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Physiological study for the effects of tramadol in male laboratory rats (*Rattus-rattus*)

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Abstract
In the current study, 24 male laboratory rats were split into four groups to examine the effects of tramadol injection on body weight and certain blood components. The control group, denoted by the first group, C1, received treatment with regular saline (0.9%). For 21 days, the fourth group (C4) received an injection at a dose of 80 mg, whereas the second group (C2) and third group (C3) received injections at concentrations of 20 and 40 mg, respectively. According to the current study's findings, rats given tramadol injections weighed much less than the control group. Significant declines were also observed in the concentration of HCT, PLT, HB, and RBC, respectively. The study's findings also showed a considerable rise in the number of white blood cells.

Keywords: Body weight, tramadol, blood, WBC, laboratory rats

Introduction
Tramadol, an opioid painkiller that is marketed under several trade names, including Ultram, is used to treat moderate to moderately severe pain when taken orally in an immediate-release formulation. Pain relief normally starts within an hour, and it can also be administered by injection. Pypendop and Ilkiw (2008) [7] and Janssen Pharmaceuticals (2016) [4]. Because it drastically lowers the need for volatile anesthetics and opioid drugs, tramadol is also utilized perioperatively in veterinary anesthesia (Alhamedi *et al*., 2015 and Seddighi *et al*., 2009) [1, 9]. Its partial affinity for the μ-opiate receptor and its suppression of serotonin and norepinephrine reuptake are responsible for its analgesic effects (Shadnia *et al*., 2008). Tramadol is regarded as a safe medication that doesn't have many of the severe side effects of conventional opioids. But lately, there have been more reports of tramadol toxicity, abuse, and dependency, as well as tramadol-related fatalities (Tjäderborn *et al*., 2007) [10]. When taken orally, tramadol is quickly absorbed; a peak concentration is found two to three hours after the intake. It is widely distributed throughout the tissue. The kidneys eliminate thirty percent of the medication in an unaltered form. The remaining portion is metabolized in the liver by N- and Odemethylation, followed by conjugation with glucuronic acid and sulphate. The elimination half-life is five to six hours. O-desmethyl tramadol, the active metabolite, having double the analgesic effectiveness of the original medication and a greater affinity for μ-opioid receptors (Khandave *et al*., 2010) [5]. Similar to other opiates, tramadol produces respiratory depression and physical and psychological addiction. Its analgesic effects can be further enhanced by combining it with a non-opioid analgesic (Lanier *et al*., 2010) [6]. In these patients, repeated tramadol treatment may raise the chance of pharmacokinetic interactions, cause the body to accumulate toxic metabolites, and/or reduce tramadol's clearance, all of which increase the drug's potential for toxicity (De Decker *et al*., 2008) [3]. Despite all efforts to avoid and control it, addiction is still a major public health concern and is becoming a bigger problem worldwide. One of the most commonly overused medicines is analgesics (Rafati *et al*., 2006; Alhamedi *et al*., 2015) [1, 8].
The overall goal of the current investigation to look into how tramadol affects blood, body weight, and metabolic factors.

Materials and methods

Test animals 24 mature domestic rats in good health, weighing between 100 and 130 grams. Prior to research, the animals were given a week to get used to the lab environment. The animals were split into four groups at random, each with six male rats, and given the following care:

- **Group C1**: a control G, injected (I.P) with 0.5ml of normal saline.
- **Group C2**: Each rat was daily injected with tramadol (20mg/kg. body weight) for 21days (according to Atici *et al*., 2005) [2].
- **GroupC3**: Each rat was daily injected with tramadol (40mg/kg. body weight) for 21 days.
- **GroupC4**: Each rat was daily injected with tramadol (80mg/kg. body weight) for21 days.

Chemicals examined tramadol

(Tramadol hydrochloride ampoules 100 mg) was obtained from a local pharmacy.

The Parameters of the study

1. Physiological parameters include (body weight before and after treatment the animals.
2. RBCs, HB, PCV, PLT, and WBCs).

Results & discussion

Tramadol's impact on body weight. When comparing the weights of the animals in the three groups with the control group, the results demonstrated that animals receiving tramadol injections had a substantial weight difference. However, there were notable variations in the weights of those groups when comparing their weights before and after receiving tramadol injections, as shown in Tables (1). The weight values of the animals in these groups, C2, C3, and C4, do, however, show a percentage decline. Additionally, in all comparison scenarios, the weight values for each group before to the tramadol injection or the control group's weight data are compared. This portion of the data supported the findings of Udegbunam *et al*. (2015) [16], who discovered that feeding mice repeated doses of tramadol caused their weight to decline.

Table 1: Showed the body weight of animals before and after treatment with tramadol.

Parameter	C1	C2	C3	C4	LSD
Body weight before tramadol injection	144.67±1.03 a	140.67±0.81 d	141.83±0.75 c	142.00±0.63 b	0.16
Body weight after tramadol injection	154.67±1.36 a	137.67±1.03 b	135.67±0.81 c	132.17±0.75 d	2.00

The different letter refers to a significant difference between treatment at $P \leq 0.05$.

Tramadol's effects on packed cell volume (pcv%), WBC count, RBC counts, PLT, and Hb concentration. The results of injecting such a drug into experimental animals are displayed in Table (2). If the total number of red blood cells decreased in accordance with the injection concentrations, it indicates changes in the values and concentrations of specific blood components.

When the drug was administered at a dose of 80 mg per 100 g of animal weight, the number of red blood cells reduced more than when the drug was administered at a concentration of 20 mg/100 g of animal weight. When compared to the hemoglobin concentration in the control group, the hemoglobin concentration likewise decreased at the various injection concentrations (20, 40, and 80 mg/100 g of body weight, respectively). However, compared to the animals in the control group, the number of platelets in the tramadol-injected animals significantly decreased. However, the concentration of 80 mg/100 g of the number of PLT decreased by the greatest percentage at body weight, whereas the decline at C2 was the smallest. These findings are consistent with those of Aldalou *et al*. (2014) [18], Nna *et al*. (2016) [12], Owoade *et al*. (2019) [14], and Elyazji *et al*. (2013) [13]. It's possible that the reduction in these blood components-caused by tramadol's inhibition of red blood cell morphological differentiation-will have an impact on the other blood components, including platelet count and hemoglobin concentration. As a result, the body's metabolic processes will generate less energy (Nna *et al*., 2016) [12]. It might result from the negative impact of the body's blood clotting process. Furthermore, numerous research in this area have demonstrated that it leads to the use of various analgesics, including tramadol (Elyazji *et al*., 2013) [14]. Many studies in this field have confirmed that the transfer of bodily fluids from parts outside the blood vessels to the inside of the blood vessels will cause HCT to decrease. This could be the cause of the decrease in HCT volume. Tramadol may also have an effect on the sympathetic nerve's decreased activity or function during blood circulation in the spleen. Or it can be the source of the extracellular fluid's enlargement due to increased secretion of aldosterone and anti-diuretic hormone, which results in salt and water retention.

According to the data displayed in Table (2), injections at varying concentrations (20, 40, 80, and mg/100 gm of body weight) have an impact on the injected animals' immune systems by increasing the overall quantity of white blood cells. One of the primary characteristics of variance in white blood cell counts is the variation in the number of diverse white blood cells, which could be caused by the immune system's defense mechanism being activated in rats. This would impact the white blood cells and cause them to form a positive response by monocytes and lymphocytes in addition to the increase in the number of white blood cells, which was caused by lymphocytes (Elyazji *et al*) [14].

Table 2: showed the effect of tramadol on (blood parameters) in male rat for 21 days.

Parameters	RBC	HB g\dl	PLT	WBC	PCV%
C1\CONROL	7.45 a±0.13	17.17a±0.75	871.67a±4.67	9.36 d±0.21	47.83 a±1.16
C2\20mg T	6.33 b±0.30	13.50b±1.04	677.17b±8.37	10.40 c±0.17	37.17 b±0.75
C3\40mgT	5.41 c±0.26	10.83 c±0.75	532.67c±3.07	12.16 b±0.75	33.33 c±1.21
C4\80mgT	4.55 d±0.18	8.33d±1.03	405.00 d±3.40	14.00 a±0.89	29.33 d±1.21
LSD	0.86	2.50	127.66	1.03	3.83

The different letter refers to a significant difference between treatment at $P \leq 0.05$.

Clinical signs

When such chemicals are used to inject animals, diseases are caused. These materials can cause constipation, lack of appetite, stomach pain, and excessive diarrhea, among other serious problems. These drugs cause cramping, tense muscles, and an inhibitory influence on bowel motions. As a result, these animals lose weight (Zebedee *et al*, 2020) [17].

Conclusions

This study demonstrated that young rats given tramadol every day for a little amount of time experience notable changes in all blood components, particularly hemoglobin, red blood cell count, and differentiation, as well as its immune system diseases. Additionally, blood platelet counts have a detrimental impact on body weight, which could lead to future growth issues.

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