacine. It was then spun using a microhaematocrit centrifuge at 1200 RPM for 5 minutes, immediately after centrifuging, the PCV was read with a hand held microhaematocrit reader, the base of the red cell column was aligned (above the sealant) on the zero mark and the top of the plasma column on the 100 mark, the PCV was read off from the scale, the reading point is the top of the cell column, just below the buffy coat layer (consisting of white blood cells and platelets)

2.5.3 Total white blood cell count (WBC)

Manual method as described by (Chessbrough 2004)[6] was used.

A 0.3ml of diluting fluid (Turk's solution) was dispensed into a tube then 0.02ml of thoroughly mixed anti-coagulated blood was added. The counting chamber was charged; this was done by sliding a cover slip into position over the grid areas of the counting chamber and pressing down on each edge until rainbow color (Newton rings) was seen. The diluted blood sample was mixed using a pipette held at an angle of about 45 degree, one of the grids of the chamber was filled with the sample.

The chamber was left undisturbed for two minutes to allow the cells settle. The chamber was placed on a microscope stage. Using 10 X objective iris sufficiently closed to give a good contrast, the ruling of the chamber and the white cells was focused, and the cells in the four large corners square of the chambers were counted.

The number of white cells per litre of blood counted was reported using the following simple calculation:

- The total number of cells counted was divided by two
- The figure obtained was divided by ten.

2.6 Lipid Profile

2.6.1 Estimation of total serum cholesterol

Oxidation method was used. The serum was diluted with distilled water in the ratio of 1:20; the cholesterol standard was diluted with glacial acetic acid in the ratio of 1:20. The test tube rack was swirled for 10 seconds to mix the contents of each test tube; the test tubes were immediately placed in boiling water for exactly 90 seconds. The test tubes were cooled in running tap water for 5 minutes; the absorbance was read at 560nm against the blank, using dry cuvette. The colour was stable for 15 minutes.

2.6.2 Triglyceride

Two test tubes were labelled standard and test, 0.1 ml of triglyceride reagent was added and 2µl of standard solution and sample were also added into the appropriate tubes, it was mixed and incubated at 37°C for 5 minutes and read in a spectrophotometer at 547nm against water and blank

Conc. of test = $\frac{absobance\ of\ test}{absorbance\ of\ standard} \times concentration$

2.6.3 High density lipoprotein

A 200 µl of sample/standard was added into a test tube followed by 500 µl of HDL dilute participant. The solution was mixed and allowed to stand for 10 minutes at room temperature and centrifuged at 400 RPM for 10 minutes. The clear supernatant was separated and the HDL cholesterol was determined using the total; cholesterol enzymatic end point method.

2.6.4 Low density lipoprotein

The formula below was used to determine the LDL- cholesterol

$$LDL = TC - \frac{TG}{2.2} \times HDL$$

2.7 Statistical analysis

The results were expressed as mean ± standard error of mean (SEM). Statistical analysis was performed by one-way ANOVA with LSD as multiple comparison to evaluate differences between the control and test groups. Values at $p < 0.05$ were considered significant.

3 Results

3.1 Effects of Carbamazepine and Levetiracetam on PCV, Hb and WBC

Table 1 shows the effects of carbamazepine and levetiracetam on the PCV, Hb and WBC at different concentrations of 100, 400 and 1000 mg/ml.

3.2 Effects of Carbamazepine and Levetiracetam on lipid profile

Table 2 shows the effects of carbamazepine and levetiracetam on the lipid profile at different concentrations of 100, 400 and 1000 mg/ml. the lipid profile include TC, TAG, HDL and LDL

3.3 Effects of Carbamazepine and Levetiracetam on Liver Enzymes

Table 3 shows the effects of carbamazepine and levetiracetam on the liver enzymes at different concentrations of 100, 400 and 1000 mg/ml. The liver enzymes include ALP, ALT and AST.

3.4 Effects of Carbamazepine on Body Weight

Table 4 shows the effects of carbamazepine and levetiracetam on the body weight of the rats at different concentrations of 100,

400 and 1000 mg/ml. The body weight was checked and recorded at 3 days intervals until the 21st day

3.5 Effects of Carbamazepine and Levetiracetam on Organ Weight

Table 5 shows the effects of carbamazepine and levetiracetam on the weight of the organs at different concentrations of 100, 400 and 1000 mg/ml. The organs evaluated include the liver, kidney, lung and heart.

3.6 Effects of Carbamazepine and Levetiracetam on the Colour and Texture of Vital Organs

Table 6 shows the effects of carbamazepine and levetiracetam on the colour and texture of the vital organs at different concentrations of 100, 400 and 1000 mg/ml. The vital organs include the liver, kidney, heart and lung.

Table 1: Effects of Carbamazepine and Levetiracetam on PCV, Hb and WBC

Drug	Dose (mg/ml)	PCV (%)	Hb (g/dl)	WBC (x 10^9 cell/L
	Control	15.67±6.40	12.37±2.01	2.65±0.33
	100	21.17±9.80	12.17±2.07	2.38±0.37
Carbamazepine	400	29.00±7.53	12.08±5.17	2.70±0.34
	1000	22.00±8.59	9.20±1.27	2.27±0.36
	100	27.33±2.14	12.73±0.35	2.57±0.12
Levetiracetam	400	21.00±2.37*	12.73±0.35*	2.50±0.17
	1000	19.80±3.48*	10.94±1.27*	2.70±0.13

Values are in mean±SD, n = 6, *significantly different at (p<0.05) from the control; PCV = Packed cell volume; Hb = Haemoglobin; WBC = White blood cells

Table 2: Effects of Carbamazepine and Levetiracetam on Lipid Profile

Drug	Dose (mg/ml)	TC (mmol/L)	TAG (mmol/L)	HDL (mmol/L)	LDL (mmol/L)
	Control	80.50±10.25	71.00±21.56	36.83±13.15	35.17±9.85
	100	83.33±11.25	73.83±27.09	45.33±11.76	37.00±10.94
Carbamazepine	400	97.33±14.89*	92.17±13.08*	51.83±11.54*	41.00±9.92
	1000	93.50±8.10*	92.50±5.45*	57.75±6.50*	40.75±3.78
	100	87.17±4.78	86.50±8.01	50.17±4.78	39.67±3.43
Levetiracetam	400	77.67±2.90	58.33±2.35	31.67±6.83	29.00±2.78
	1000	90.00±6.10	78.60±11.37	48.80±6.84	39.00±3.11

Values are in mean±SD, n = 6, *significantly different at (p<0.05) from the control. TC = Total Cholesterol, TAG = triglyceride, HDL = High density lipoprotein, LDL= Low density lipoprotein

4 Discussions

There was no significant difference in the PCV of groups treated with 100 and 1000 mg/kg of CBZ, but there was a significant increase in PCV (p=0,05) for those that received the 400 mg/kg dose when compared with the control (Table 1). Studies by (Aliyu et al)[5] showed that CBZ did not cause any change in PCV. There was no significant change in the Hb and WBC values of animals treated with CBZ. AEDs are hematotoxic i.e. there is a decrease in haemoglobin concentration, RBC & WBC counts after long term antiepileptic therapy[7]. It has also been established that CBZ can cause aplastic anaemia. Their observed adverse effect has not been linked to the dosage, duration of CBZ use or patient age[8,9].

Animals treated with CBZ showed a significant increase in total cholesterol (TC) and HDL levels at 400 and 1000mg/kg doses when compared with the control (p=0,05 & p=0.05 for TC and p=0,05 & p=0.05 for HDL, respectively) (Table 2).. This result agrees with findings by (Nickolaos *et al*, 2004)[10] which demonstrated increased TC and HDL levels in CBZ treated animals.

There is a correlation between our finding and other reported works. There was a report showing an increase in tryglycerides

in 35 epileptics on long-term treatment with CBZ[11]. Reynolds et al. (1976)[12] has also observed that an increase in tryglycerides, cholesterol and VLDLc is associated with long-term treatment of epileptics with of anticonvulsant drugs. This finding may impose a great challenge on long-term anticonvulsant treatment as it increases the risk of coronary heart disease. Therefore, patients on long term therapy of CBZ should be monitored regularly for their serum cholesterol. However, there was no significant change in TC and HDL levels of those treated with 100 mg/kg which implies that increase in TC and HDL levels is dose dependent.

Table 3: Effects of Carbamazepine and Levetiracetam on Liver Enzymes

Drug	Dose (mg/ml)	ALP (U/L)	ALT (U/L)	AST (U/L)
Carbamazepine	Control	47.83±8.13	17.87±6.86	17.78±6.73
	100	48.83±11.11	23.92±5.87	23.20±5.47
	400	63.83±10.41*	29.07±2.58*	30.37±2.08*
	1000	69.25±7.18*	28.75±4.54*	26.75±5.02*
Levetiracetam	100	48.83±4.53	23.92±2.40	27.70±5.37*
	400	62.17±4.09*	27.40±1.28*	28.53±1.80*
	1000	69.60±2.47*	27.38±2.25*	26.90±1.64

Values are in mean±SD, n = 6, *significantly different at ($p<0.05$) from the control. ALP = Alkaline Phosphatase, ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase

Table 4: Effects of Carbamazepine on Body Weight

Drug	Dose (mg/kg)	Day 0 (g)	Day 3 (g)	Day 6 (g)	Day 9 (g)	Day 12 (g)	Day 15 (g)	Day 18 (g)	Day 21 (g)
Carbamazepine	**Control**	120.67 ± 7.76	121.33 ± 5.57	123.33 ± 5.16	127.00 ± 7.12	130.33 ± 6.50	135.67 ± 5.99	135.33 ± 5.47	135.33 ± 5.16
	100	126.33 ± 3.20	129.33 ± 3.01	133.67 ± 2.34	139.33 ± 2.42	141.67 ± 1.97	148.33 ± 4.63	152.67 ± 3.01	156.00 ± 5.37
	400	137.33 ± 5.32	139.00 ± 6.03	144.33 ± 5.57*	148.00 ± 4.56*	152.33 ± 4.80*	155.33 ± 4.84*	160.33 ± 2.97*	161.67 ± 3.20*
	1000	161.60 ± 8.65	170.00 ± 8.49	171.60 ± 7.27*	174.00 ± 8.72*	180.40 ± 7.13*	184.80 ± 5.76*	186.40 ± 5.18*	189.60 ± 4.77*
Levetiracetam	100	135.00 ± 2.17	139.00 ± 1.98	140.74 ± 1.68	146.00 ± 1.93*	147.67 ± 1.58	149.83 ± 1.42	153.67 ± 1.33	153.67 ± 2.39
	400	145.67 ± 2.75	147.33 ± 2.95	150.00 ± 3.69*	154.33 ± 5.40*	157.67 ± 5.23*	157.83 ± 4.29*	156.00 ± 4.34*	155.17 ± 4.80*
	1000	180.80 ± 8.66	187.20 ± 8.75	189.60 ± 9.39*	190.40 ± 9.10*	192.00 ± 9.48*	194.40 ± 9.32*	195.40 ± 9.59*	197.33 ± 9.89*

Values are in mean±SD, n = 6, *significantly different at ($p<0.05$) from the control.; ALP = Alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase

A study carried out by Manimekalai *et al*, (2014)[13] showed that there was no statistically significant increase in the TC, HDL-C, LDL-C and TG in patients treated with LEV for more than six months. There was no significant change in the LDL and TG levels for treated animals when compared with the control. From our findings, it appears that the newer AEDs like levetiracetam is preferred, especially for patients who are predisposed to cardiovascular problems than the first line AEDs - CBZ because of non elevation of serum cholesterol.

Table 5: Effects of Carbamazepine and Levetiracetam on Organ Weight

Drug	Dose (mg/ml)	Liver (g)	Kidney (g)	Lung (g)	Heart (g)
	Control	4.92±0.46	0.47±0.10	1.95±0.61	0.57±0.10
	100	5.37±0.81	0.47±0.82	1.55±0.22	0.63±0.14
Carbamazepine	400	4.67±0.18	0.48±0.18	1.60±0.18	0.48±0.41
	1000	6.07±0.62*	0.60±0.81*	1.65±0.30	0.65±0.10*
	100	6.23±0.24*	0.52±0.02	1.87±0.34	0.62±0.03
Levetiracetam	400	6.70±0.29*	0.60±0.04*	1.68±0.04	0.58±0.03
	1000	6.98±0.22*	0.58±0.08*	2.54±0.23	0.70±0.03*

Values are in mean±SD, n = 6, *significantly different at ($p<0.05$) from the control

Table 6: Effects of Carbamazepine and Levetiracetam on the Colour and Texture of Vital Organs

Drug	Dose (mg/kg)	Liver		Kidney		Heart		Lung	
		Colour	Texture	Colour	Texture	Colour	Texture	Colour	Texture
	Control	Dark brown	Smooth	Reddish brown	Smooth	Red	Smooth	Red	Smooth
	100	Brown	Smooth	Reddish brown	Smooth	Red	Smooth	Red	Smooth
Carbamazepine	400	Light brown	Smooth	Reddish brown	Smooth	Red	Smooth	Red	Smooth
	1000	Very Light brown	Smooth	Reddish brown	Smooth	Red	Smooth	Red	Smooth
	100	Pale brown	Smooth	Brown	Smooth	Reddish brown	Smooth	Reddish brown	Smooth
Levetiracetam	400	Pale brown	Smooth	Brown	Smooth	Reddish brown	Smooth	Reddish brown	Smooth
	1000	Very pale brown	Smooth	Brown	Smooth	Reddish brown	Smooth	Reddish brown	Smooth

Groups treated with 400 and 1000 mg/kg of CBZ showed significant increase in ALT ($p=0.05$), AST ($p=0.05$), and ALP ($p=0.05$), but there was no significant change in the level of these enzymes for those treated with 100 mg/kg of CBZ (Table 3). Increase in ALT , AST and ALP values in CBZ treated animals agrees with the findings by (Sonmez *et al*, 2006)[14] which may be as a result of strong inducing effect of CBZ on hepatic microsomal enzymes. CBZ is also known to cause liver fracture[15]; this effect can also induce liver enzymes. Groups that were treated with LEV showed significant increase in ALT ($p=0.05$), AST ($p=0.05$) and ALP ($p=0.05$) levels at 400 and 1000 mg/kg (Table 3). This work is in agreement with the findings of Nian et al (2012)[16]. They had earlier in their work reported an elevation in the liver enzyme markers. Acute liver failure has been reported by following the use of LEV in treatment of epilepsy[17] (Ylse *et al* 2013).

CBZ and LEV treated animals at the doses of 400 and 1000 mg/kg showed a significant increase in body weights from the

6th day after commencement of treatment when compared with the control (p=0.05) (Table 4). There has been a report on clinically significant weight gain with several AEDs, both the first-line and second-line generations. CBZ is associated with weight gain[18]. This is of clinical importance in various ways. When there are changes in weight, there are usually associated health hazards, body image and self-esteem are impaired, and this can lead to noncompliance with therapy[19]. It can also lead to obesity, another serious risk factor for cardiovascular diseases and type 2 diabetes.

The liver weight for CBZ treated animals showed a significant increase at 1000 mg/kg dose (p=0.05) (Table 5). This study also implies that increase in liver weight for CBZ treated animals is dose related as there was no significant change for those treated with 100 and 400 mg/kg when compared with the control.

There was also a significant increase in the weights of kidney (p=0.05) and heart (p=0.05) for groups treated with 1000 mg/kg dose of CBZ, while those treated with 100 and 400 mg/kg doses showed no significant change indicating that effect of CBZ on heart and kidney weights is also dose-dependent. On the contrary, the lungs of treated animals (with CBZ and LEV) showed no significant change in weight when compared with the control. The group treated with LEV showed a significant increase in the liver weight (p=0.05) at all the concentrations used. There was also a significant increase in the weights of kidney (p=0.05) and heart (p=0.05) for groups treated with 1000 mg/kg dose of LEV.

CBZ showed no effect on colour of organs of treated animals (table 6) except for the liver that changed from dark brown to light brown as the dose increased indicating that CBZ is hepatotoxic[15], but the texture of the organs of animals treated with CBZ showed no significant change when compared with the control. The colour of the liver changed and became lighter as the dose of LEV increased. The texture of the liver didn't change with an increase in a dose as it was still smooth just like the control. The colour and texture of other organs including the heart, lungs and kidney didn't change with an increase in a dose of LEV.

In a case report by Evangelia et al (2013)[20], they evaluated a 12-year-old epileptic child undergoing chronic treatment with 400 mg of carbamazepine daily for 15 months who was found comatose. The patient was considered to have acute severe carbamazepine drug toxicity resulting from prolonged carbamazepine half-life from poor drug clearance.

5 Conclusion

The findings exhibited that administration of carbamazepine and levetiracetam in rats over a long period of time has marked effects on some haematological and biochemical parameters.

6 Conflict of interest

The authors declare no conflict of interest

7 Contribution details

TCA designed the work. TCA, ZI, CNJ and OOO carried out the experiments. Data analysis were done by TCA and SNO. The manuscript was prepared by SNO and edited by TCA. All authors have approved the final article.

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