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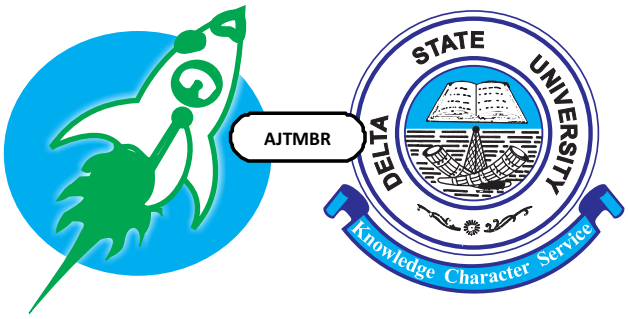

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The African Journal of Tropical Medicine and Biomedical Research is a multidisciplinary and international journal published by the College of Health Sciences, Delta State University of Abraka, Nigeria. It provides a forum for Authors working in Africa to share their research findings on all aspects of Tropical Medicine and Biomedical Sciences and to disseminate innovative, relevant and useful information on tropical medicine and biomedical sciences throughout the continent. The journal will publish original research articles, reviews, editorials, commentaries, short reports, case reports and letters to the editor. Articles are welcome in all branches of medicine and dentistry including basic sciences (Anatomy, Biochemistry, Physiology, Pharmacology, Psychology, Nursing etc) and clinical sciences (Internal Medicine, Surgery, Obstetrics and Gynaecology, Dental surgery, Child Health, Laboratory Sciences, Radiology, Community Medicine, etc). Articles are also welcome from social science researchers that document the intermediating and background social factors influencing health in countries of Africa. Priority will be given to publication of articles that describe the application of the principles of primary health care in the prevention and treatment of diseases.

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The title page should include the following information: 1. the title and sub-title; 2. the name(s) of the author(s); 3. the affiliation(s) of the author(s); 4. name and address of the corresponding author and 5. three to six key words for indexing and retrieval purposes.

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Assessment Of Haematological And Antioxidants Changes In Male Albino Wistar Rats Treated With Tramadol

Ojieh Anthony Emeka[1], Ossai Nduka Richard[1], Nwogueze BC[2]

Abstract

Introduction

Illicit drug use disorders are a major public health burden that contributes significantly to the global burden of disease and tramadol is one of the most common illicit psychoactive substances being abused especially amongst the young adults. This research aims to assess the haematological and antioxidants activities of male wistar rats treated with tramadol.

Materials and Methods

Thirty adult male Wistar rats weighing 120-180 g were selected for the study and was randomized into 6 groups. Group 1 was not treated within the period of the study before sacrificing, Group 2 to 5 received 30 mg/kg body weight of tramadol for 7, 14, 21 and 42 days respectively while treatment for group 6 was withdrawn for 3 weeks after 21 days treatment period before sacrificing. The animal's Brain, Liver, kidney and Testis were excised for biochemical analysis. Generated data were analyzed using SPSS package and results expressed as mean ± SEM.

Results

Results obtained showed significant decrease in the haemtololgical parameters as well as in the WBC count, Catalase, SOD and Glutathione activities in the chronic tramadol-treated rats when compared to the normal control at $p<0.05$. This study also revealed that chronic tramadol use increases the level of MDA significantly when compared with the non-treated group.

Conclusion

Tramadol consumption lowers RBC count, haemoglobin level, PCV, platelet count, WBC count, CAT, SOD, and GSH activities while significantly raising MDA levels. Therefore tramadol should only be used under medical supervision and only on prescription, avoiding indiscriminate and long-term.

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1.0 INTRODUCTION

Tramadol, a centrally acting analgesic agent with activity at μ-opioid, adrenergic and 5-hydroxytryptamine (5-HT) receptors (18, 25), has recently become a cause of major addiction in Nigeria especially amongst young adult, and of recent, many reports confirm the scourge of tramadol addiction of which many health workers were unaware of the scale of its non-medical use and abuse (22). The central role of liver and kidney in drug metabolism predisposes them to toxic injury, however, tramadol has been heralded as a non-abusable replacement option for many of the existing opiate painkillers, and the potential for abuse naturally does exist. If a user

takes tramadol repeatedly over a period and develops a tolerance for the drug, an overdose may occur when that user takes more than normal to achieve the desired effect; hence, tramadol overdoses had been reported to be very serious and can cause neurological toxicity, Respiratory failure, Serotonin syndrome and Mild, moderate or even severe cardiovascular disruption (19, 21). Although fatal intoxications of tramadol are rare and appear to be associated with large overdoses and co-ingestion of other drugs and /or alcohol (21). Symptoms of overdose may include; depression, addiction and seizures, change in consciousness, decreased awareness or responsiveness, difficulty with breathing, lack of muscle tone, light-headedness, loss of consciousness, pinpointed pupils of the eyes, severe sleepiness, slow or irregular heartbeat and unusual tiredness (20) With the current abuse of tramadol in Nigeria, this study therefore aim to access the haematological and antioxidant properties in albino wistar rats treated with tramadol.

2.0 MATERIALS AND METHOD

2.1 Chemicals and Drugs

Tramadol was purchased from Demeck pharmaceutical, Obiaruku, Delta State, Nigeria, All the chemicals and drugs used were of analytical grade

2.2. Experimental Animal

Thirty (30) adult male Wistar rats were purchased for this research at the Faculty of Basic Medical Sciences Animal Farm, Delta State University, Abraka, Nigeria, and housed in metabolic cages. They were kept on the animal feed growers' daily mash diet, a product of Top Feed in Sapele, Delta State. Feed components include: 17.0 percent protein, 4.5 percent min. fat, 0.96 percent min. calcium, 3.92 percent usable min. phosphorus, and 2450kcal energy and water ad libitum.

2.3 Ethical Consideration

The Research, Ethics and Grants Committee of the Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria, reviewed and approved the protocol for this study, and the experiment was performed in accordance with the ethical guidelines for the care and use of animals as laid down Helsinki, 1964 (51).

2.4 Drugs Preparation and Administration

300 g of tramadol was dissolved in 50 ml of water and was administered orally to the rats acceding to their body weight.

2.5 Experimental Design:

Group 1 (n - 5) – Control Group Wister Rats were not treated within the period of the study before sacrificing.

Group 2 (n - 5) – Received 30 mg/kg body weight of tramadol for 7 days and was sacrificing.

Group 3 (n - 5) – Received 30 mg/kg body weight of tramadol for 14 days and was sacrificing.

Group 4 (n - 5) – Received 30 mg/kg body weight of tramadol for 21 days and was sacrificing.

Group 5 (n - 5) – Received 30 mg/kg body weight of tramadol for 42 days and was sacrificing.

Group 6 (n - 5) –Withdrawn for 3 weeks after receiving tramadol 30 mg/kg for 21 days before sacrificing

2.6 Sample Collection

Each rat was sacrificed by cervical dislocation and was placed on its dorsal surface, a laparotomy was carried out to reveal the internal organs, and blood was collected by cardiac puncture, using 5ml syringes and 23G needle into blood sample

containers and centrifuged for 10 minutes at a rate of 4000 rpm, and serum was collected and stored in blood sample containers.. The brain, liver, testis and kidney was harvested for biochemical analysis.

2.7 Biochemical Analysis

Biochemical analysis was carried out on the samples collected as follows;

2.7.1 Determination of Haematological parameters

Haematological parameters were measured using automated cell counter (Coulter Electronics, Luton, Bedfordshine, UK) having standard calibrations in line with the instructions of the manufacturer. Parameters measured were: RBC count, platelet count, PCV and Hb concentration.

2.7.2 Determination of Total and Differential White Blood Cell Count.

Total and differential White blood cell count was calculated using manual cell counting chamber with Neubaurer Chamber according to Dhurba (50)

2.7.3 Determination of Catalase Activity

The activity of catalase was determined in the tissue homogenates by the method adopted by Viviam (14) and Ossai *et al.* (17)

2.7.4 Determination of SOD Activity

The activity of SOD in the tissue homogenates was estimated spectrophotometrically using the method of Misra and Fredorich (15) and adopted by Ossai *et al.* (17)

2.7.5 Determination of GSH Activity

The reduced glutathione was estimated in serum and tissue homogenates using the method of Ellman (12) and adopted by Beulter *et al.* (13)

2.7.6 Determination of MDA Activity

A breakdown product of lipid peroxidation thiobarbitoric acid reactive substance (TBARS) was measured in the tissue homogenates by the method of Gutteridge and Wilkins (16) and adopted by Ossai *et al.* (17)

2.8 Statistical analysis

The data were analyzed by comparing the values for individual controls for different treatment groups and the results were expressed as mean values ± standard mean error (mean ± SEM). Using the student's t-test, ANOVA variance analysis, and the results were considered significant at P-values of less than 0.05 ($P<0.05$) using SPSS version 23 software, significant differences between control and experimental groups were measured.

3.0 RESULTS

Table 1: Effects of Tramadol consumption on relative organ weight of male Wistar rat

Group	Brain Weight	Liver Weight	Kidney Weight	Testis Weight
Group 1	.....	3.10±0.16	0.54±0.06	1.03±0.11
Group 2	0.79±0.11	3.21±0.06	0.63±0.03	1.55±0.09
Group 3	1.20±0.08	3.09±0.23	0.53±0.12	0.84±0.06
Group 4	1.16±0.09	2.55±0.08	0.30±0.02	0.59±0.07
Group 5	0.86±0.09	3.23±0.11	0.69±0.08	1.36±0.13
Group 6	1.36±20.48	2.93±0.07	0.69±0.03	1.32±0.19

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at P<0.05. [a]P<0.05 indicate significant increase and [b]P>0.05 indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 2: Outcome of Tramadol consumption on hematology in male Wistar rat

Group	RBC	HB	PCV	PLT
Group 1	9.90±0.50	15.43±0.69	41.20±1.39	360.40±33.96
Group 2	10.36±0.40	16.81±0.12	43.40±1.36	342.80±22.42
Group 3	10.55±0.45	16.23±1.07	44.40±3.41	334.60±63.95
Group 4	10.76±0.41	15.21±0.49	41.20±0.86	288.00±38.47
Group 5	10.23±0.47	16.27±0.60	42.20±0.92	390.40±9.89
Group 6	9.85±0.45	16.03±0.61	41.40±1.25	375.20±15.02

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at P<0.05. [a]P<0.05 indicate significant increase and [b]P>0.05 indicate no significant difference

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Table 3: Outcome of Tramadol consumption on total and differential count of WBC in male Wistar rat

Groups	WBC	LYM	MID	GRA	LYM%	MID%	GRA%
1	10.87±0.87	7.11±0.67	1.70±0.24	2.82±0.30	67.87±3.82	14.16±1.57	24.28±2.91
2	9.86±0.85	6.51±0.67	1.40±0.12	2.31±0.44	67.43±4.17	14.76±1.71	24.06±3.85
3	10.23±1.02	7.48±0.73	1.37±0.20	2.16±0.12	69.79±3.51	12.70±1.39	21.94±2.13
4	10.29±1.10	7.14±0.73	1.53±0.16	2.75±0.23	62.71±2.90	11.50±1.19	25.70±2.49
5	10.37±0.60	6.91±0.55	1.34±0.18	2.88±0.33	65.37±3.11	13.02±1.88	27.88±2.67
6	9.81±0.87	7.29±0.79	1.52±0.22	2.61±0.30	66.89±3.43	14.24±1.81	25.16±3.22

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at $P<0.05$. $^{a}P<0.05$ indicate significant increase and $^{b}P>0.05$ indicate no significant difference

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Table 4: Outcome of Tramadol consumption on Catalase Activates in male wistar rats

Group	CAT (U/mg protein)			
	Brain	**Testis**	**Kidney**	**Liver**
Group 1	64.82 ± 0.98^{a}	22.62 ± 2.18^{a}	47.59 ± 1.89^{a}	52.60 ± 1.33^{a}
Group 2	53.88 ± 3.76^{b}	26.82 ± 1.26^{a}	43.92 ± 2.51^{b}	49.43 ± 1.47^{b}
Group 3	35.63 ± 4.77^{b}	25.36 ± 3.03^{a}	27.29 ± 0.96^{c}	43.35 ± 2.69^{b}
Group 4	31.62 ± 0.98^{b}	29.88 ± 2.01^{a}	27.90 ± 1.37^{c}	41.80 ± 3.16^{c}
Group 5	32.85 ± 0.31^{b}	22.25 ± 1.29^{a}	25.738 ± 2.39^{c}	43.02 ± 1.63^{c}
Group 6	22.79 ± 2.18^{b}	21.31 ± 1.29^{a}	20.39 ± 1.04^{c}	44.09 ± 3.50^{b}

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at $P<0.05$. $^{a}P<0.05$ indicate significant increase and $^{b}P>0.05$ indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 5: Outcome of Tramadol consumption on SOD Activates in male wistar rats

Group	SOD (U/mg protein)			
	Brain	**Testis**	**Kidney**	**Liver**
Group 1	41.29±1.66[a]	40.64±6.10	48.09±1.87[a]	52.28±1.52[a]
Group 2	39.44±1.79[b]	35.99±5.49	41.81±3.40[b]	48.42±1.70[b]
Group 3	26.43±1.47[b]	30.21±.629	30.62±0.62[c]	39.09±1.25[c]
Group 4	33.40±0.70[b]	32.22±2.39	41.67±2.75[b]	43.16±1.60[c]
Group 5	36.11±2.51[b]	35.00±1.54	41.54±1.66[b]	46.33±3.33[b]
Group 6	34.65±2.29[b]	43.80±1.20	38.97±3.38[b]	47.27±2.95[b]

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at P<0.05. [a]P<0.05 indicate significant increase and [b]P>0.05 indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 6: Outcome of Tramadol consumption on GSH Activates in male wistar rats

Group	GSH (Unit/mg protein)			
	Brain	**Testis**	**Kidney**	**Liver**
Group 1	40.25±1.51	38.29±2.36	44.17±6.08	38.24±2.49
Group 2	49.12±3.88	32.13±1.93	51.86±2.57	52.36±12.94
Group 3	47.21±2.04	30.51±4.36	50.64±1.08	47.77±3.88
Group 4	41.10±3.04	35.21±3.22	48.30±1.70	36.53±2.18
Group 5	56.76±8.01	53.14±2.97	49.31±5.48	45.87±3.21
Group 6	52.31±1.20	45.16±1.82	47.04±7.31	45.07±4.81

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at P<0.05. [a]P<0.05 indicate significant increase and [b]P>0.05 indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

Table 7: Outcome of Tramadol consumption on MDA Activates in male wistar rats

Group	MDA (Unit/mg protein)			
	Brain	**Testis**	**Kidney**	**Liver**
Group 1	1.03±0.23	0.93±0.44	1.03±0.23	1.08±0.17
Group 2	1.59±0.36	0.37±0.03	1.59±0.36	1.10±0.18
Group 3	2.10±0.94	0.39±0.09	2.10±0.94	1.84±0.77
Group 4	2.77±0.72	0.43±0.15	2.77±0.72	1.73±0.17
Group 5	2.34±0.47	0.79±0.18	2.34±0.48	2.03±0.62
Group 6	1.42±0.17	0.39±0.13	1.42±0.17	1.10±0.34

Values are expressed as mean±SEM. ANOVA followed by PostHoc (LSD) multiple range tests. Values not sharing a common superscript differ significantly at $P<0.05$. $^{a}P<0.05$ indicate significant increase and $^{b}P>0.05$ indicate no significant difference

KEY: Group 1 = Normal Untreated rats, Group 2 = Received tranadol 30mg/kg for one week; Group 3 = Received tramadol 30 mg/kg for two weeks, Group 4 = Received tramadol 30 mg/kg for three weeks, Group 5 = Received tramadol 30 mg/kg for six weeks and Group 6 = withdrawn from receiving tramadol 30 mg/kg after three weeks.

4.0 DISCUSSION

Toxicity to tramadol can happen to those who take overdoses of the drug as a treatment of different types of pain as well as those who abuse it (23). Tramadol abuse had been known to be one of the most frequent health problems worldwide, and like other opioids, it is known to induce a decrease in plasma antioxidant levels, which may reflect a failure of the antioxidant defense mechanism against oxidative damage (24). It has been reported that abuse of tramadol causes antidepressant–like behaviour, impaired spatial memory, elevated 5–HT levels in the cerebral cortex and hippocampus, induced oxidative stress and apoptosis in brain tissue and deleteriously altered brain structure (37, 38). Withdrawal period has also been reported to show a reverse in antidepressant –like behavior, with no improvement of the spatial memory, and marked depletion of 5–HT as well as more improvement in antioxidants, apoptotic markers and incomplete recovery of brain histopathological alteration (39).

Tramadol in this study was given at a dose of 30mg/kg body weight orally (10% of oral LD_{50} of tramadol in rats) according to the study by "El-Gaafarawi (45)." Our findings in table 1 shows a relative organ weight gain in group 4 and 5 and no significant increase in group 2, 3 and 6 compared to control group 1. The significant weight gain after administration of tramadol (30mg/kg) could be as a result of tramadol effect which is believed to have caused little or no impact on user's eating habits. This is similar to a report by Mohammed and Mahmoud, (27) on body weight changes in control and tramadol-induced rats after administration of 30 and 60 mg/kg tramadol for 8 weeks but didn't induce significant changes

in the body weight.

Debate regarding the effect of tramadol on haematological parameters and bleeding profile exist in several literatures (28, 29, 30). In this present study, oral tramadol administration (30 mg/kg) to wistar rats within 6 weeks produce significant decrease in the haemtololgical parameters as shown in table 2. Haemoglobin c oncentration (Hb), packed cell volume (PCV), Red blood cell (RBC) and platelet counts were significantly decreased in all tramadol-treated group compared with controls. This results is in tandem with the findings of Nna *et al.* (31), Aldalou *et al.* (32), Udegbunam *et al.* (33), however, the significant decrease observed in Red Blood Cell (RBC) count, Packed Cell Volume (PCV) and hemoglobin (Hb) can be attributed to possible impairment of Haem-biosynthesis during erythropoiesis, as earlier reported by Nna *et al.* (31), blood loss due to serious gastrointestinal tract bleeding, invivo haemolysis (destruction of matured red blood cells) and poor iron absorption in the intestine which may have cause a decrease in oxygen supply to different tissues. Similar reports by Goeringer *et al.* (34), Mohammed *et al.* (35) and Abiodun *et al* (36) on hematological and biochemical changes in blood, liver and kidney tissues under the effect of tramadol treatment showed a decrease in RBC and Hb content. The decreased number of platelet count by tramadol in this study is in supports of pervious work by Abiodun and companion whose report on morphine administration resulted in thrombocytopenia (36).

In haematological studies conducted by Elyazji *et al.* (40), tramadol was found to increase WBC count, lymphocyte count and MCV, but decreased PCV, Hb, RBC count, MCH, MCHC and platelets count. Their finding showed signs of improvement of blood indices in the recovery periods after tramadol abstinence. Another study by Akhtardanesh *et al.* (41) in dogs showed that short-term injection of high doses of tramadol did not change haematological parameters significantly.

The free radicals and reactive oxygen species generated from the disruption of haematological parameters is a sign of toxicity or disease conditions (1, 2). In table 3 of this study, the effect of tramadol administration on white blood cell in male wistar rats was evaluated. Result shows a reduction in white blood cells count in all treated groups when compared to the control group wistar rats; this confirms the findings that tramadol administration in wistar rats causes a reduction in white blood cell count and this could suppress the immune system and possibly expose individuals to infectious disease (3, 4, 33). The disruptions in white blood cell observed in this study may be due to decreased population of unquenched free radicals caused by tramadol administration; a report which is in line with Owoade *et al.,* (36) findings.

Results from table 4 and 5 reveals a significant decrease in Catalase and superoxide dismutase activities of the brain, testis, kidney and liver tissues of male rats treated with tramadol, when compared with the control group 1. Group 4 and 5 showed a significant reduction in Catalase and superoxide dismutase activities at $P<0.05$, whereas, group 2, 3 and 6 was not statistically significant when compared to control group at $P>0.05$. A similar report by Haytham *et al.* (46) revealed a significant increase in MDA level, while antioxidant enzymes; GSH, superoxide dismutase and Catalase were significantly decreased after tramadol-treatment.

The pathological changes and oxidative damage induced by chronic use of tramadol can be explained by its capability to generate oxygen free

radicals that can attack and lead to destabilization and disintegration of the cell membrane as a result of lipid peroxidation (44). From our findings in table 4 and 5, after three-week withdrawal of chronic tramadol use, the same oxidative reduction changes were observed in group 6 as that in group 2. The oxidative reduction changes observed in group 6 animals could be as a result of depression, a well–documented withdrawal symptom of tramadol (42, 43), and the role of oxidative stress in the development of cognitive and memory impairment has be proved by several research studies (5, 6).

Toxic effect of tramadol administration can lead to a large population of unquenched free radicals leading to a state of oxidative stress (7). This is evidence in inhibition in the activities of antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT) in rat tissue as seen in this study. Superoxide dismutase and Catalase are important antioxidant enzymes which played a pivotal role in scavenging of oxidative free radicals (7).

Glutathione (GSH) has been known in preventing damage to important cellular components caused by reactive oxygen species such as free radicals, peroxides, lipid peroxides, and heavy metals (8). While GSH protects cells by neutralizing or reducing reactive oxygen species (9, 10), Malondialdehyde (MDA) level indirectly reflect the extent of cellular damage by free radicals and are widely used as an index of free radical mediated lipid peroxidation (47).

In table 6 and 7, there was a decreased in reduced GSH and a significant increase in MDA level in rats treated with tramadol (30mg/kg) when compared to the control group. These results was similar with the recorded data of Elwy and Tab, (48) which reported that administration of tramadol for 30 days induced significant decrease in hepatic tissue SOD, CAT activities and GSH concentration as compared to control rats. Furthermore, Nafea *et al.* (49) demonstrated that abuse of tramadol for one month caused significant elevation in MDA (marker of lipid peroxidation) with reduction in the antioxidant (CAT) activity. Ahmed and Kurkar, (44) recorded a similar finding in testicular tissue as they reported that tramadol increases the testicular levels of nitric oxide (NO) and lipid peroxidation and significantly decreases the enzymatic antioxidant activities compared with the control group; as well as immune-histochemical examinations showed that tramadol increased the expression of endothelial nitric oxide synthase in testicular tissues. El-Gaafarawi (45, 46) also reported a significant increase in serum malondialdehyde levels in tramadol-treated rats indicating an increase in lipid peroxidation. Chronic tramadol use in research had been reported to significantly increase the level of adrenal MDA, in addition to a significant decrease in the level of antioxidant enzymes (GSH-Px and TR) in the blood (11). Ghoneim *et al.* (43) and Nna and Osim, (42) also studied the oxidative stress markers during and after withdrawal of tramadol administration. Their study revealed that chronic tramadol use increases the level of MDA and decreases the level of catalase, superoxide dismutase, and glutathione peroxidase in both testicular and brain tissues and improvement of these markers occurred after tramadol withdrawal. This was evident in the results of table(s) 4, 5, 6 and 7 of this study. These findings are of importance to be considered in patients who use tramadol as a pain killer, especially in the long term conditions.

5.0 Conclusion

Tramadol consumption lowers RBC count,

haemoglobin level, PCV, platelet count, WBC count, Catalase, SOD, and GSH activities while significantly raising MDA levels, resulting in hypoxic hypoxia, which can lead to severe and rapid apotosis, poor immunity, and the inability to pivot the role in scavenging oxidative free radicals and protecting cells by neutralizing or reducing reactive oxygen species. Hence, tramadol should only be used under medical supervision and only on prescription, avoiding indiscriminate and long-term use because therapeutic doses or severe doses might cause harm.

ETHICAL APPROVAL

The protocol of the experiments in this study was examined and approved by the Research, Ethics and Grants Committee of the Faculty of Basic Medical Sciences, Delta State University, Abraka, Nigeria. This research was performed in accordance with the ethical standards on the care and use of animals as laid down (Helsinki, 1964).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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