

Effect of Tramadol Addiction Alone and Its Co-abuse with *Cannabis* on Urinary Excretion of Copper, Zinc, and Calcium among Egyptian Addicts

Ibrahim A. El-Safty^{1*}, Elsayed H. Eltamany², Ahmed E. Shouman³, Omayma A. El-Gamel⁴, Ahmed S. Nada⁵,
Wesam A. Ali²

¹Chemistry Department, Faculty of Education, Ain-Shams University, Heliopolis, Roxy, Cairo, Egypt

²Chemistry Department, Faculty of Science, Suez Canal University, Ismailia, Egypt

³Department of Community, Environmental and Occupational Medicine, Faculty of
Medicine, Ain-Shams University, Cairo, Egypt

⁴Clinical Pathology Department, El-Demerdash Hospital, Faculty of Medicine, Ain-Shams
University, Cairo, Egypt

⁵Atomic Energy Authority, Nasr City, Cairo, Egypt

ABSTRACT

The use of illicit drugs has become a worldwide health problem. Substances with the potential to be abused may have direct or indirect effects on physiologic mechanisms that lead to organ system dysfunction and diseases. The present study aims to investigate the structural and reabsorption integrity of the nephron among Egyptian addicts of tramadol alone and coabused with cannabis. Sixty-five males were included in the study, they were classified into control group ($G_1=19$), tramadol addicts group ($G_2=18$), and tramadol co-abused with *Cannabis* addicts group ($G_3=28$). Parameters investigated for structural integrity were urinary levels of leucineaminopeptidase and N-acetyl- β -D-glucosaminidase, and urinary parameters for reabsorption integrity were levels of copper and zinc as well as calcium, also urinary creatinine was measured. In addition, urinary levels of tramadol and tetrahydrocannabinol were estimated. Among the two addicted groups, all measured parameters were not significantly different in comparison with the control group except for urinary calcium excretion which was found to be significantly increased among the two addicted groups. Both tramadol addiction alone or co-abused with cannabis causes increased urinary excretion of calcium, indicating reabsorption dysfunction of calcium without affecting structural integrity along the nephron.

Keywords: Calcium, Copper, Enzymuria, Reabsorption impairment, Tubular structural integrity, Zinc.



INTRODUCTION

The use of illicit drugs has become a worldwide health problem. It leads to numerous consequences at the health, economic, social and legal levels. These consequences interfere with the development of the countries and their efforts to respond to the needs of their populations. Apart from its economic cost, drug abuse leads to social problems among family members, abnormal behavior, crime, health and psychological problems as well as economic difficulties (Okasha, 2004).

Tramadol (Tr) is a synthetic opioid from the aminocyclohexanol group and is commonly used in clinical practice as an analgesic for the treatment of moderate to severe pain (Bamigbade and Langford, 1998). Tramadol is free of side effects of a traditional opioid such as the risk for respiratory depression (Houmes *et al.*, 1992) and drug dependence (Richter *et al.*, 1985). So, the abuse potential of tramadol is considered low or absent (Cicero *et al.*, 2005), which is in contrast to other opioids.

Cannabis was used a long time ago for both recreational and medicinal purposes. The plant *Cannabis sativa* (Indian hemp) is the source of different psychoactive

products. Marijuana comes from leaves, stems, and dried flower buds of the plant. Hashish is a resin obtained from flowering buds of the hemp plant (Hazeekamp and Grotenhermen, 2010).

Δ^9 -tetrahydrocannabinol (Δ^9 -THC) is the primary psychoactive compound and contributes to the behavioural toxicity of cannabis (Huestis, 2007). Calcium (Ca) is the most abundant divalent ion (Ca^{2+}) in the body (Reddi, 2014). Calcium is reabsorbed along all segments of the nephron. The proximal tubule is the primary tubular segment where most of the filtered calcium is reabsorbed. Under normal condition, 98-99% of the calcium which passes into the tubule is reabsorbed. Approximately 60-70% of the filtered calcium is reabsorbed in the proximal convoluted tubule, 20% in the loop of Henle, 10% by the distal convoluted tubule, and 5% by the collecting duct (Blaine *et al.*, 2014). Any calcium that is not reabsorbed then passes into what is now urine and into the bladder.

Copper (Cu) is important for all functions of many cellular enzymes (Ellingsen *et al.*, 2015). The copper transporters ATP7A and ATP7B are expressed at distinct regions of the kidney (Moore and Cox, 2002). They are both expressed in the glomeruli in minor amo-

* Corresponding author: elsafty54@yahoo.com

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unts. ATP7A is localized in the proximal and distal tubules, while ATP7B is expressed in the loop of Henle. The two copper transporters work together to maintain copper balance within this tissue. The ability of ATP7A to traffic to basolateral membrane (an event associated with copper export) in response to copper elevation strongly suggests that ATP7A plays the major role in exporting copper from renal cells for reabsorption into the blood and in protecting renal cells against copper overload (Linz *et al.*, 2008). In another research, ATP7B expression in the loops of Henle suggests that once in the filtrate, ATP7B is responsible for copper reabsorption (Moore and Cox, 2002). Previous data suggest that copper may be reabsorbed by the same pathway as that involved in iron reabsorption (Wareing *et al.*, 2000), which occurs between the proximal and distal convoluted tubules, interpreted as the loops of Henle.

Zinc (Zn) exists as a divalent cation (Zn^{2+}). The kidney epithelium is the site of urinary zinc excretion and reabsorption. Zinc reabsorption occurs in all the downstream segments of the nephron; proximal tubule, Loop of Henle, and terminal nephron segments (Barbier *et al.*, 2004). Most of the filtered Zn is reabsorbed along kidney proximal tubule (Ranaldi *et al.*, 2002).

The kidney is considered the primary eliminator of exogenous drugs and toxins; impairment of excretion predisposes it to various forms of injury. Development of new biomarkers is needed for the specific diagnosis of nephrotoxicity at an earlier stage (Ferguson *et al.*, 2008). These biomarkers include brush border enzymes such as *Leucine aminopeptidase* (LAP) (Ren *et al.*, 2015), a Lysosomal enzyme such as *N-acetyl- β -D-glucosaminidase* (NAG) (Waikar and Bonventre, 2008), and a cytosolic enzyme such as α -glutathione S-transferase (α -GST) (Perazella, 2005). Thus, detection of enzymes in the urine potentially provides valuable information not only related to the site of tubular injury (proximal and distal tubule) but also to the severity of injury (Ferguson *et al.*, 2008).

Renal tubular cells, in particular, proximal tubule cells, are vulnerable to the toxic effects of drugs because their role in concentrating and reabsorbing glomerular filtrate exposes them to high levels of circulating toxins (Perazella, 2005). Although most nephrotoxicity occurs in the proximal part of the nephron, some chemicals damage distal tubules. The function of these structures facilitates their vulnerability to toxicants (Covington and Schnellmann, 2008). Drug addiction has been associated with various forms of renal diseases which may be related to direct effect of the drugs themselves while others are caused by complications related to drug abuse (Kunis *et al.*, 2008).

The present work aims to investigate the effect of tramadol addiction on urinary excretion of some metals (e.g. copper, zinc, and calcium) in relation to the structural integrity of proximal tubules which were evaluated by measuring the urinary excretion of proximal

tubular specific enzymes e.g. LAP and NAG. In addition, the study was extended to evaluate the effect of tramadol addiction co-abused with *Cannabis*.

MATERIAL AND METHODS

The study was designed to be a comparative cross-sectional one from December 2015 to March 2016. Participants in the present investigation were recruited on voluntary bases from non-smoking males attending the outpatient clinic, El-Demerdash hospital, Ain-Shams University, for treatment of drug addiction. All participants were subjected to interview using a questionnaire designed to obtain information about previous medical and occupational history, medication intake, actual health status, and subjective symptoms. All subjects underwent a routine clinical examination and a routine urinalysis. The interview and clinical examination were performed by the clinic physicians under the supervision of one of the authors. Participants of the control group were recruited from relatives of the addicted participants after applying the same exclusion criteria and clinical examination. A participant was excluded from the present study if he had:

- 1 A history of disease affecting the kidney before the onset of addiction or any disease likely to impair renal function or affect the urinary excretion of the investigated parameters e.g. (diabetes mellitus, hypertension, collagen diseases as systemic lupus erythromatosis, Urinary tract disease, Rheumatoid arthritis, and gout).
- 2 A previous or present exposure to agents capable of damaging the kidney, heavy metals such as lead (Pb^{2+}) and cadmium (Cd^{2+}) as well as other nephrotoxins such as organic solvents.
- 3 Regular and prolonged treatment by drugs affecting the kidney e.g. aminoglycosides and antirheumatic drugs.
- 4 Dental mercury amalgam filling as it may affect the kidney.
- 5 Cigarette smoker.

A total of sixty-five males were included in the present study and divided into three groups as follows: Control group (G_1) was comprised of 19 males, Tramadol addicts (G_2) were comprised of 18 males, and Tramadol coabused with cannabis addicts (G_3) was comprised of 28 males.

Sampling

Before starting treatment from addiction, morning urine sample was collected from each participant into 100 ml sterilized plastic container and centrifuged at 4500 rpm for 5 minutes, and then the clear supernatant was distributed in polyethylene vials (1.5 ml capacity). One vial was used on the same day of urine collection for measuring tramadol (Tr) and cannabis in urine, the rest of vials were stored at $-20^{\circ}C$ without preservatives until analyzed within 2 weeks.

Each urine sample was analyzed for determining the following:

- 1 Urinary tramadol (U.Tr) concentration by immunoanalysis using immunoanalysis EIA kit (immunoanalysis corporation, USA).
- 2 Urinary Δ^9 -THC concentration by DRI[®] cannabinoid assay (Microgenics, USA).
- 3 Urinary NAG and LAP concentration for the assessment of proximal tubular structural integrity by colorimetric method using NAG kit (Diaz-yamelaboratories, USA) and LAP kit (Randox, UK).
- 4 Urinary Cu, Zn, and Ca concentration for assessment of reabsorption integrity of the proximal tubules by Thermo Scientific ICE 3000 Series Atomic Absorption Spectrophotometer, England.
- 5 Urinary creatinine (U. Cr) concentration by Jaffe kinetic method using the kit (Greiner Diagnostic GmbH, Germany).

Statistical Analysis

Data was tabulated as mean \pm SD. ANOVA was used to compare between more than two means of independent groups. In case of parametric data, if ANOVA was statistically significant, Post Hoc test was used to compare between each two means, while Mann-Whitney and Kruskal-Wallis tests were used for nonparametric data. The correlation coefficient was calculated to examine the relation between investigated urinary parameters.

Results were considered statistically significant at $P < 0.05$.

RESULTS

On comparing the three investigated groups using ANOVA, (Table 1) revealed a significant increase ($P < 0.05$) in the urinary excretion of calcium and insignificant differences regarding all others investigated parameters.

In addition, table (2) demonstrated a significant difference ($P < 0.05$) in the urinary calcium excretion in each of the two addicted groups (G_2 and G_3) on comparing each of them with the control group (G_1), as well as on comparing both of them together.

Results of the present work (Table 3) revealed a significant positive correlation between U.LAP/U.Cr and each of U.Zn/U.Cr and U.Ca/U.Cr, and also between U.Cu/U.Cr and U.Zn/U.Cr, as well as between U.NAG/U.Cr and U.Ca/U.Cr.

Data from the table (4) demonstrate a positive correlation between age and addiction duration, and between U.THC/U.Cr and each of U.LAP/U.Cr, U.Cu/U.Cr, U.Zn/U.Cr and U.Ca/U.Cr, as well as between U.NAG/U.Cr and U.LAP/U.Cr, also between U.LAP/U.Cr and each of U.Cu/U.Cr, U.Zn/U.Cr and U.Ca/U.Cr, as well as between U.Cu/U.Cr with both U.Zn/U.Cr and U.Ca/U.Cr, and between U.Zn/U.Cr and U.Ca/U.Cr.

Table (1): Data (Mean \pm SD) of investigated parameters among different studied groups.

parameters	G ₁ (n=19)	G ₂ (n= 18)	G ₃ (n= 28)	P
Age (Years)	23.79 \pm 3.91	28.78 \pm 6.76	26.82 \pm 5.45	$P > 0.05$
Addiction Duration (Years)	----	3.97 \pm 3.97	7.79 \pm 4.70	$P > 0.05$
U.Tr/U.Cr (mg/gm)	----	2629.92 \pm 5381.81	1394.61 \pm 2951.20	$P > 0.05$
U.THC/U.Cr (mg/gm)	----	----	0.18 \pm 0.22	$P > 0.05$
U.NAG/U.Cr (U/gm)	8.93 \pm 6.30	9.85 \pm 8.91	13.09 \pm 14.77	$P > 0.05$
U.LAP/U.Cr (U/gm)	4.70 \pm 2027	4.54 \pm 2.10	8.58 \pm 10.76	$P > 0.05$
U.Cu/U.Cr (μ g/mg)	0.12 \pm 0.08	0.11 \pm 0.07	0.19 \pm 0.30	$P > 0.05$
U.Zn/U.Cr (μ g/mg)	16.97 \pm 7.10	14.72 \pm 4.36	23.22 \pm 37.48	$P > 0.05$
U.Ca/U.Cr (μ g/mg)	39.41 \pm 12.19	70.50 \pm 46.97	84.48 \pm 73.54	$P < 0.05$

N: Number of individuals participated in each investigated group

Table (2): Comparison between different investigated groups regarding urinary calcium excretion.

Studied groups	U. Ca/U. Cr μ g/mg Cr
G ₁ Control group (N= 19) Mean \pm SD	39.41 \pm 12.19
G ₂ Tramadol addicts group (N= 18) Mean \pm SD	70.50 \pm 46.97
P ₁	< 0.05
G ₃ Tramadol coabused with cannabis group (N= 28) Mean \pm SD	84.48 \pm 73.54
P ₂	< 0.05
P ₃	< 0.05

N: Number of individuals participated in each investigated group.

P₁: G₂ compared with G₁.

P₂: G₃ compared with G₁.

P₃: G₃ compared with G₂.

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Table (3): Correlation coefficient (r) between investigated parameters in the tramadol addicted group.

	Age	Addiction duration	Urinary parameters					
			U.Tr/U. Cr mg/gm	U.NAG/U.Cr U/gm	U.LAP/U.Cr U/gm	U.Cu/U.Cr µg/mg	U.Zn/U.Cr µg/mg	U.Ca/U.Cr µg/mg
Age	1	0.260	-0.004	0.016	-0.223	0.009	0.027	0.001
Addiction duration		1	-0.098	0.079	-0.413	-0.98	-0.433	-0.087
U.Tr/U.Cr			1	0.118	0.043	0.311	0.020	0.363
U.NAG/U.Cr				1	0.298	0.119	0.150	0.635**
U.LAP/U.Cr					1	0.442	0.769**	0.519*
U.Cu/U.Cr						1	0.488*	0.174
U.Zn/U.Cr							1	0.298
U.Ca/U.Cr								1

*r is significant as (P < 0.05) **r is highly significant as (P < 0.01).

Table (4): Correlation coefficient (r) between investigated parameters in the tramadol coabused with cannabis addicted group

	Age	Addiction duration	Urinary parameters						
			U.Tr/U. Cr mg/gm	U.THc/U.Cr mg/gm	U.NAG/U.Cr U/gm	U.LAP/U.Cr U/gm	U.Cu/U.Cr µg/mg	U.Zn/U.Cr µg/mg	U.Ca/U.Cr µg/mg
Age	1	0.552**	0.187	0.054	-0.149	-0.189	-0.011	-0.033	-0.152
Addiction duration		1	0.002	-0.126	-0.207	-0.211	-0.072	-0.144	0.039
U.Tr/U. Cr			1	-0.218	-0.207	-0.202	-0.091	0.092	-0.273
U.THc/U.Cr				1	0.211	0.826**	0.754**	0.771**	0.500**
U.NAG/U.Cr					1	0.388*	0.211	0.267	0.120
U.LAP/U.Cr						1	0.633**	0.707**	0.508**
U.Cu/U.Cr							1	0.963**	0.679**
U.Zn/U.Cr								1	0.678**
U.Ca/U.Cr									1

*r is significant as (P < 0.05) **r is highly significant as (P < 0.01).

DISCUSSION

Regarding age, results of the present study (Table 1) showed that the three investigated groups were of comparable age since there was insignificant difference between G₁ and each of G₂ (P₁>0.05) and G₃ (P₂>0.05) as well as between G₂ and G₃ (P₃>0.05), suggesting that age has no effect on the investigated urinary parameters. Concerning the investigated urinary enzymes of structural integrity of the proximal tubules (U.NAG/U.Cr and U.LAP/ U.Cr), data in table (1) demonstrated insignificant difference between the three investigated groups, suggesting that tramadol did not cause a damaging effect on the structural integrity of the proximal tubules, and even co-abuse of *Cannabis* with tramadol addiction has no effect on the structural integrity of the proximal tubules. This suggests that neither tramadol addiction alone nor tramadol co-abused with *Cannabis* affects the structural integrity of the proximal tubules among the investigated addicted individuals in the present study. These findings support the results reported by others (El-Safty *et al.*, 2015).

Regarding the effect of addiction on reabsorption integrity of the nephron for U.Cu/U.Cr and U.Zn/U.Cr as well as U.Ca/U.Cr results in table (1) showed insignificant changes (P₂ > 0.05) in urinary excretion of U.Cu/U.Cr and U.Zn/U.Cr among the three investigated groups, suggesting also that neither tramadol addiction alone nor co-abused with cannabis could affect the reabsorption integrity of the nephron for both Cu and Zn. Also, this suggests that cannabis itself has no effect on

the reabsorption integrity of the nephron for U.Cu/U.Cr and U.Zn/U.Cr.

Concerning the effect of addiction on urinary excretion of U.Ca/U.Cr, results in table (2) revealed a significant increase in U.Ca/U.Cr excretion among tramadol addicted group (G₂) (P₁<0.05) when compared with (G₁), suggesting that tramadol addiction causes reabsorption impairment of the nephron function regarding urinary calcium. This finding and suggestion receive support from the report that opioids cause increased levels of growth hormone and vasopressin (Seyfried and Hester, 2012). It was reported that growth hormone excess such as occurs in acromegaly causes hypercalciuria which appears to be a tubular effect and that vasopressin may increase calcium excretion due to its effect on reducing calcium transport the thick ascending limb (Dirks, 1988). Furthermore, table (2) showed a significant increase in U.Ca/U.Cr excretion among tramadol co-abused with *Cannabis* group (G₃) (P₂ < 0.05) when compared with (G₁), and this excretion was also significantly increased more than the one in tramadol addicted group (G₂) on comparison between (G₃) and (G₂), suggesting that cannabis may have a synergetic effect on the impairment effect of tramadol on reabsorption of calcium along the nephron. This suggestion is supported by results in table (2) which demonstrated a significant increase in U.Ca/U.Cr excretion in tramadol coabused with cannabis group (G₃) (P₂<0.05) when compared with tramadol addicted group (G₂), and the finding of a significant correlation (r = 0.5, P₂ < 0.01) between U.Ca/U.Cr and U.THc/U.Cr

levels in (G³) table (4). Moreover, other investigators (Vupputuri *et al.*, 2004) reported mild kidney function decline among patients who had used marijuana, and others reported that tramadol has negative impacts on kidney function in human (Elmanama *et al.*, 2015) and experimental animals (Atici *et al.*, 2005) as evidenced by an increase in BUN and serum creatinine levels. Other studies reached similar results (Elyazji *et al.*, 2013; Rukhshanda *et al.*, 2014).

Results of the present study (Table 1) showed that the two addicted groups were having different addiction duration, and since the addiction duration in G₃ is longer than in G₂, it could be suggested that the abuser had started addiction with only one drug and after a period of time (that is with increasing age) the abuser started the co-abuse of the second drug. This suggestion is supported by the report of others (Cicero *et al.*, 1999) who found that for the cases of tramadol abuse, 97% of the drug addicts used tramadol in combination with other drugs or they had a previous history of addiction to a substance of co-abuse. In addition, results in table (4) revealed a significant correlation ($r = 0.552$, $P < 0.01$) between age and addiction duration in G₃, thus adding more support to the above suggestion.

Limitation of the study

Absence of cannabis addicted group and the small number of recruited participants are the limitations in the present study.

Conclusion

Among the investigated addicted individuals, neither the addiction of tramadol alone nor in combination with cannabis was found to affect the structural integrity of proximal tubules. Moreover, reabsorption integrity of the nephron is affected only with respect to calcium reabsorption and not with respect to copper and zinc reabsorption. Also, to the best of our knowledge, this is the first study that investigated the effect of addiction of tramadol alone or co-abused with cannabis on the reabsorption integrity of the nephron regarding urinary excretion of copper and zinc as well as calcium.

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تأثير ادمان الترامادول بمفرده بالإضافة الى ادمانه مع القنب على الإخراج البولي للنحاس والزنك والكالسيوم بين المدمنين المصريين

إبراهيم الصفطي^١، السيد التماماني^٢، أحمد شومان^٣، أميمة الجمل^٤، أحمد ندا^٥،
وسام علي^٦

^١ قسم الكيمياء، كلية التربية، جامعة عين شمس، مصر الجديدة، روكسي، القاهرة، مصر
^٢ قسم الكيمياء، كلية العلوم، جامعة قناة السويس، الإسماعيلية، مصر
^٣ قسم خدمة المجتمع وتنمية البيئة، كلية الطب، جامعة عين شمس، القاهرة، مصر
^٤ قسم الأمراض الباطنية، مستشفى الدمرداش، كلية الطب، جامعة عين شمس، القاهرة، مصر
^٥ هيئة الطاقة الذرية، مدينة نصر، القاهرة، مصر

الملخص العربي

تعتبر هذه دراسة مبدئية لبعض المدمنين من المصريين للترامادول والقنب لبيان تأثير إدمان الترامادول على الإخراج البولي لبعض المعادن مثل النحاس والزنك والكالسيوم فيما يتعلق بالسلامة الهيكلية للأنابيب القريبة والتي يتم تقييمها من خلال قياس الإخراج البولي لبعض الإنزيمات. بالإضافة الى ذلك تم توسيع نطاق الدراسة لتقييم تأثير إدمان القنب عندما يتم تواجده مع الترامادول. وقد أظهرت الدراسة أن إدمان الترامادول وحده او بالإشتراك مع القنب لا يؤثر على السلامة الهيكلية للأنابيب القريبة بالإضافة الى ذلك لا تتأثر إعادة الامتصاص للنيرون إلا فيما يتعلق بالكالسيوم، وليس فيما يتعلق بإعادة امتصاص النحاس والزنك. أيضاً هذه الدراسة هي الدراسة الأولى الى أظهرت تأثير إدمان الترامادول وحده أو بالإشتراك مع القنب على إعادة الامتصاص للنيرون بالنسبة للإخراج البولي للنحاس والزنك والكالسيوم.