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# The Effect of Tramadol Administration on the Levels of Some Trace Elements in Male Rabbits

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## Abstract

Tramadol sold under brand name Ultram among others, is an opiod pain medication used to treat the moderate to severe pain. It was hypothesized that acute and chronic administration of Tramadol may impair trace elements homeostasis in the body. The aim of this study was to determine the levels of some trace elements in Rabbits administered with different concentrations of Tramadol on acute and chronic bases. Twenty four rabbits were used for the study; divided into 8 groups of 3 rabbits each based on similarities in weight and varying doses of tramadol. Groups A, B and C were given 10, 15 and 20mg/kg body weight Tramadol intramuscularly for 15days while groups D and E were given 10 and 20mg/kg body weight Tramadol intravenously for 30days. Groups F and G were given 10 and 20mg/kg body weight for 15 days, Tramadol withdrawn and observed for 15days while group H was given only water and feeds (controls). Blood sample was collected from the vein lining ear of the rabbits at the end of drug administration. The plasma was digested using Perchloric acid and nitric acid in 1:3 ratio and copper, zinc and iron were analyzed using Atomic Absorption Spectrophotometer (AAS). The result obtained showed a significantly higher level of copper in rabbits in groups A to G. There mean levels of zinc and iron decreased with increasing concentrations of administered Tramadol in experimental animals. The result also showed no significant difference in copper in rabbits administered with 10mg of tramadol for 15 days and allowed to recover for 15 days (group F) compared with rabbits administered with 20mg of tramadol and allowed to recover for 15 days (group G). The blood levels of copper were higher while zinc and iron were lower in rabbits treated with Tramadol irrespective of concentration but levels of measured micronutrients did not return to the concentrations observed in the controls after 15days withdrawal of Tramadol administration. Acute and chronic administration of Tramadol might adversely affect measured micronutrients homeostasis.

## Keywords

Tramadol, Serum Copper, Iron and Zinc

## 1. Introduction

Tramadol is used in clinical practice for the treatment of pain, but despite the benefits derived from its use, abuse and overdose may result in undesired toxic outcomes [1, 2], but effects on micronutrients homeostasis has not been sufficiently addressed. It is often combined with paracetamol (acetaminophen) as this is known to improve the efficiency of tramadol in relieving pain [3]. It has dual mode of action. Its analgesic efficacy is attributed to its partial affinity for the μ-opiate receptor and its inhibition of norepinephrine and serotonin re-uptake [4]. Tramadol is considered a safe drug devoid of many serious adverse effects of traditional opioids. In the last decade however, abuse and dependence of tramadol has been reported. In addition, Tramadol toxicity related deaths have been increasingly reported [4]. Tramadol is rapidly absorbed orally; a peak concentration is detected 2-3 hours post oral dose. It has extensive tissue distribution. Thirty percent of the drug is excreted through the kidneys in an unchanged manner. Elimination half-life is 5–6 hours, while the remaining is metabolized in liver by N- and O-demethylation, followed by conjugation with glucuronic acid and sulphate. The active metabolite, o-desmethyl tramadol

shows higher affinity for the μ-opioid receptors and has twice the analgesic potency of the parent drug [5]. Tramadol causes respiratory depression, psychological and physical addiction similar to that of other opiates and the analgesic efficacy of tramadol can further be improved by combination with a non-opioid analgesic [6, 7]. Repeated tramadol administration in such patients might lead to the accumulation of toxic metabolites in the body, increase the risk for pharmacokinetic interactions, and/or decrease the clearance of tramadol, thus increasing its potential for toxicity [7, 8]. Nowadays addiction is an ever-increasing problem in the world and despite all efforts to prevent and control it, it continues to be a tremendous public health issue. Analgesics are among the most popular drugs which are being abused [7].

It was hypothesized that during acute and chronic administration of tramadol some essential micronutrients homeostasis may be affected. Since micronutrients act as cofactors in neurotransmitter synthesis and metabolism, where they act as rate limiting factors, the use of Tramadol may alter their concentrations. Single micronutrient deficiencies have been reported to cause psychiatric symptoms [9]. Adequate intake of micronutrients has been reported to be helpful for coping with stress [10]. It is not known whether tramadol administration affects some essential nutrients in subjects who take this drug. Some of the side-effects were reported to be nausea and constipation which affects nutrient absorption or nutrient-nutrient interaction. This study therefore seeks to determine the effect of acute and chronic administration of tramadol on plasma level of zinc, copper and iron in rabbits and to know whether withdrawal of administration will restore the measured micronutrients to levels observed in untreated control rabbits.

# 2. Materials and Methods

## 2.1. Experimental Animals and Study Design

Twenty four male rabbits, Oryctolagus cuniculus were purchased in Owo through the Department of Biological Science, Achievers University, Owo - Nigeria and housed in ventilated cages at the animal house, Department of microbiology Achievers university Owo. The animals were allowed to acclimatize for one week during which they were fed with grower's mash.

Experimental and observational study involved twenty four rabbits which were divided into 8 groups of 3 animals each.

i. Group A: The 3 rabbits were fed with normal feeds and administered with 10 mg/kg body weight of tramadol intramuscularly for 15 days
   a. Group B: The 3 rabbits were fed with normal feeds and administered with 15 mg/kg body weight of tramadol intramuscularly for 15 days.
   b. Group C: The 3 rabbits were fed with normal feeds and administered with 20 mg/kg body weight of tramadol intramuscularly for 15 days.
ii. Group D: The 3 rabbits were fed with normal feeds and administered with 10 mg/kg body weight of tramadol intramuscularly for 30 days.
   a. Group E: The 3 rabbits were fed with normal feeds and administered with 20 mg/kg body weight of tramadol intramuscularly for 30 days.
iii. Group F: The 3 rabbits were fed with normal feeds and administered with 10 mg/kg body weight of tramadol intramuscularly for 15 days and treatment withdrawn to recover for 15 days.
   a. Group G: The 3 rabbits were fed with normal feeds and administered with 20 mg/kg body weight of tramadol intramuscularly for 15 days and treatment withdrawn to recover for 15 days.
iv. Group H: The 3 rabbits were fed with normal feeds and water only (Control group).

## 2.2. Sample Collection

Five milliliters of blood samples were collected from the vein lining the ear of the rabbits in groups A to c into lithium heparinized bottles after 15 days of tramadol administration, while 5mL of blood was collected from the rabbits in groups D and E after 30 days of tramadol administration.

Five milliliters of blood sample was collected from the rabbits in groups F and G into lithium heparinized bottles on day 30 after 15 days of administration of 10mg/kg body weight of tramadol and allowing the rabbits to recover for 15 days after withdrawal of treatment.

In the control (Group H), 5mL of blood sample was collected from the vein lining the ear of each of the 3 rabbits into lithium heparinized bottles after 15 days of feeding with normal feeds and water only.

Sample Preparation: The whole blood sample was centrifuged at 1000g for 5minutes and plasma separated into plain containers. The separated plasma was kept frozen at -20 degree Celsius until the sample was analyzed.

## 2.3. Sample Analyses

The plasma was digested using Perchloric acid and nitric acid in 1:3 ratio and copper, zinc and iron were analyzed using Atomic Absorption Spectrophotometer (AAS). The principle is based on the fact when a beam of electromagnetic radiation is passed through a substance, the radiation may either be absorbed or transmitted depending upon the wavelength of the radiation. The absorption of radiation would bring about an increase in the energy of the molecule. The energy gained by the molecule is directly proportional to the wavelength of radiation. A particular wavelength that a given molecule can absorb depends upon the changes in vibrational, or rotational or electronic states.

## 2.4. Statistical Analysis

Statistical analysis was done using the Statistical Package for Social Scientists (SPSS, Chicago, IL, USA) version 20.0. All values were expressed as Mean± Standard deviation. Results from the specimen were compared using Student t

test. Level of significance at 95% confidence interval and P value less 0.05 was considered significant.

## 3. Results

The result obtained shows significantly higher ($p<0.001$) level of copper, lower ($p<0.001$) levels of Zn and Fe in experimental rabbits when compared with controls. The results indicate that the levels of serum cu increased while the levels of Fe and Zn decreased with increasing concentrations of administered Tramadol from 10mg/kg body weight to 20mg/kg body weight.

The levels of measured parameters did not return to the concentrations observed in control animals after 15days of Tramadol withdrawal. Tables 2, 3 and 4 show the comparison of measured parameters between experimental groups while figure 1 indicates the graphical representation of measured parameters in experimental animals.

The result obtained shows significantly higher levels of copper lower levels of Zn and Fe in experimental rabbits when compared with control. Higher levels of copper were observed in rabbits administered with 10mg of tramadol for 15 days (Group A) compared with rabbits administered with 15mg of tramadol for 15 days (Group B). Also, a significantly higher level of copper was obtained in rabbits administered with 10mg of tramadol for 15 days (Group A) compared with rabbits administered with 20mg of tramadol (Group C) for 15 days. The result obtained also showed a significant increase in copper in rabbits administered with 15mg of tramadol for 15 days (GROUP B) compared with rabbits administered with 15mg of tramadol for 15 days (Group C). In addition, the result showed a significant increase in copper in rabbits administered with 10mg of tramadol for 30 days (Group D) compared with rabbits administered with 20mg of tramadol for 15 days (Group E). The result also showed no significant difference in copper in rabbits administered with 10mg of tramadol for 15 days and allowed to recover for 15 days (Group F) compared with rabbits administered with 20mg of tramadol and allowed to recover for 15 days (Group G)

***Table 1.*** *Plasma levels of measured micronutrients in Experimental Rabbits.*

| Groups | Plasma Iron (µg/mL) | Plasma copper (µg/dL) | Plasma zinc (µg/dL) |
|---|---|---|---|
| A (10mg/kg body weight for 15 days. | 1.43±0.002 | 42.2±0.01 | 30.7±0.042 |
| B (15 mg/kg body weight for 15days | 1.38±0.017 | 49.4±0.01 | 28.9±0.01 |
| C (20mg/kg body weight for 15days. | 1.140±0.07 | 58.4±0.09 | 26.7±0.02 |
| D (10mg/kg body weight for 30dys | 0.967±0.01 | 66.8±0.02 | 20.1±0.01 |
| E (20mg/kg body weight for 30days | 0.866±0.01 | 79.4±0.01 | 21.1±0.01 |
| F (10mg/kg body weight for 15days and withdrawn treatment for 15days | 0.82±0.01 | 33.3±0.01 | 19.5±0.01 |
| G (20mg/kg body weight for 15days and withdrawn treatment for 15days | 0.8±0.01 | 36.8±0.01 | 18.0±0.05 |
| H (Controls) | 2.87±0.02 | 28.5±0.01 | 48.8±0.01 |

***Table 2.*** *Comparison of serum Iron between groups of experimental animals.*

| IRON | GROUP A | GROUP B | GROUP C | GROUP D | GROUP E | GROUP F | GROUP G |
|---|---|---|---|---|---|---|---|
| GROUP A | | 0 | 0 | 0.0001 | 0 | 0.2269 | 0.02 |
| GROUP B | | | 0.0002 | 0 | 0 | 0.0043 | 0.2416 |
| GROUP C | | | | 0.0032 | 0 | 0 | 0.029 |
| GROUP D | | | | | 0.0037 | 0.0003 | 0.0015 |
| GROUP E | | | | | | 0.0002 | 0.011 |
| GROUP F | | | | | | | 0.013 |

***Table 3.*** *Comparison of serum copper between groups of experimental animals.*

| COPPER | GROUP A | GROUP B | GROUP C | GROUP D | GROUP E | GROUP F | GROUP G |
|---|---|---|---|---|---|---|---|
| GROUP A | | 0.001 | 0.044 | 0.0018 | 0.0006 | 0.11 | 0.023 |
| GROUP B | | | 0.108 | 0.002 | 0 | 0.0043 | 0.0002 |
| GROUP C | | | | 0,1262 | 0.278 | 0.0121 | 0.0259 |
| GROUP D | | | | | 0.0076 | 0.012 | 0.0011 |
| GROUP E | | | | | | 0.0062 | 0.0004 |
| GROUP F | | | | | | | 0.283 |

***Table 4.*** *Comparison of serum zinc between groups of experimental animals.*

| ZINC | GROUP A | GROUP B | GROUP C | GROUP D | GROUP E | GROUP F | GROUP G |
|---|---|---|---|---|---|---|---|
| GROUP A | | 0.280 | 0.1534 | 0.027 | 0.034 | 0.023 | 0.074 |
| GROUP B | | | 0.068 | 0.0001 | 0.0093 | 0.0041 | 0.0416 |
| GROUP C | | | | 0.0045 | 0.029 | 0.0121 | 0.0692 |
| GROUP D | | | | | 0.228 | 0.278 | 0.297 |
| GROUP E | | | | | | 0.108 | 0.228 |
| GROUP F | | | | | | | 0.3469 |

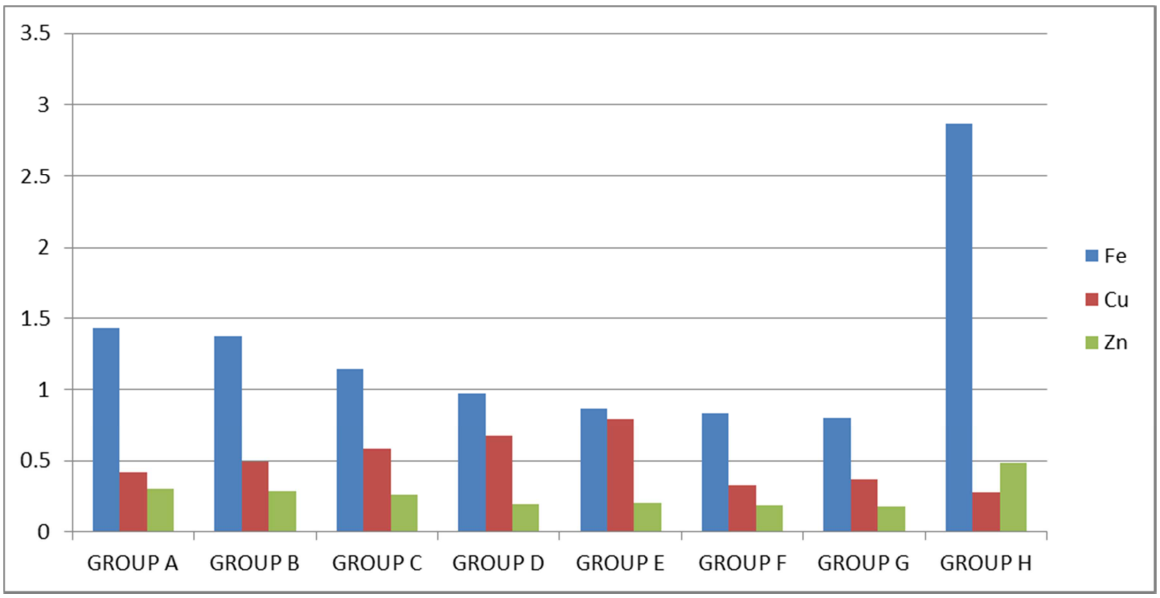


***Figure 1.*** *Graphical representation of Zn, Cu, and Fe in Test and control rabbits.*

## 4. Discussion

Tramadol hydrochloride (TH) is a synthetic opioid with effects similar to those of codeine. It is analgesic of significant and has a wide range of application mostly in the treatment of moderate to severe pain including the treatment of fibromyalgia, cancer and musculoskeletal pain. Tramadol hydrochloride is metabolized in the liver and excreted by the kidney; the role of liver and kidney in drug metabolism predisposes them to toxic injury leading to impaired liver and kidney functions. Whereas the concentrations of copper increased with increasing concentrations and duration of administered Tramadol, the levels of zinc and iron decreased with concentrations and duration of Tramadol administration. In addition, withdrawal of Tramadol administration did not restore the levels of measured micronutrients to the levels observed in the control animals. This study is consistent with that of Iyengar et al [11] who reported a decrease in zinc level in serum of humans administered with opiods due to increased renal elimination. Ruiz et al [12] also reported a decrease in zinc level in serum level in human administered with opiods-accompanied by increased copper.

Trace elements play important roles in the various metabolic processes and are crucial for many physiological processes. Impaired metabolism of trace elements like copper (Cu) and zinc (Zn) has been reported to result in higher sensitivity to oxidative damage [13]. Of these elements, zinc, magnesium, copper, iron, and lithium may be related to altered physiological mechanisms in persons addicted to drugs. Zinc is essential for many physiological processes such as protein synthesis, tissue repair, and immunological functions, and also plays a role in the protection against infections. Copper is important for the synthesis of the hemo group, and for metabolism in connective, bony, and nerve tissue, while Cu deficiency interferes with humoral immunity. Microminerals or trace elements play a versatile function in human body ranging from developing immunity to provide antioxidant defense [14]. Zinc is essential for its catalytic, structural and regulatory functions. Its metalloenzymes are involved in immune development, cognitive functioning, reproductive maturation and physiological growth [15]. Zinc is required for DNA replication, RNA transcription, cell division and cell activation. Copper and iron are also crucial for physiological functions, antioxidant defense, and immune development [16]. Deficiency of any of these elements badly affects normal functions in the human body. It is also further reported that overload of micromineral or trace elements produces immunotoxicity [17]. Currently some investigators have reported changes in serum trace element levels among drug dependent individuals [18]. The result of this study showed a significant decrease in iron and zinc level in experimental rabbits when compared with controls. Use and abuse of Tramadol could induce zn and Fe deficiencies and copper toxicity.

Various studies have showed that illicit drug use produced an increase in serum copper concentrations and a decrease in iron and zinc concentrations. Change in trace element level due to drug abuse has also been reported by some investigators [19], where they observed an increase in copper and a decrease in zinc in most of the addicts or drug dependent individuals, and in a few cases, both an increase and a decrease in iron concentration was reported. The increase in copper level may possibly be associated with stress, inflammation and infections and, these were reported to be common among drug addicts or drug dependents [20, 21]. Zinc, the second most abundant trace element in the human body (after iron), plays mainly catalytic and structural roles [22]; as a co-factor of Cu-Zn superoxide dismutase and is important for the anti-oxidant defence [23]. Between zinc and copper there is a certain degree of antagonism at the

level of biological actions; as decreased zinc is accompanied by increase serum and intraerythrocytic copper and given that copper urinary elimination is decreased under methadone maintenance treatment [11].

## 5. Conclusion

Serum concentrations of iron and Zinc were lower in rabbits administered with varying doses of tramadol while increased levels of serum copper was observed in rabbits administered with varying doses of tramadol. The measured parameters did not returned to the levels observed in the control animals upon withdrawal of Tramadol administration. Acute and chronic administration of Tramadol might adversely affect serum copper, zinc and iron homeostasis. It is suggested that serum copper, zinc and iron could be monitored in Tramadol users.

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