

# Repeated Tramadol Administration Induced Bleeding in Albino Rats

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## ABSTRACT

### KEYWORDS

Tramadol,  
Bleeding,  
PT,  
APTT,  
Platelet aggregation,  
Albino rats

Tramadol abuse is a major health problem. Its effects on hemostasis showed controversial findings. The aim of the present study was to investigate the subchronic toxic effects of tramadol on some hemostatic parameters in Wistar albino rats. Before performance of the study, bleeding time, prothrombin time (PT), activated partial thromboplastin time (APTT) as well as Adenosine Diphosphate (ADP) induced platelet aggregation percentage were measured to get reference values for normal levels. Rats were then given tramadol by gavage in a dose of 20 mg/kg once daily for six weeks and the previously mentioned haematological parameters were measured at two, four and six weeks. The results reveal that tramadol enhanced bleeding tendency along the six weeks of the study as evidenced by prolonged bleeding time, PT, APTT, and decreased ADP-induced platelet aggregation. It can be concluded that tramadol could affect hemostatic parameters in favour of bleeding tendency. Further studies are warranted to confirm these effects and to investigate the possible underlying mechanisms and the potential reversibility of toxicity after drug abstinence.

## Introduction

Data highlight the increased incidence of tramadol abuse especially in North Africa and Middle East (WHO, 2014). Noteworthy, tramadol is illicitly trafficked with the aim to decrease pain, increase endurance power, and to alter sensations (Santacrocea et al., 2018). Tramadol abuse became a major health problem in Egypt due to its low price, illegal transaction and availability with no prescription from pharmacies, black market and media as reported by Ismaiel and Hosny (2012).

Tramadol effects on hemostasis showed controversial results. It has been claimed that

tramadol reduced the procoagulant actions of serotonin and norepinephrine resulting in reduction of thrombus weight (McMillan et al., 2008; Galan et al., 2009; Hallbäck et al., 2012). Moreover, hemorrhage has been reported in tramadol treated patients following tonsillectomy (Courtney and Cabraal, 2001; Işik et al., 2009).

It has been described that tramadol can be safely used in patients undergoing surgery in terms of hemodynamic and respiratory side effects. However, there have been no sufficient studies on the direct effects of tramadol on hemostasis (Bilir et al., 2014). Hence, the aim of the present work was to investigate the subchronic toxic effects of repeated administration of tramadol on some hemostatic parameters in adult albino rats.

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## Material and Methods

### *Study design and animals:*

The present work is a repeated dose subchronic toxicity study of tramadol which was performed in the Medical Experimental Research Center (MERC), Faculty of Medicine, Mansoura University. Fifteen Wistar albino rats weighing 180-200 g, were obtained from MERC. They were housed in clean cages under standardized laboratory conditions including good lighting (12 hours light/dark cycles) and good aeration. They were fed a standard laboratory diet and tap water. All procedures were approved by the Institutional Review Board of Faculty of Medicine (code number: MS/16.05.21).

### **Tramadol administration and samples collection:**

Before performance of the study, bleeding time was measured, then two milliliter blood samples were collected from retro-orbital plexus in all rats to measure prothrombin time (PT), activated partial thromboplastin time (APTT) and Adenosine Diphosphate-induced platelet aggregation (ADP) percentage. Results were used as reference values for normal levels (zero time). Thereafter, rats were given Tramadol (Tramadol HCl capsules (50 mg), Mina-Pharm, Egypt) in a dose of 20 mg/kg once daily (according to a preliminary pilot study) for six weeks. The calculated doses were delivered in normal saline and given orally to each animal by gavage. This dose equals 7% of the LD50 (oral LD50 values are around 300–350 mg/kg body weight for rats) as stated by Matthiesen et al. (1998). Then, bleeding time, PT, APTT and ADP induced platelet aggregation percentage were measured at two, four and six weeks after tramadol administration. Blood

samples were homogenized and stored at room temperature in sterile tubes containing 3.2% sodium citrate. The citrated samples were spun at (150-200 rpm) for 10 minutes to obtain the platelet rich plasma that was used for platelet aggregation tests and then samples were further spun at (2000 rpm) for 10 minutes to obtain the platelet-poor plasma to estimate prothrombin time and activated partial thromboplastin time.

### *Haematological investigations:*

- 1) Bleeding time was performed by puncture with a specific scalpel in the vein located on the external surface of the ear. Time from puncture to the end of bleeding was measured in seconds by a chronometer (*Brondani et al., 2009*).
- 2) Prothrombin time was estimated using Thromborel S Reagent (Siemens Healthcare Diagnostics products, Marburg, Germany) as described by Quick et al. (1935).
- 3) Activated partial thromboplastin time was measured in seconds using Pathromtin SL (Siemens Healthcare Diagnostics products, Marburg, Germany) according to *Brondani et al. (2009)*.
- 4) ADP-induced platelet aggregation percentage was estimated using optical chrono-log platelet lumi-aggregometer (Chrono-Log Corp., Havertown, Pennsylvania, USA). The assay is based on the measurement of the increase in light transmission through the optically dense sample of platelet rich plasma after the addition of ADP as an exogenous platelet agonist (*Brondani et al., 2009; Panizza et al., 2015*).

## Statistical analysis

Results were analyzed by using the computerized statistical package for the social sciences (SPSS) version 20.0. Data was tabulated as mean  $\pm$  standard deviation (SD) for quantitative analysis. Student t-test was used to detect the significant change of the parameters in comparison to control samples. Statistical significance was realized at probability  $p \leq 0.05$ .

## Results

The effects of repeated tramadol administration on different haemostatic parameters in the studied groups of albino rats were demonstrated in table (1). There was progressive significant increase in bleeding time on repeated doses (after two, four and six weeks) compared to the reference value at zero time (base level). It also produced insignificant increase in prothrombin time (PT). Activated partial thromboplastin time (APTT) is insignificantly increased at two and six weeks, while it significantly decreased at four weeks. There was also a significant increase in ADP-induced platelet aggregation after tramadol administration at two and six weeks duration.

**Table (1):** Effects of repeated tramadol administration on different haemostatic parameters in the studied groups of albino rats (n=60 samples).

Haemostatic parameters	Study groups			
	Reference group (zero time) (n=15)	2 weeks (n=15)	4 weeks (n=15)	6 weeks (n=15)
<b>Bleeding time</b>	28.13 $\pm$ 5.15	34.73 $\pm$ 8.88 $\uparrow$	42.66 $\pm$ 4.169 $\uparrow$	53.6 $\pm$ 6.114 $\uparrow$
<b>p</b>		<0.001*	<0.001*	<0.001*
<b>p1</b>			<0.001*	0.001*
<b>p2</b>				<0.001*
<b>Prothrombin time</b>	16.30 $\pm$ 0.965	16.89 $\pm$ 924 $\uparrow$	16.40 $\pm$ 825 $\uparrow$	17.02 $\pm$ 2.621 $\uparrow$
<b>p</b>		0.161	0.717	0.298
<b>p1</b>			0.161	0.86
<b>p2</b>				0.4
<b>APTT</b>	25.64 $\pm$ 3.13	26.62 $\pm$ 6.123 $\uparrow$	23.58 $\pm$ 2.126 $\downarrow$	24.63 $\pm$ 2.102 $\downarrow$
<b>p</b>		0.47	0.019*	0.22
<b>p1</b>			0.05 *	0.17
<b>p2</b>				0.08
<b>ADP induced platelet aggregation percentage</b>	63.69 $\pm$ 19.5	79.10 $\pm$ 15.58 $\uparrow$	59.85 $\pm$ 14.92 $\downarrow$	78.67 $\pm$ 17.42 $\uparrow$
<b>p</b>		0.05*	0.5	0.07
<b>p1</b>			0.003*	0.39
<b>p2</b>				0.001*

n: number, all values are expressed as (mean  $\pm$ SD), SD: standard deviation, APTT: activated partial thromboplastin time, ADP: adenosine diphosphate. p: Comparison with reference levels, p<sub>1</sub>: comparison of four and six weeks with two weeks duration p<sub>2</sub>: comparison of six weeks with four weeks duration \*: significant at  $p < 0.05$ .

## Discussion

Debate regarding the effect of tramadol on bleeding profile exists in the literature (Brondani et al., 2009; İşik et al., 2009). In the present work, oral tramadol administration (20 mg/kg) to albino rats produces progressive significant increase in bleeding time on repeated doses (after two, four and six weeks) compared to the reference value at zero time (base level) as shown in table (1).

Bleeding time depends largely on the rate of formation of platelet plug and is affected by both platelet count and function (Adhikary and Jacob, 2005). Studies on the direct effect of tramadol on bleeding time are insufficient and most of the researchers focussed on studying the effect of tramadol on other hematological parameters including platelet count. For instance, tramadol significantly decreased platelet count in domestic rabbits (Aldalou et al., 2014) and rats (Nna et al., 2016).

The exact mechanism of decreased platelet count is not clear, however, it may be attributed to the presence of drug-dependent antibodies or drug metabolites that bind to glycoproteins (GPs) on the platelets (Arnold et al., 2013). It may be also explained by the disturbed manufacture of thrombopoietin as a result of tramadol-induced liver dysfunction leading to decreased platelet production (Lisman et al., 2002). It is known that long term repeated use of tramadol exposes the liver to toxic injury with increased alanine transaminase levels indicating the failing functions of liver cells (Saleem et al., 2014; Hafez et al., 2015). Hence, prolonged bleeding time may be due to decreased platelet count that was unfortunately not measured in the present study.

The present findings reveal that tramadol produced insignificant increase in

prothrombin time (PT) after two, four and six weeks compared to the base reference values. Activated partial thromboplastin time (APTT) is also insignificantly increased at two and six weeks, while it significantly decreased at four weeks compared to the reference base levels.

Prolonged PT was previously reported by Taromsari et al. (2012) in patients intoxicated with tramadol. Furthermore, Bilir and his colleagues (2014) studied the in vitro effects of tramadol on coagulation system and found that blood medicated with high-dose tramadol (6 µl/ml) clotted slowly.

Similarly, Hafez et al. (2015) investigated the toxic impact of tramadol in albino rats. They used four different intramuscular doses of tramadol; 12.5 mg, 25 mg, 50 mg and 300 mg/kg /day for two weeks. There were significant increases in prothrombin time and activated partial thromboplastin time. The results were explained by liver dysfunction after long term use of tramadol.

It is known that PT and APTT reflect the integrity of the extrinsic and common coagulation pathways (Slaughter, 2010). Furthermore, abnormal APTT is a mirror for most of the coagulation factor deficiencies except factor VII (Adhikary and Jacob, 2005).

The combination of thrombocytopenia with a prolonged PT and APTT are common laboratory findings in patients with liver failure (Tripodi et al., 2005; Caldwell et al., 2006). This might partially explain the current results as the liver plays a central role in haemostasis as it synthesizes the majority of coagulation factors as well as proteins involved in fibrinolysis (Monroe and Hoffman, 2006).

The fluctuation of APTT throughout the study period (significant shortening at four weeks relative to the zero and two weeks groups, then prolongation at six weeks) may be attributed to a transient stressful condition. It was reported that APTT is very sensitive to the

level of factor VIII (an acute phase protein that is increased in response to inflammation or trauma). Hence, APTT may be misleadingly short during the acute phase reaction which when resolved, the APTT returns to normal. Short APTT may be also due to problems of samples gathering resulting in activation of coagulation within the collection tube (Chopin et al., 2006).

In the current research, significant increase in ADP-induced platelet aggregation is observed after tramadol administration at two weeks duration. Thereafter, it is significantly decreased at four weeks compared to the two weeks group. Interestingly, this parameter returns to be significantly increased after six weeks of tramadol administration compared to the four weeks group and even exceeding the percentages detected at the start of the study (zero level) in spite of being insignificant as shown in table (1).

In agreement with the present results, increased platelet aggregation was reported by Casella et al. (2013). The authors evaluated the in vitro effects of tramadol on adenosine diphosphate (ADP)-induced platelet aggregation in plasma of fed and fasted horses. Platelet aggregation was higher in fed than in fasted horses.

In contrast, Brondani et al. (2009) stated that perioperative subcutaneous administration of tramadol (2mg/kg one hour before induction of anesthesia and every eight hours up to 72 hours after surgery) did not interfere either with platelet aggregation or bleeding time.

In order to explain the effects of tramadol on the platelets in the present study, it is necessary to know that tramadol may act by various mechanisms which could in turn affect different hemostatic parameters. To begin with, tramadol inhibits serotonin and norepinephrine reuptake (Fouad et al., 2015).

It is well known that the inhibition of noradrenaline inhibits the release of prostacyclin (PGI<sub>2</sub>) and nitric oxide, both of which are known to be potent inhibitors of platelet aggregation (Jones et al., 1993).

Furthermore, tramadol-like morphine potentiates agonist-induced platelet aggregation by binding to  $\alpha$ -2 adrenoceptors in human platelets, with a resulting inhibition of adenylate cyclase, thereby reducing intracellular cyclic AMP formation followed by increased activation of phospholipase C and the Na<sup>+</sup>/H<sup>+</sup> exchanger. This leads to increased intracellular Ca<sup>2+</sup> mobilization, and finally potentiation of platelet aggregation (Hsiao et al., 2003; Höcker et al., 2008). The foregoing facts could partially explain the increased percentage of ADP-induced platelet aggregation at two and six weeks of tramadol administration.

On the other hand, Galan et al. (2009) claimed that serotonin primes platelet activation and potentiates procoagulant response of platelets. A transporter protein is necessary to the transfer of serotonin into the platelet. Interestingly, tramadol is antagonist to this transporter, and because platelets do not produce serotonin, they are dependent on plasma uptake of serotonin. Thus, blockade of the serotonin transporter leads to serotonin depletion within the platelet, along with inhibition of platelet aggregation (de Abajo, 2011; Watts et al., 2012).

Moreover, tramadol acts as a local anesthetic and may induce changes in the membrane of platelets blocking the ion channels. Thus, it could inhibit alpha-granule release and thromboxane A<sub>2</sub> signaling preventing platelet aggregation (Mert et al., 2007; Leppert, 2009). The previously mentioned opinions could explain the resultant decreased platelet aggregation at four weeks of tramadol administration after the initial increase at two weeks in the current work.

In conclusion, the current findings indicate that tramadol seems to affect hemostatic

parameters in favour of bleeding tendency all over the six weeks of daily oral administration as evidenced by prolonged bleeding time, PT and APTT in addition to decreased ADP-induced platelet aggregation. Furthermore, bleeding time was still significantly prolonged in spite of the shortening of PT and APTT at four weeks and the significant increase in ADP-induced platelet aggregation, at two and six weeks. Further recovery abstinence period studies are recommended in order to assess the reversibility of these findings.

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## تكرار تعاطي الترامادول يحفز النزف في الجرذان البيضاء

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يعد تعاطي الترامادول مشكلة صحية كبرى كما أن تأثيره على تخثر الدم أظهر نتائج مثيرة للجدل. لذا كان الهدف من هذا البحث هو دراسة التأثيرات السمية شبه المزمنة للترامادول على بعض معاملات منع عملية تخثر الدم في الجرذان البيضاء. وقبل إجراء الدراسة، تم قياس زمن النزف، زمن البروثرومبين (PT)، زمن تنشيط الثرومبلاستين الجزئي (APTT)، وكذلك نسبة تجمع الصفائح الدموية المستحثة عن طريق (ADP) للحصول على قيم مرجعية للمستويات العادية. ثم أعطيت الجرذان الترامادول عن طريق الفم بالتزقيم بجرعة ٢٠ مجم / كجم مرة واحدة يوميا لمدة ستة أسابيع وتم قياس معاملات منع عملية التخثر المذكورة سابقا عند أسبوعين وأربعة وستة أسابيع.

وقد أثبتت النتائج أن الترامادول قد عزز النزف على مدى الأسابيع الستة للدراسة كما يتضح من طول زمن النزف، والتأثير الملحوظ والمتفاوت على زمن البروثرومبين وزمن تنشيط الثرومبلاستين الجزئي، وكذلك تناقص تجمع الصفائح الدموية المستحثة بواسطة ADP وعلى الرغم من الزيادة الكبيرة في تجمع الصفائح الدموية بعد أسبوعين وستة أسابيع، وقصر زمن البروثرومبين وزمن تنشيط الثرومبلاستين الجزئي بعد أربعة أسابيع، كان وقت النزف لا يزال طويلاً وذو دلالة احصائية ملحوظة. ومن هذه الدراسة يمكن أن نخلص إلى أن الترامادول يستطيع أن يؤثر على معاملات منع عملية التخثر مؤدياً لزيادة النزف. وننصح بإجراء المزيد من الدراسات لتأكيد هذه الآثار والكشف عن الآليات المحتملة وإمكانية عكس السمية بعد الامتناع عن تعاطي الترامادول.