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Original article

Sensorimotor changes following acute exposure to carbamazepine and phenytoin in male Wistar rats

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ABSTRACT

Introduction: The use of antiepileptic drugs (AEDs) such as carbamazepine and phenytoin are part of strategies for the management of epilepsy. Acute exposure of epileptic patients to AEDs can cause sensory impairment.

Aim: This study seeks to assess sensorimotor changes in male Wistar rats upon single-large dose exposure to carbamazepine, phenytoin and their mixture.

Methods: 24 male Wistar rats (160-210 g) were randomly separated to four groups with 6 rats each. Groups I, II and III was given distilled water (2 ml/kg), carbamazepine (1950 mg/kg); and phenytoin (820 mg/kg) respectively, while Group IV (CBZ+PHY) was co-exposed to carbamazepine (1950 mg/kg) and phenytoin (820 mg/kg). The treatment was orally administered once by gavage (on Day(D) 1), then followed by weekly monitoring of body weight, clinical signs and neurobehavioural parameters for four weeks (D0, D1, D7, D14, D21 and D28).

Results: The body weight revealed insignificant improvement ($p > 0.05$) in all groups. A significantly ($p < 0.05$) lower grooming frequency, increased locomotor activity and a reduction in the frequency of urination and defecation were recorded in the CBZ and PHY groups. Also, the number of missed rungs, inclined plane and grip fore-paw time reduced significantly ($p < 0.05$) in CBZ, PHY and CBZ+PHY groups.

Significance: A single large dose of CBZ, PHY and their combination caused anxiogenic and sensorimotor impairment.

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Introduction

Rational use of antiepileptic drugs (AEDs) forms the basis of epilepsy care plan (Sun *et al.*, 2002). Polytherapeutic use of AEDs in patient with epilepsy may cause sensory impairment (Bernardi and Barros, 2004). AEDs have been reported to have cognitive and neurological effects, and adversely affect biochemical and haematological parameters in patients with epilepsy (Aliyu *et al.*, 2016). Carbamazepine (CBZ) is used to treat epilepsy patient, as well as mood disorder (Almgren *et al.*, 2008). It acts by reducing persistent neuronal triggering by inhibiting / blocking the voltage-gated sodium channels (Mathew *et al.*, 2011). It also potentiates receptors of the gamma-aminobutyric acid (GABA) (Granger *et al.*, 1995). Acute carbamazepine exposure is accompanied with neuromuscular disturbances, coma, tremor, restlessness, athetoid movements, psychomotor disturbances, dizziness, drowsiness, mydriasis, and nystagmus, respiratory depression, ECG abnormalities, tachycardia, shock, and urinary retention (Mochizuki *et al.*, 2016).

Phenytoin is an anticonvulsant widely used for the management of partial or generalized seizures (Vijay *et al.*, 2009). Phenytoin (PHY) functions via inhibition of sodium ion channels and blockage of persistent sodium currents in the neurones, thereby

preventing neuronal excitation (Bryan and Waxman, 2005).

It also protects against axonal degeneration of spinal cord axons (Luszczycki, 2004). As a Central Nervous System (CNS) depressant, phenytoin affects rearing activity (Aliyu *et al.*, 2016), through inhibition of calcium-induced secretory processes (Thakur *et al.*, 2011). Phenytoin also alters motor incoordination and cause muscle weakness in rats (Aliyu *et al.*, 2017). The combine use of phenytoin and carbamazepine can considerably reduce locomotive activity (Luszczycki, 2004). The other signs of carbamazepine and phenytoin toxicity include coma, involuntary eye movement, hypotension, nausea, sluggishness, slurred speech, tremors and vomiting (Dasari *et al.*, 2016). This study seeks to assess sensorimotor changes in male Wistar rats upon single-large dose treatment with carbamazepine, phenytoin and their mixture.

Materials and Methods

Drugs used and preparation

Carbamazepine commercial grade (200 mg) marketed as Tegretol® (Novartis Farma, Italy) and phenytoin capsules (100 mg) (Biomedicine, Belgium) were obtained from a reliable pharmacy in Ilorin, Nigeria. They were dissolved to make solution in a suitable amount of distilled water.

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Animals used

The 24 male Wistar rats (160-210 g) required for this study were acquired from the Department of Veterinary Pharmacology and Toxicology's Animal House, Ilorin University, Nigeria. following ethical standard practices of the Faculty of Veterinary Medicine, University of Ilorin, Nigeria, all animals were accommodated in plastic cages, fed with a pelleted grower's feed (Chikun Feed®, Nigeria) and supplied with water *ad libitum*. Until the beginning of this study, the animals were allowed adaptation for two weeks.

Treatment protocols

The animals were selected at random into four groups of 6 rats each and administered the following regimens: Group I (DW) was exposed to distilled water (2 ml / kg); group II (CBZ) received carbamazepine (1950 mg/kg ~ 1/2 of LD₅₀); group III (PHY) received phenytoin (820 mg / kg ~ 1/2 of LD₅₀), group IV (CBZ+PHY) was co-exposed to carbamazepine (1950 mg/kg) and phenytoin (820 mg/kg). The regimen was administered orally by gavage once (on Day 1), followed by weekly monitoring of body weight, clinical signs and behavioural/neuromuscular parameters were carried out and recorded for four consecutive weeks.

Evaluation of neuromuscular pattern

Motor activity

The effect of the regimens on motor activity was evaluated weekly till the end of the experiment using the open-field apparatus (Zhu *et al.*, 2001). Motor activity was assessed by placing animal in the box and allow it to move freely within three minutes to become familiar with the environment. The amount of squares that were crossed with all the paws was reported over the next two minutes. Soapy water and 90% alcohol solution were used to clean the arena between trials to eliminate odours from the preceding animal.

Rearing activity

Rearing activity was also evaluated weekly till the end of the experiment. Rearing activity was examined by placing animal in the box and allow it to move freely for three minutes to become familiar with the environment. The frequency at which an animal stood on its hind limb trying to peep out of the box in the next 2 minutes was recorded.

Frequency of urination and defecation

The frequency of urination and defecation was the number of puddles or urine streaks and faecal boli produced, respectively, during the 5 minutes' duration in the open-field maze.

Neuromuscular coordination

The neuromuscular coordination was assessed using inclined plane method (Ambali and Aliyu, 2012).

Locomotion efficiency

Locomotion efficiency was determined using ladder-walk test (Ambali and Aliyu, 2012).

Motor strength

The fore-paw grip time was used to assessed the rat motor strength (Abou-Donia *et al.*, 2001). This was achieved by hanging rats down with both forepaws from a wood dowel of 5mm diameter. In seconds, time taken for each rat to held on to the wood dowel before releasing its grips was documented. This parameter was assessed on days (D) 0, 1, 7, 14 and 28.

Body weight

The rats were weighed once every week till, the end of the experiment with electronic weighing scale (Sensor Disc Exclusive Tech, USA).

Data analysis

The obtained data were evaluated as mean $\pm$ standard error of mean (SEM) and then subjected to one-way analysis of variance (ANOVA), using Tukey's post hoc test. GraphPad Prism Version 5.03 San Diego, California, USA) was used for analysis. Value $p < 0.05$ was deemed significant.

Results

Clinical signs

All the animal in the groups showed unapparent signs of toxicity, except for the signs of discomfort, staggering gait and drawling (partial paralysis) of the hind limb observed in the group administered CBZ (1950 mg/kg) only, which later disappear after some days.

Effects of treatment on neuromuscular patterns

Motor function

The square crossed by animal in the PHY group increased significantly ($p < 0.05$) at D7 when compared to the CBZ+PHY group (Table 1).

Table 1. Effect of single large dose of carbamazepine and phenytoin on long-term locomotion changes in male Wistar rats.

Day	DW	CBZ	PHY	CBZ+PHY
0	3.00 $\pm$ 1.73	12.25 $\pm$ 4.0	11.25 $\pm$ 1.11	13.25 $\pm$ 2.59
1	9.00 $\pm$ 3.49	1.25 $\pm$ 1.25	11.25 $\pm$ 3.54	2.00 $\pm$ 1.41
7	8.25 $\pm$ 3.09	3.50 $\pm$ 2.02	13.00 $\pm$ 3.81 ^a	1.00 $\pm$ 0.71
14	12.75 $\pm$ 7.36	8.25 $\pm$ 4.80	17.50 $\pm$ 2.10	8.25 $\pm$ 2.84
21	6.00 $\pm$ 3.67	1.50 $\pm$ 1.50	9.50 $\pm$ 4.87	12.75 $\pm$ 4.48
28	14.5 $\pm$ 2.78	6.50 $\pm$ 2.50	4.25 $\pm$ 4.25	9.50 $\pm$ 4.66

Note:

All results are presented in Mean $\pm$ SEM (standard error of mean)

a – $p < 0.05$, higher Vs CBZ+PHY group, DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin

Rearing frequency

At D0, when compared to DW and PHY groups, the CBZ+PHY increased significantly ($p < 0.05$) in rearing activity. The CBZ group showed relative decrease in frequency of rearing at D0, when compared with Day1 (13%). The rearing activity recorded in CBZ+PHY group increased ($p < 0.05$) significantly on Day0 than in D1, D7 and D14 (Table 2).

Table 2. Effect of single large dose of carbamazepine and phenytoin on long-term changes in frequency of rearing in male Wistar rats

Day	DW	CBZ	PHY	CBZ+PHY
0	1.75 ± 0.48	3.50 ± 0.96	2.00 ± 0.00	5.25 ± 0.48 ^a
1	2.25 ± 0.75	0.25 ± 0.25	1.25 ± 0.95	0.75 ± 0.75
7	3.00 ± 1.47	2.75 ± 1.11	3.75 ± 1.80	1.25 ± 0.95
14	4.25 ± 2.14	2.00 ± 0.68	1.25 ± 0.95	0.75 ± 0.48
21	1.50 ± 0.87	0.50 ± 0.29	2.75 ± 1.55	1.75 ± 0.75
28	3.00 ± 0.82	1.75 ± 0.75	0.00 ± 0.00	2.50 ± 1.50

Note:

All results are presented in Mean ± SEM (standard error of mean).

a – $p < 0.05$, higher Vs CBZ+PHY group.

DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin

Grooming frequency

At D0, there was a substantial ($p < 0.05$) reduction in grooming frequency of the PHY group, unlike that of the CBZ+PHY group. In the CBZ+PHY group the grooming frequency at D1 reduced ($p < 0.05$) significantly, unlike in the DW and PHY groups. While grooming frequency increased ($p < 0.05$) apparently in the PHY group, unlike in the CBZ group (Table 3).

Table 3. Effect of single large dose of carbamazepine and phenytoin on long-term changes in frequency of grooming in male Wistar rats

Day	DW	CBZ	PHY	CBZ+PHY
0	5.25 ± 2.21	6.75 ± 1.32	1.75 ± 1.44 ^a	10.5 ± 0.87
1	2.75 ± 0.63	0.50 ± 0.50 ^b	4.50 ± 0.96	0.00 ± 0.00 ^c
7	3.00 ± 1.08	2.00 ± 0.71	2.25 ± 2.25	0.25 ± 0.25
14	3.75 ± 1.65	2.00 ± 0.82	1.00 ± 0.41	1.75 ± 0.85
21	1.50 ± 0.96	2.25 ± 0.65	1.00 ± 0.71	0.75 ± 0.48
28	3.00 ± 1.08	2.50 ± 1.66	2.75 ± 1.80	1.75 ± 1.81

Note:

All results are presented in Mean ± SEM (standard error of mean).

a – $p < 0.05$, lower Vs CBZ+PHY group; b – $p < 0.05$, lower Vs PHY group; c –

$p < 0.05$, lower Vs DW, CBZ and PHY groups.

DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin.

Frequency of urination

The rate at which the animal in the CBZ group urinate reduced significantly ($p < 0.05$) as compared to PHY group. However,

urination frequency in DW group decreased substantially ($p < 0.05$) at D21 unlike D28 (Table 4).

Table 4. Effect of single large dose of carbamazepine and phenytoin on long-term changes in frequency of urination in male Wistar rats

Day	DW	CBZ	PHY	CBZ+PHY
0	0.25 ± 0.25	0.00 ± 0.00	0.50 ± 0.29	0.25 ± 0.25
1	0.25 ± 0.25	0.75 ± 0.25	1.00 ± 0.41	0.50 ± 0.29
7	0.50 ± 0.29	0.00 ± 0.00 ^a	1.25 ± 0.25	0.50 ± 0.29
14	0.50 ± 0.29	0.75 ± 0.25	1.00 ± 0.00	0.75 ± 0.48
21	0.00 ± 0.00	0.00 ± 0.00	0.25 ± 0.25	0.50 ± 0.29
28	1.00 ± 0.00	0.25 ± 0.25	0.25 ± 0.25	0.75 ± 0.25

Note:

All results are presented in Mean ± SEM (standard error of mean).

a – $p < 0.05$, lower Vs PHY group, DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin.

Frequency of defecation

Table 5 revealed a substantially higher ($p < 0.05$) level of defecation in PHY group at D1 compared to other groups.

Table 5. Effect of single large dose of carbamazepine and phenytoin on long-term changes in frequency of defaecation in male Wistar rats

Day	DW	CBZ	PHY	CBZ+PHY
0	1.50 ± 0.29	1.25 ± 0.75	2.25 ± 0.25	0.50 ± 0.29
1	1.25 ± 0.75	0.00 ± 0.00 ^a	3.25 ± 0.25	0.25 ± 0.25
7	3.50 ± 0.29	1.00 ± 1.00	3.50 ± 0.65	2.50 ± 1.66
14	3.50 ± 0.87	1.25 ± 0.48	3.00 ± 0.41	1.25 ± 0.63
21	1.50 ± 0.65	0.75 ± 0.48	2.50 ± 0.29	1.75 ± 0.63
28	2.75 ± 0.25	1.50 ± 0.65	2.50 ± 0.50	0.75 ± 0.48

Note:

All results are presented in Mean ± SEM (standard error of mean).

a – $p < 0.05$, lower Vs DW and PHY groups.

DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin.

Neuromuscular coordination

A substantially ($p < 0.05$) reduced inclined plane performance was observed in the CBZ group at D1 unlike other groups. At D7, inclined plane performance increased significantly ($p < 0.05$) in the DW group when compared to CBZ and CBZ+PHY groups. At D28, inclined plane performance reduced significantly ($p < 0.05$) in the CBZ+PHY group unlike those of DW and PHY groups. The inclined plane performance in the PHY group reduced significantly ($p < 0.05$) at D1 as compared to D14 and D28 (Table 6).

Table 6. Effect of single large dose of carbamazepine and phenytoin on long-term changes in neuromuscular coordination (Inclined plane performance) in male Wistar rats

Day	DW	CBZ	PHY	CBZ+PHY
0	57.5 ± 1.44	58.75 ± 1.25	57.5 ± 1.44	56.25 ± 1.25
1	56.25 ± 2.39	37.5 ± 1.44 ^a	51.25 ± 2.39	50.00 ± 0.00
7	60.00 ± 2.04 ^b	51.25 ± 1.25	56.25 ± 2.39	50.00 ± 2.04
14	62.50 ± 1.44	57.5 ± 1.44	61.25 ± 1.25	58.75 ± 1.25
21	62.50 ± 1.44	60.00 ± 2.89	58.75 ± 1.25	56.25 ± 1.25
28	58.75 ± 1.25	56.25 ± 3.15	61.25 ± 1.25	48.75 ± 1.25 ^c

Note:

All results are presented in Mean ± SEM (standard error of mean).

a – p < 0.05, lower Vs DW, CBZ and CBZ+PHY groups; b – p < 0.05, higher Vs CBZ and CBZ+PHY groups; c – p < 0.05, lower Vs DW and PHY groups.

DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin.

Table 7. Effect of single large dose to carbamazepine and phenytoin administration on efficiency of locomotion (ladder walk performance) in male Wistar rats

Day	DW	CBZ	PHY	CBZ+PHY
0	8.50 ± 0.29 ^a	10.50 ± 0.50	11.25 ± 0.63	10.25 ± 0.25
1	16.50 ± 0.87	5.00 ± 3.79 ^b	14.25 ± 0.48	13.00 ± 1.58
7	12.75 ± 1.11	11.75 ± 3.92	17.25 ± 0.85	15.75 ± 5.54
14	14.50 ± 1.50	8.50 ± 2.87	12.50 ± 0.87	11.50 ± 0.65
21	13.00 ± 1.29	16.00 ± 0.41	13.00 ± 0.82	13.00 ± 0.91
28	18.25 ± 0.48	17.00 ± 0.82	18.00 ± 0.71	14.00 ± 1.08 ^c

Note:

All results are presented in Mean ± SEM (standard error of mean).

a – p < 0.05, lower Vs CBZ and PHY groups; b – p < 0.05, lower Vs DW and PHY groups; c – p < 0.05, lower Vs DW and PHY groups.

DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin.

Table 8. Effect of single large dose of carbamazepine and phenytoin on long-term changes in motor strength in male Wistar rats

Day	DW	CBZ	PHY	CBZ+PHY
0	66.00 ± 5.58	90.00 ± 23.91	55.50 ± 18.87	66.75 ± 15.52
1	36.00 ± 6.29 ^a	7.00 ± 1.58	12.50 ± 0.87	8.75 ± 1.11
7	21.00 ± 3.76	16.50 ± 3.38	14.50 ± 7.21	13.50 ± 5.33
14	39.75 ± 15.57	44.75 ± 20.64	15.25 ± 2.50	33.00 ± 8.35
21	13.50 ± 1.66	25.00 ± 9.50	22.00 ± 5.35	19.75 ± 3.35
28	16.25 ± 3.20	8.25 ± 3.04	4.75 ± 3.68	13 ± 3.70

Note:

All results are presented in Mean ± SEM (standard error of mean).

a – p < 0.05, lower Vs CBZ, PHY and CBZ+PHY groups.

DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin.

Table 9. Effect of single large dose of carbamazepine and phenytoin on long-term body weight changes in adult male Wistar rats

Week (W)	DW	CBZ	PHY	CBZ+PHY
1	203.500 ± 3.12	189.30 ± 2.18	193.50 ± 9.51	199.80 ± 7.92
2	211.30 ± 5.19	177.00 ± 4.32 [*]	210.50 ± 11.88	212.50 ± 26.91
3	218.80 ± 8.59	192.30 ± 1.75	223.50 ± 12.91	210.00 ± 6.57
4	214.50 ± 5.84	196.30 ± 4.37	216.30 ± 12.46	220.30 ± 7.51

Note:

All results are presented in Mean ± SEM (standard error of mean). * - p < 0.05, lower Vs W3 and W4, DW – Distilled water, CBZ – Carbamazepine, PHY – Phenytoin.

Locomotion efficiency

Significantly ($p < 0.05$), the number of rung missed noticed in the DW group at D0 was lower than observed for the CBZ and PHY groups. At D1, a substantial ($p < 0.05$) lower rungs missed was recorded in CBZ group, unlike those of DW and PHY groups. While at D28 the number of missed rungs reduced significantly ($p < 0.05$) in CBZ+PHY unlike those of DW and PHY groups (Table 7).

Forelimb grip time

The forelimb grip time increased significantly ($p < 0.05$) in the DW group when compared to CBZ, PHY and CBZ+PHY groups at D1. Unlike D1, D7, D21 and D28, a markedly ($p < 0.05$) higher forelimb grip time was recorded in all groups at D0 (Table 8).

Weight gain

At week 2, the weight gains markedly ($p < 0.05$) reduced in CBZ group unlike the weeks 3 and 4 (Table 9).

Discussion

The partial paralysis of the hind limb observed in the CBZ group at D1 indicates the consequence of acute (overdose) CBZ administration.

The reduction in grooming frequency as observed in this present study, indicates apparent increase in anxiety. Consequently, increased grooming behaviour usually result to deficit in locomotion. Grooming behaviour however, may be seen in stress, conflict and uncomfortable situations (Sarkisova *et al.*, 2003; Kalueff and Tuohimaa, 2005).

The increase in locomotor activity recorded at D7 of the study in the PHE group may be due to the development of tolerance (Löscher and Schmidt, 2006). Phenytoin affects the direct activation of the motor system by stimulation of the sensorimotor cortex in matured rats (Kšerk *et al.*, 1998). The reduced locomotion seen in the CBZ+PHY group, is in accordance with previous work (Luszcki, 2004). This shows that polytherapy with CBZ and PHE affect locomotor activity apparently due to the fact that CBZ as an enzyme inducer, lower PHE bioavailability, hence, reducing the effects of the drugs (Lai *et al.*, 1992).

Rearing reflect is an adaptive strategy for the animals to explore their environment and also response to environmental novelty and emotional states (Ambali, 2009). The reduction in rearing activity observed in CBZ group agree with previous studies (Thakur *et al.*, 2011; Aliyu *et al.*, 2016).

The present study demonstrated reduced frequency of urination and defecation (decrease in number of faecal boli) in the CBZ group. This further affirmed the anxiolytic effect of acute CBZ exposure since urination and defecation frequency can be used to measure anxiety.

The deficit in efficiency of locomotion (ladder walk) recorded in CBZ Group shows that the rats' legs were often stationary above the rungs for a long time, hence induced locomotor deficit. However, antiepileptic agents such as CBZ may evoke deficit in locomotion activity via sustainable decrease in AChE

activity at the cholinergic receptor, and later result to paralysis (Ambali and Ayo, 2012), as observed in this study.

The poor performance recorded in acute CBZ and PHY exposure on the inclined plane confirmed the toxic effect of AEDs on sensorimotor and neuromuscular coordination. This may be as a result of oxidative challenge or lipid peroxidation to the mechanism of impairment of sensorimotor performance and neuromuscular coordination.

The reduced grip time observed in this research, implies deficient motor strength activity. It can be ascribed to reduction in the reserved oxygen presented in the muscle (Ambali and Ayo, 2012), thereby alter the energy output needed to perform the task. This may also be attributed to acute lipoperoxidative damage to the muscle from the combined effect of the agents.

Conclusion

This present study concluded that large single dose exposure to carbamazepine, phenytoin and their combination affect locomotion activity and anxiogenesis, sensorimotor reflex measuring motor and neuromuscular coordination and motor strength. Therefore, patient under carbamazepine and phenytoin therapy should be monitored and guided with the appropriate dosage to be use.

Conflict of interest

No authors declare conflicting interest.

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