International Research Journal of Gastroenterology and Hepatology

Volume 6, Issue 1, Page 87-92, 2023; Article no.IRJGH.101814

Effect of Tramadol Hydrocholoride on the Biomarkers of Liver and Kidney Function and Oxidative Stress in Male Albino Rats

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/101814

Original Research Article

Received: 19/04/2023
Accepted: 22/06/2023
Published: 05/07/2023

ABSTRACT

Background: Tramadol is an opioid-like analgesic or pain-relieving agent, used parenterally and orally for the treating moderate or severe painful sensation. Because the drug is inexpensive and is not classified as control drug by the government, the authors attempt to establish the possible effect of tramadol (TM) hydrochloride on the biomarkers for liver and kidney function along with oxidative stress in male wistar albino rats was carried out to verify the likelihood of it translational correlation in human beings.
Methods: 32 male albino rats which were 16 weeks of age weighing 180g-200g were gotten from the National Vertinary Research Institutes (NVRI), Vom, Plateau state, Nigeria, used as parallel study design and divided into 4 groups of 8 animals each. Group 1; the normal control (NC)

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administered saline solution only. Group 2 ,3 and 4 received oral dose of 0.1, 0.2 and 0.4 mg/kg/b.wt tramadol hydrochloride (HCl) suspended in saline solution as low, mid and high dose respectively. All the animals were fed the same diets throughout the period of (12) weeks from October 2022-December 2022. The rats were allowed to fast overnight then blood samples were collected and analysed at Department of Vertinary Medicine Laboratory, University of Nigeria, NSUKKA, Enugu State Nigeria for the biochemical markers of liver function, kidney function and oxidative stress.

Results: The result obtained for liver function, showed a significant ($p<0.05$) increase in ALT in group 4, AST in group 3 and 4, ALP in group 4, T. Bilirubin in group 3, D. bilirubin in group 4 when compared to the control group. The kidney function result showed significant ($p<0.05$) increase in Na^+ in group 3, Cl^- in group 2 and HCO_3 significantly ($p<0.05$) increased across all the test groups compared to the control, Urea increased significantly ($p<0.05$) in group 4, Creatinine concentration was high across all the test groups when compared to the control. Changes in antioxidant enzyme of catalase activity is significantly ($p<0.05$) reduced across the test groups compared to group 1. Similarly, the activities of superoxide dismutase decreased significantly ($p<0.05$) across all the test groups compared to the control group.

Conclusion: The outcome of this study revealed that tramadol HCl when ingested in high amounts can interfere with the normal functioning of the liver and kidney and cause oxidative stress.

Keywords: Tramdol hydrochloride; oxidative stress; biochemical markers.

1. INTRODUCTION

Most drugs are biologically active substances which are generally natural or synthetic in nature and are been used for medicinal purposes. But it has been found that arbitral use of drugs may lead to abuse and inability of users to desist from using such drugs, leading to addiction which has becoming a very disturbing trend to the people. Research have shown that about 46% of the general population faces this challenge. This has lead many people to contacting other dangerous diseases such as Hepatitis B infection and HIV infection leading to the death of millions of people [1,2,3,4]. The abuse of substances such as Tramadol, heroin, oxycodone, and buprenorphine is common in modern society [5,6].

The drug “Tramadol” is a central nervous system acting synthetic drug in the category of “opioid” analgesic agent, administered either parenterally or orally to treat moderate or severe sensation of pain. The drug has a complex mechanism of action action. Although many authors have reported that the analgesic activity as well as other clinical effectsthat can be derived from it are due to the opioid and non-opioid mechanism of actions. The drug binds to the μ-opioid receptor on cell surface, even though it is found to be much more weakly bound when compared to morphine. It is also known to inhibit the neuronal re-uptake or reabsorption of some substances such as norepinephrine and serotonin as do the known antidepressant drugs such as amitriptyline and Desipramine [7,8,9,10].

The drug “Tramadol” is known to be among the top most widely used drugs in the world. The Liver which is one of the body organs is known to be the largest internally in the human body. The liver is involved in multiple metabolic functions, but may however be hampered when it is inflamed in a diseased condition known as hepatitis [11,12].

The kidneys are a pair of bean-like organs located internally on both the left and right abdominal regions of the body and the kidneys are involved in the excretion of biotransformed chemicals which have become less harmful and soluble in water in the form of urine [13,14]. “Sometimes however, metabolites of the drug origin that are excreted by the kidneys may also cause a cellular damage leading to a kidney dysfunction and may have a higher activity and/or a greater toxicity than the original drug, hence the need to always confirm the toxicity level of drugs” [15].

“In the case of Tramadol overdose, it may lead to abnormal conditions such as nausea and vomiting, Central Nervous System (CNS) depression, tachycardia, coma, respiratory depression and cardiovascular collapse and seizures” [16,17].

The term “Oxidative stress” refers to situation which is assocoated to the development of multiple pathophysiological conditions arising from excessive concentration of free radicals in the system. They may include cardiovascular diseases, diabetes mellitus, rheumatoid arthritis,

cancer, and neurodegenerative diseases [18]. This research was conducted to assess effect of tramadol hydrochloride on the biochemical markers of liver and kidney function, oxidative stress in male wistar albino rats.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Thirty –two (32) male wistar albino rats of 16 weeks old weighing 180-250g were used *ad libitum*. The rats were purchased from the National Veterinary Research Institute, Vom, Plataeu State , Nigeria. They were transported in cages to the animal Hose, Department of Biochemistry, Nasarawa State University, Keffi, Nigeria and acclimatized for seven days, during which they were fed with normal chicken feed and allowed free access to water. After the acclimatization period, the rats were randomly grouped for the experiment.

2.2 Materials and Reagent

Tramadol Hydrochloride 50mg, Diethyl ether p-nitrophenyl phosphate, buffer solution for ALP containing 0.5mmol magnesium chloride, 2,4-nitrophenyl hydrazine, buffer solution containing 100mmol/L phosphate buffer.

2.3 Experimental Design

After acclimatization to the laboratory conditions, the animals were randomly divided into four groups placed in individual cages and classified as follows:

Group I (Control normal group): Eight normal non-medicated rats served as control for all experimental groups, and received 1 ml (0.9% NaCl) oral doses of saline solution for 12 weeks.

Group II (Low dose): received a daily oral dose of tramadol HCl suspended in saline solution equivalent to 0.1 mg/kg/b.wt for twelve weeks.

Group III (Mid dose): received oral dose of tramadol HCl suspended in saline solution at doses of 0.2mg/kg/b.wt for 12 weeks.

Group IV (High dose): received a daily oral dose of tramadol HCl suspended in saline solution equivalent to 0.4 mg/kg/b.wt for twelve weeks.

After the treatment period, the rats were allowed to fast overnight and sacrificed under mild euthanasia with pentobarbital. Blood samples were collected by cardiac puncture for analysis.

2.4 Biochemical Analysis

Biochemical analysis was carried out to determine liver function (serum concentrations of AST, ALT, ALP, conjugated and total bilirubin), Kidney function (Urea, Creatinine and electrolytes) using Automated Biochemical Analyzer. The antioxidant activity of Superoxide dismutase (SOD) was estimated according to the method by Misra and Fridovich, [19] and the Catalase (CAT) was estimated according to the method by Aebi H [20].

2.5 Statistical Analysis

One-way analysis of variance was used in analyzing the results using the Predictive Analytics Software (International Business Machines (IBM), United States) Statistics 18 package. All the results were expressed as mean ± standard error and $P < 0.05$ was taken to be significant.

3. RESULTS

3.1 Effect of Tramadol Hydrochloride on Liver Function

As shown in Table 1 above, the results showed a significant ($p<0.05$) increase in ALT in group 4 compared to group 1, AST significantly ($p<0.05$) increased in group 3 and 4, ALP significantly ($p<0.05$) increased in group 4. T. Bilirubin significantly ($p<0.05$) increased in group 3. Direct bilirubin significantly ($p<0.05$) increased in group 4. The total protein showed no significant ($p<0.05$) changes compared to the control.

3.2 Effect of Tramadol Hydrochloride on Kidney Function

Table 2 is a presentation of the results of kidney function parameters in albino rats administered Tramadol hydrochloride which shows a significant ($p<0.05$) increase in sodium ion in group 3, no significant ($p<0.05$) changes were observed for potassium ion in the test groups compared to the control. Chloride ion increased significantly($p<0.05$) in group 2. The concentration of bicarbonate ion increased significantly($p<0.05$) across all the test groups

compared to the control, the concentration of urea increased significantly ($p<0.05$) in group 4 compared to the control. Creatinine concentration was significantly ($p<0.05$) higher across all the test groups compared to the control.

3.3 Effect of Tramadol Hydrochloride on Antioxidant Enzyme Activity

As shown in Table 3, the activities of catalase significantly ($p<0.05$) reduced across the test groups compared to group 1. Similarly, the activities of superoxide dismutase decreased significantly ($p<0.05$) across all the test groups compared to the control group.

4. DISCUSSION

"Substance abuse can lead to an increased risk of chronic diseases, family breakdown, job loss, reduced longevity, crime and increased violence" [21]. "Repeated tramadol administration in such patients leads to the accumulation of toxic metabolites in their bodies, increase the risk for pharmacokinetics interactions and or decreases the clearance of tramadol thus increasing its potential for toxicity" [22].

The results of ALT, AST and ALP were significantly ($p<0.05$) increased at the high dose of Tramadol compared to the control. These results were comparable with the findings of Youssef and Zidan [21] who reported "increased ALT, AST and ALP activities in rats after acute and long-term administration of Tramadol". These data are in agreement with [23], who reported that liver exposes to sever oxidative stress is associated with the elevation of serum liver function tests. This also affirms the report of Bethesda [22] that "serum aminotransferase levels can be elevated in a small proportion of patients receiving tramadol, particularly with high doses".

The hydration of the body is maintained by the osmotic gradients of electrolyte, which in turns regulate the hydration and pH, being critical for the muscle and nerve function, and mechanisms such as tubular reabsorption play important roles in keeping the concentrate of various electrolytes under strict control. The results showed significant ($p<0.05$) increased of Na^+ and HCO_3^- upon administration of tramadol indication imbalance of electrolytes compared to control Significant ($p<0.05$) increase in the values of creatinine and urea is an indication of interference by the drug with creatinine metabolism leading to decreased synthesis in a dose-dependent pattern effect. Previous studies have shown the correlation between renal injury and disease with free radicals. These free radicals can lead to oxidative stress as demonstrated by significant ($p<0.05$) decrease in CAT and SOD activities with Tramadol administration compared to control.

Table 1. Effect of tramadol hydrochloride on Liver Function

Groups	ALT (IU/L)	AST (IU/L)	ALP (IU/L)	T. Billirubin (mg/dl)	D. Billirubin (mg/dl)	T. Protien (mg/dl)
1	35.00 ± 1.15^a	18.75 ± 0.95^a	60.75 ± 1.50^a	82.50 ± 1.73^a	0.43 ± 0.08^a	6.50 ± 0.25^a
2	36.00 ± 1.63^a	19.25 ± 0.50^a	61.50 ± 2.08^a	84.00 ± 0.81^a	0.51 ± 0.02^a	6.60 ± 0.16^a
3	35.50 ± 0.57^a	23.00 ± 0.81^b	61.00 ± 0.81^a	87.00 ± 0.81^b	0.57 ± 0.01^a	6.50 ± 0.24^a
4	37.00 ± 0.81^b	24.00 ± 0.81^b	64.00 ± 0.81^b	83.00 ± 0.81^a	0.60 ± 0.03^b	6.55 ± 0.04^a

Results are presented in Mean ± SD, (N = 8), mean values with different letters as superscripts are considered at p < 0.05. Group 1= control, group 2= Low dose, group 3= Mid dose, group 4= High dose

Table 2. Effect of tramadol hydrochloride on Kidney Function

Groups	Na^+(mg/dl)	K^+ (mg/dl)	Cl^- (mg/dl)	$HCO3^+$ (mg/dl)	UREA (mg/dl)	CREAT (mg/dl)
1	5.73 ± 0.47^a	2.18 ± 1.12^a	2.39 ± 0.25^a	6.82 ± 0.67^a	62.00 ± 0.81^a	4.80 ± 0.51^a
2	5.53 ± 0.09^a	19.25 ± 0.4^a	3.53 ± 0.08^b	8.53 ± 0.08^b	62.00 ± 1.63^a	5.30 ± 0.09^b
3	6.46 ± 0.34^b	2.15 ± 0.03^a	2.92 ± 0.62^a	8.42 ± 0.15^b	61.00 ± 2.44^a	6.15 ± 0.02^c
4	5.78 ± 0.13^a	2.90 ± 0.45^a	3.12 ± 0.00^a	8.32 ± 0.11^b	64.75 ± 1.25^b	6.59 ± 0.20^d

Results are presented in Mean ± SD, (N = 8), mean values with different letters as superscripts are considered at p < 0.05. Group 1= control, group 2= Low dose, group 3= Mid dose, group 4= High dose

Table 3. Effect of tramadol hydrochloride on antioxidant enzyme activity

Groups	CAT (mg/dl)	SOD (mg/dl)
1	0.934± 0.35[a]	11.47± 3.63[a]
2	0.51± 0.04[b]	8.55± 0.07[b]
3	0.59± 0.00[b]	8.92± 0.25[b]
4	0.61±0 .02[b]	9.62±0.00[a]

Results are presented in Mean ± SD, (N = 8), mean values with different letters as superscripts are considered at p < 0.05. Group 1= control, group 2= Low dose, group 3= Mid dose, group 4= High dose

5. CONCLUSION

Findings from this research showed that intake of Tramadol hydrochloride, at high dose increase liver enzymes activities which are signs of hepatotoxicity. Also, there were signs of nephrotoxicity shown by increased in bicarbonate, urea and creatinine. Furthermore, Tramadol generates oxidative stress as shown by decreased in SOD and CAT activities. Further research should be done on detection of Tramadol in biological samples in order to reduced rat of abuse of the drug and finding remedy for Tramadol complications such as antioxidants to neutralized the free radicals generated.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Animal Ethic committee approval has been collected and preserved by the author(s).

ACKNOWLEDGEMENT

The authors are indebted to the Department of Biochemistry, Faculty of Natural and Applied Sciences, Nasarawa State University, Keffi, Nigeria.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/101814