# Brain Tissues Affection After Oral Tramadol: An Experiment Study

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## Abstract

Tramadol may lead to the accumulation of toxic components in the body. This study aims to detect the toxic effect of tramadol on brain tissues. The clinical experiment was carried out at the Department of Neurosurgery, Ibn Sina Hospital. Ten rats of both sex weighing (180-300 g) were selected from the veterinary house. Brain tissues were immediately removed and put into 10% neutral buffer formalin for fixation, then stained with Hematoxylin-Eosin stain. A significant decrease in the brain weight in rats when given the tramadol in dose 50 mg/ kg. Changes included a mild degree of tissue injury in the cerebral cortex, increase in vacuolar degeneration, with atrophy and degeneration of neurons. There are toxic effects when tramadol describes for a long time on the brain tissues.

**Key Words:** Tramadol, Brain Trauma, Brain tissues, Glial Cell, Neuron.

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## Introduction

In terms of medicine, tramadol has been used for relieving mild to moderate pain (Seddighi et al, 2009; Faria et al, 2017; Faria et al, 2018). It is absorbed orally, and 30% excreted through the kidney with half-life elimination (5-6) hours and metabolized in the liver (Dickman, 2007; Barbosa et al, 2020; Barbosa et al, 2021). The accumulation of toxic metabolites increases the risk for these toxic kinetics effects, and/or lowers the clearance of tramadol can occur due to tramadol overuse (Shadnia et al., 2013). The most common cause of death from overdose are cardiorespiratory depression, resistance shock, and liver failure (Verri, 2015).

Neurotoxicity was reported in patients administrated tramadol both at the recommended dosage and the high dosage ranges (Ibrahim and Hala, 2017; Baghishani et al, 2018). The neurotoxicity of tramadol commonly manifests as generalized tonic-clonic seizures (Nakhaee et al, 2021). A study by Atici et al, (2005) found biochemical and histological changes in the rat`s liver with significantly higher serum Alanine aminotransferase, Aspartate aminotransferase, Lactate dehydrogenase, creatinine, and hepatocytes congestion and focal necrosis. Essam et al, (2015) observed that the toxic effect on the parenchymatous organs such as liver, kidney, and thyroid glands in rats occurs after two weeks.

Here, the objective was to evaluate the toxic impaction of tramadol on the brain tissues in laboratory rats.

## Methods

### Experimental Rats

Ten Albano Waster rats weighing (180-300 g) were handled. The rats were kept in stainless steel bottomed wire cages at a temperature of 25°C, and relative humidity of 50%.



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## Ethical and Administrative Considerations

Following the principles of laboratory animal care as contained in the NIH Guide for laboratory animal welfare and the experimental protocol was approved by the Local Ethics Committee (No. 40041 in 2020).

## Design

The protocol was performed and the rats were grouped into two groups: the Control group was fed only diet and water, and the Tramadol group was fed diet and Tramadol HCL (tablet) orally in dose 50mg/ kg. B.W dissolved in (5ml) NS (0.9%) by gastric tube, daily for one month.

## Intervention

Beyond the end of the experiment, the rats were overnight fasted and sacrificed after 24 hours of the last dose. Brain tissues were immediately removed taking care to handle tissues gently, then weighted, and put into 10% neutral buffer formalin for fixation, and then stored in 70% ethyl alcohol. The specimens were dehydrated through a graded series of ethanol and embedded in paraffin and sectioned for histological examination.

## Statistical Analysis

Statistical analyses were made with ANOVA to compare between the experimental groups by SPSS for windows version 17. $P<0.05$ was considered statistical significance.

## Results

Brains weight were obtained from the rats shown in Table 1. The findings documented a significant decrease in the weight of the brain in the tramadol group when compared with a control group ($p<0.0001$).

**Table 1.** Brain of rat weights (g) of control and tramadol groups

| Rats | Control group | Tramadol group |
|---|---|---|
| 1 | 1.63+ 0.49 | 1.23+ 0.55 |
| 2 | 1.64+ 0.65 | 1.35+ 0.64 |
| 3 | 1.7+ 0.45 | 1.26+ 0.66 |
| 4 | 1.6+ 0.43 | 1.30+0.58 |
| Mean+SD | 1.62+0.48 | 1.12+0.49 |

In terms of histopathology, the microscopic examination of brain tissue sections of the control group revealed normal cerebral cortex, normal neurons fibers distribution, and normal structure of the glial cells and oligodenderial cells, as shown in Figure 1.

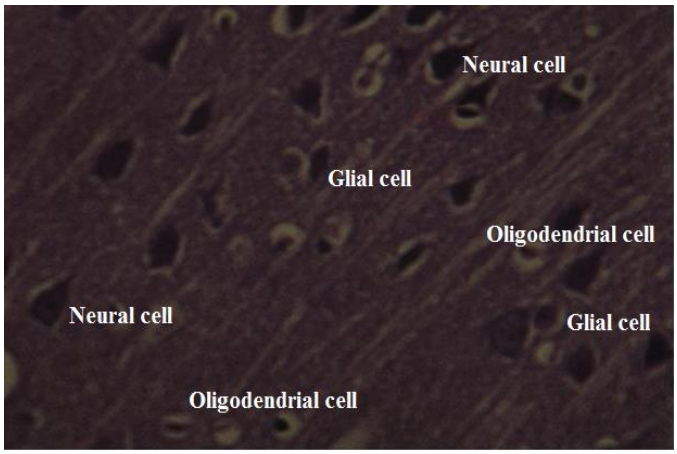


**Figure 1.** The brain of the rat section in the control group stained with H&E (X400) showed normal cerebral cortex, normal neurons fibers distribution, and normal structure of the glial cells and oligodenderial cells.

Whereas in tramadol group revealed an increase in the vacuolar degeneration, atrophy of the neural cells, and complete reduction of the neural process and pyknosis of the nucleus, besides, the traumatic neural cells and gliosis, as shown in Figure 2.

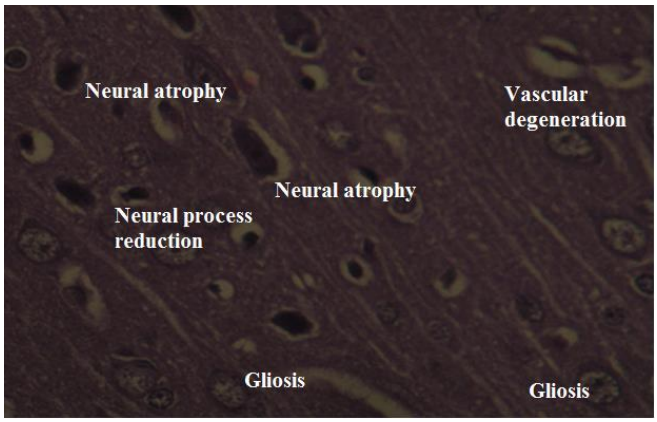


**Figure 2.** The brain of the rat section of the tramadol group stained with H&E (X400), showed an increase in the vacuolar degeneration, atrophy of the neural cells, and complete reduction of the neural process and pyknosis of the nucleus, besides, the traumatic neural cells and gliosis

## Discussion

Tramadol HCL as a potent analgesia, therefore used for treating moderate to severe pain but in recent years the tramadol abuse increased among youngers and teens in several countries. The findings revealed a significant decrease in the brain

weight in the tramadol group as compared with the control group, this result goes along with Balhara et al., (2018) that found that administration of tramadol caused a reduction in the cells volume and nuclear condensation in the brain of rats which probably contribute to cerebral dysfunction.

This study noticed different adverse effects in morphological and histopathological structures of the brain tissues. Essam et al (2015) found histopathological changes in the brain tissues of rats after continuous administration of tramadol for a chronic period.

Abou Elfatoh et al (2014) found blood vessels congestion and neural cells degeneration. Kabel and van Puijenbroek (2005) said that repeated tramadol taken can cause degenerative changes in brain cells, and these are supported by other studies (Lagard et al, 2018; Raj et al, 2019).

Chronic administration of tramadol with increasing the doses of the drug may cause degeneration in the red neurons and brain apoptosis which contribute to cerebral dysfunction (Atici et al, 2005).

Some researchers have reported the side effect in another organ in the body, where Abdellatief et al., (2015) documented the effect on the testicular tissues and deposition of acidophilic PSA-positive materials in male rats. Youssef and Sheweita et al., (2018) reported hepatocytes degeneration and dilatation in the central vein with dilation in the sinusoid.

The study was performed by Abou Eluaga et al., (2020) to investigate the effect of tramadol on the histological structures of the testes in Albano rats observed abnormal changes in the seminiferous tubules. Salama et al., (2003) recorded an increased accumulation of free radicals led to an increase in nitric oxide level in the brain and hypofunction of Leydig cells with consequent reduction of the testosterone secretion occur. Hussein et al., (2017) recorded an increase in creatinine levels in rats due to evidence of renal damage and impaired renal function.

## Conclusion

We concluded that the tramadol group have a significant reduction in the weight of the brain when compared with a control group. The normality of brain is observed in the control group revealed normal cerebral cortex, normal neurons fibers distribution, and normal structure of the glial cells and oligodenderial cells. On the contrary, the tramadol group clearly showed adverse effects on brain tissues in the form of the vacuolar degeneration, atrophy of the neural cells and complete reducing the neural process and pyknosis of the nucleus, with the traumatic neural cells and gliosis. A hard toxic effect on the histopathological structures and function of the brain rats when prescribe the tramadol for chronic time, therefore an abuse of tramadol should be avoided except with medical prescription.

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