Mansoura University

Mansoura Journal Of Chemistry

Preliminary Study among Addicted Egyptians on Urinary Assessment of Subclinical Nephrotoxicity of Tramadol Alone and in Combination with Cannabinoid

Ibrahim A. M. El-Safty[1], PhD; Omayma Elgamel (Clin.Pathol.)[2], MD; Ahmed Shouman[3], MD; Gamal Mady[4], MD; Amany Haroon[2], MD; Hesham Sadek[2], MD; Mohamed F. M. El-Ashmawy[5],BSc.

[1]Biochem. Sec., Chem. Dept., Faculty of Education, [2]Institute of Psychiatry, [3]Dept. of Community, Environmental and Occupation Med, [4]Internal Med. and Nephrology Dept., Fac. of Med., Ain Shams University, [5]Chemistry Dept., Faculty of Science, Port-Saed University

Received 31 May 2014; Accepted 25 June 2014.

Key words
Alpha-1-microglobulin; Cannabinoid; Tramadol; Leucine aminopeptidase; N-acetyl-beta-D-glucosaminidase; Nephrotoxicity.

Abstract Experimental animals and human post-mortem studies concerning renal effects of tramadol addiction and cannabinoid abuse showed histopathological changes in the glomeruli and proximal tubules. This study investigates early changes in function and structure of glomeruli and proximal tubules to tramadol addiction alone and in combination with cannabinoid. The study included 72 males (G_1 = 23 controls, G_2 = 21 tramadol addicts and G_3 = 28 tramadol coabused with cannabinoid addicts). The measured urinary parameters were: urinary total protern (U.TP), urinary microalbumin (U.µalb), urinary alpha-1-microglobulin (U.α_1M), urinary leucine aminopeptidase (U.LAP), urinary N-acetyl-β-D-glucosaminidase (U.NAG). Urinary tramadol (U.Tr) was measured in G_2 and G_3, while urinary delta-9-tetrahydrocannabinol (U.THC) was measured in G_3. In G_2, levels of U.TP and U.µalb were decreased while U.α_1M, U.LAP and U.NAG were increased in comparison with G_1. These changes were insignificant. In G_3, all parameters were increased insignificantly when compared with each of G_1 and G_2. In addition, U.THC was significantly correlated with U.α_1M ($r = 0.507$, $P < 0.01$) and U.LAP ($r = 0.888$, $P < 0.01$) in G_3, while U.Tr did not show any correlation with any parameter in G_2 or G_3. Tramadol addiction may affect only proximal tubules, while tramadol addition coabused with cannabinoid may cause glomerular functional impairment and increase the proximal tubular dysfunction than tramadol addition alone. Therefore, the combination of cannabinoid and tramadol may be more nephrotoxic than tramadol alone. This study assessed the subclinical renal effects of tramadol and cannabinoid, and suggests an association of increased excretion of U.LAP and U.α_1M with U.THC and a synergetic effect of cannabinoid to tramadol on kidney.

* Corresponding Author: Prof. Ibrahim A. M. El-Safty.
E-mail: elsafty54@yahoo.com.

Introduction

In Egypt, drug addiction is considered one of the serious problems that worry both people and the government. It affects young people within their productive years. It may lead to many problems such as social maladaptation, decreased work productivity and job loss (El-Akabawi., 2001).

Tramadol hydrochloride was initially developed in the 1970's. It was registered in 1977 in Germany, 1994 in the UK, and 1995 in the US (Grond, et al., 2004). Clinical and experimental studies demonstrated that tramadol did not induce tolerance and dependence on repeated administration (Miranda, et al., 1998 and Kitahara, et al., 2009). On the other hand, results of other studies suggest that tramadol may have abuse liability under some conditions or in certain populations (Jjaderborn, et al., 2009 and Lanier, et al., 2010). Post-marketing surveillance studies consistently showed that the abuse and diversion of tramadol was relatively low (Knisely, et al., 2002). However, a significant finding was 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 substance of abuse (Cicero, et al., 1999), implying that the abuse liability of tramadol might be ignored in poly-drug abuser population (Degenhardt, et al., 2006). Another epidemiological surveys demonstrated that tramadol was very popular in the drug abuse population, which was often used as a substitutive for heroin and other opioids, or combined with other drugs to achieve certain desired effects, or to avoid some undesired effects (Li, et al., 2011 and Liu, et al., 2011), indicating that tramadol may have a higher abuse liability when co-abused with other opioids even though the abuse potential of tramadol itself is relatively low.

In humans body, tramadol undergoes extensive and complex metabolism in the liver via cytochrome P450 system, with 23 metabolites identified: 11 phase I identified and 12 phase II conjugates (Wu. et al., 2002). Thirty per cent of the tramadol is excreted through the kidneys unmetabolised, while the remaining is metabolised by O-and N-demethylation, followed by conjugation with glucuronic acid and sulphates (Gutustein, et al., 2001 and Leppert, et al., 2011).

Bango is the name of cannabis leaves used in Egypt and North Africa. There has been noticeable increase in consumption of cannabis and its products among teenagers and adults (Guxens, et al., 2007). The crude drug derived from the plant *cannabis sativa* is called marijuana which contains more than 400 compounds, of which 66 are defined as cannabinoids (El-Sohly., 2002) based on their typical 21-carbon structure. Among the 66 different cannabinoids, delta-9-tetrahydrocannabinol (THC) was described as the principle highly psychoactive constituent (Pertwee., 2008).

Cannabis use, despite being the most wide-spread of the illicit substances, caused very few deaths due to its low toxicity. Six deaths due to acute cardiac problems (Bachs, et al., 2001), and several reports of renal infarctions associated with cannabis addiction (Lambrecht, et al., 1995 and LeGuen, et al., 2011) have been described.

Cannabinoids are metabolized rapidly in the liver by cytochrome P450 system. Approximately 80 metabolites of THC have been reported (Agurell, et al, 1986). Only negligible amounts of THC are excreted as unchanged drug (Wall, et al., 1983).

Metabolites of the drugs that are excreted from kidneys may cause cellular damage leading to kidney dysfunction. Various urinary parameters of the kidney such as microalbumin (μalb) and alpha-1-microglobulin (α_1M) were proved useful to assess functional integrity of glomeruli and proximal tubules respectively, whereas urinary kidney-specific enzymes such as brush-border leucine-aminopeptidase (LAP) and lysosomal N-acetyl-β-D-glucosaminidase (NAG) are indicators for structural integrity of proximal tubules (Mueller, et al., 1997).

The present work is a preliminary study to investigate the effect of tramadol addiction among Egyptian drug addicts on some aspects of glomerular and proximal tubular functions as

well as structural integrity of proximal tubules by measuring urinary kidney parameters as indicators of early alterations of the kidney normal function. In addition, the study is extended to evaluate the effect of cannabinoid addiction when it is co-abused with tramadol .

Subjects and Methods

A) Subjects

Male drug addicted participated in the present study were recruited on voluntary bases from those attended the out-patient clinic, Institute of Psychiatry, Ain-Shams University, for treatment of drug addiction. All participants were subjected to interview using a questionnaire designed to obtain information on 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. The drug addicts were excluded from the present study if they had :

1. A history of kidney disease or any disease likely to impair renal function or affect the urinary excretion of the investigated parameters (e. g. diabetes mellitus, hypertension, urinary tract disease).
2. A previous or present exposure to agents capable of damaging the kidney (heavy metals such as lead, cadmium and other nephrotoxins such as organic solvents).
3. Regular and prolonged treatment by drugs affecting the kidney (e. g. aminoglycosides).
4. A urinalysis which revealed 2 plus or greater proteinuria.
5. Dental mercury amalgam fillings as it may affect the kidney.

72 Males were then included in the study. The tramadol addicts group (G_2) was comprised of 21 males (age: 18 - 40 years, mean ± SD: 28.71 ± 6.64, addiction duration: 6 months – 17 years, mean ± SD: 4.41 ± 4.12), and tramadol co-abused with cannabinoid addicts group (G_3) was comprised of 28 males (age: 16 - 40 years, means ± SD: 26.82 ± 5.45, addiction duration: 3 - 20 years, mean ± SD: 7.86 ± 4.83). Another 23 healthy non-addicted males (G_1) (age: 19-38 years, mean ± SD: 25.44 ± 5.25) were recruited from relatives of the addicted participants after applying the same exclusion criteria and clinical examination .

B) Biological Sampling and Methods

Morning urine sample was suggested as the best sample for detecting early kidney abnormalities (Zuppi, et al., 1995). Spot morning urine sample was collected by each participant who was instructed to void the urine sample directly 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 the urine was collected for measuring tramadol and THC using Immunalysis Tramadol EIA kit (Immunalysis Corporation, USA), DRI® Cannabinoid assay kit (Microgenics, USA), respectively, and the instrument Biolis 24i Premium (Tokyo Boeki Medical System, Japan). According to the manufacturer of the kits, both methods have 100% correlation with GC/MS when 200 ng/ml and 50 ng/ml cutoff calibrator are used, respectively. The rest of the vials were stored at -20^{0}C without preservatives until analyzed within 2 weeks for the assessment of :

1. Glomerular function by measuring urinary total protein (U.TP) using dye-binding method kit (Stanbio Laboratory, USA), and urinary microalbumin (U.µalb) using ELISA method kit (Orgentec Diagnostika GmbH, Germany.
2. Tubular function by measuring urinary alpha-1-microglobulin (U.α_1M) using ELISA method kit (Assaypro, USA).
3. Tubular structural integrity by measuring urinary activities of Leucine-aminopeptidase (U.LAP) using kit from Randox (UK) and N-acetyl-β-D-glucosaminidase (U.NAG) using kit from Diazyme (USA).

4. Urinary creatinine concentration (U.Cr) using kit from Greiner Diagnostic GmbH (Germany).

Spot urine measurements were used because it has been shown that urinary protein/creatinine ratio (Lemann, et al., 1987) and albumin/creatinine ratio (Woolerton, et al., 1987 as well as enzyme activity/creatinine (Jung, et al., 1991) in a random urine sample correlate with 24-hour urinary excretion and eliminate variations caused by changing rates of urine output and provide a measure independent of urine concentration.

C) Statistical Analysis

Data were presented as mean ± SD. Student t-test and ANOVA were used to compare between the means of parametric data, while Mann-Whitney test and Kruskall-Wallis were used for non-parametric data. Correlation coefficient (r) was calculated to test the association between two quantitative variables. P-values < 0.05 were considered statistically significant. SPSS version 16.0 was used.

Results and Discussion

Among G_1, data of the present study (Table 1) showed a positive correlation between age and each of U.LAP (r= 0.492. P= 0.017) and U.α_1M (r= 0.521, P= 0.011). Also, regarding the age, the present results (Table 2) showed insignificant difference (P > 0.05) between G_1 and each of G_2 and G_3. Urinary parameters of glomerular function were decreased in G_2 as compared to G_1 while function and structure of proximal tubules was increased (Table 2). These changes were statistically insignificant (P > 0.05). The results (in Table 2) revealed insignificant increase (P > 0.05) in the urinary parameters among subjects in G_3 as compared to G_1 or G_2. Furthermore, there was a significant correlation between U.THC/U.Cr and each of U.α_1M/U.Cr and U.LAP/U.Cr in G_3, while U.Tr/U.Cr showed no correlation with any of the measured urinary parameters in G_2 or G_3 (Table 3).

Table 1 Correlation Coefficient (r) between age and urinary parameters of G_1.

	U.TP/U.Cr	U.µalb/U.Cr	U.NAG/U Cr	U.LAP/U Cr	U.α_1M/U.Cr
Age	0.185	-0.149	0.057	0.492*	0.521*

*r is statistically significant as P < 0.05.

Table 2 Comparison (Mean ± SD) between variables of the different studied groups**:-**

Parameter	**G_1**	**G_2**	**G_3**	**P**
	(N=23)	**(N=21)**	**(N=28)**	
A) Age (years)	25.44 ± 5.25	28.71 ± 6.64	26.82 ± 5.45	> 0.05
B) Glomerular Functional integrity				
U.TP/U.Cr (mg/mg cr)	98.59 ± 84.66	80.65 ± 70.18	124.50 ± 155.88	> 0.05
U.µalb/U.Cr (µg/mg cr)	17.85 ± 19.16	11.38 ± 8.11	22.21 ± 40.72	> 0.05
C) Tubular Functional integrity				
U.α_1M/U.Cr (µg/ mg cr)	7.70 ± 5.18	10.42 ± 11.89	10.94 ± 12.00	> 0.05
D) Tubular Structural integrity				

U.NAG/U.Cr (U/mg cr)	9.15 ± 6.21	11.35 ± 9.57	13.10 ± 14.76	> 0.05
U.LAP/U.Cr (U/mg cr)	5.52 ± 3.68	7.45 ± 14.03	9.65 ± 14.76	> 0.05

N (Number of volunteer).

Table 3 Correlation coefficient (r) between different urinary parameters and levels of Urinary tramadol and THC among the two addicted groups:-

Uninary parameter	**G_2**	**G_3**	
	U.Tr/U.Cr	**U.Tr/U.Cr**	**U.THC/U.Cr**
U.TP/U.Cr	-0.121	-0.157	0.360
U.μalb/U.Cr	-0.124	-0.154	-0.185
U.NAG/U.Cr	0.104	-0.208	0.211
U.LAP/U.Cr	0.095	-0.178	0.888**
U.α_1M/U.Cr	-0.252	-0.239	0.507**

** r is statistically significant as $P < 0.01$.
U. Tr/U. Cr (Urinary Tramadol urinary creatinine ratio).
U.TP/U.Cr (Urinary total protein urinary creatinine ratio).
U.μalb/U.Cr (Urinary microalbumin urinary creatinine ratio).
U.α_1m/U.Cr (Urinary alpha-1-microglobulin urinary creatinine ratio).
U.LAP/U.Cr (Urinary Leucine-aminopeptidase urinary creatinine ratio).
U.THC/U.Cr (Urinary delta-9-tetrahydrocannabinol urinary creatinine ratio).
U.NAG/U.Cr (Urinary N-acetyl-β-D-glucosaminidase urinary creatinine ratio).
G_1 (Controls group), G_2 (Tramadol addicts group), G_3 (Tramadol coabused with cannabinoid addicts group).

Results of the present study (Tables 1 and 2) demonstrated that structural and functional integrity of proximal tubules are deteriorated with age, supporting the report that structural and physiological changes in the kidney are associated with aging (Musso, et al., 2011), and that G_1 matched with both G_2 and G_3 to avoid the effect of age on the measured urinary parameters. Substances with the potential to be abused may have direct or indirect effects on physiologic mechanisms that lead to organ system dysfunction and disease. A multitude of renal diseases are associated with drug abuse because of many different substances used with widely varying pharmacologic effects. Such drugs have been associated with several renal syndromes by varied mechanisms (Kimme, et al., 2001).

Results of the present study (Table 2) for the effect of tramadol addiction on glomerular function showed insignificant decrease in U.TP and U.µalb in G_2 as compared to G_1, suggesting no glomerular damage. This result is an accordance with finding of other investigators who reported that no histological changes in the glomeruli were observed in experimental rats given tramadol intraperitoneally at doses of 20, 40 and 80 mg/kg/day in the first, second and the third ten days of the study, respectively (Atici, et al., 2005).

It was reported that THC is the principle constituent of cannabinoid (Pertwee, et al., 2008), and the concentration of THC from autopsy tissues (liver, kidney, spleen, stomach and intestine) was highest in the kidney followed by the liver (Tewari, et al., 1980).

Subjects used cannabinoid in combination with tramadol showed increased levels of U.TP and U.µalb in G_3, and this may be due to increase glomerular filteration of these substances in comparison with G_1 and G_2, but the difference of this increase was statistically insignificant (Table 2). This suggestion is supported by the report that heavy marijuana use caused membranous glomerulonephritis (MGN) due to granular deposits of immunoglobulin G (IgG) and C9 along the outer surface of the capillary wall in all glomeruli (Bohatyrewicz, et al., 2007). Also, other investigator s showed that histopathological examination of kidney tissues of experimental animals given the extract of cannabis leaves showed destruction of some of the renal corpuscles which are formed of a glomerulus and Bowman's capsule (Yassa, et al., 2010).

Although total protein in urine provides information of severity of proteinuria, it is protein type that renders a more specific picture of protein composition of urine. Data of the present study (Table 2) for the effect of tramadol addiction on proximal tubular function showed an increase in the urinary excretion of α_1M in G_2, suggesting impairment in renal proximal tubular reabsorption function, but the increased level was insignificant when compared with G_1. This suggestion is supported by other investigators who reported a histopathological changes in renal tubules due to tramadol alone in animal experiments (Atici, et al., 2005) and in human post-mortem microscopy examination of a young patient who died of fatal tramadol intoxicaton due to acute tubular necrosis of the kidney (DeDecker, et al., 2008).

Regarding the effect of cannabinoid use in combination with tramadol addiction on tubular function, data of the present study (Table 2) showed an increase in urinary excretion of α_1M in G_3 more than in G_2, suggesting an increase in impairment of reabsorption capacity of proximal tubules due to cannabinoid use, but the increase of U.α_1M in G_3 was insignificant when compared with each of G_1 and G_2. This suggestion is supported by the results of the present study (Table 3) which showed a positive correlation between U.THC and U.α_1M ($r = 0.507$, $P = 0.006$) in G_3. This suggestion is also supported by a report that all of the pathological findings among 101 addicts (opiates 18, barbiturates 9, benzodiazepines 22, methaqualone 10, cannabis 42) pointed to tubular damage in the proximal region, and they concluded with high probability that tubular dysfunction is frequent in addicts (Sommer, et al., 1985). Moreover, a reported showed that histopathological examination of kidney tissues from experimental animals given the extract of cannabis leaves demonstrated congestion of the peritubular blood vessels and dilated as well as swollen tubules (Yassa et al., 2010).

Many enzymes have been detected in urine and a few appear to possess diagnostic relevance in recognition of renal injury. Choice of investigated urinary enzymes in this study was made on the basis of site specificity.

Data of the present study (Table 2) for the effect of tramadol addiction on the tubular structure showed an increase in the U.NAG and U.LAP excretion, but the increase was insignificant when compared with G_1. The increased leakage of enzymes characteristic of these cells results from tubular damage, suggesting the possibility of a nephrotoxic effect of tramadol addiction. This suggestion is supported by other studies elsewhere that revealed proximal tubular histopathological effect due to tramadol alone in human post-mortem (DeDecker, et al., 2008) and experimental studies in animals (Atici, et al., 2005).

Results of the present study (Table 2) concerning the effect of cannabinoid use in combination with tramadol addiction on tubular structure showed an increased excretion of U.LAP and U.NAG in G_3 more than in G_2, suggesting the possibility of more damage to proximal tubules in G_3 due to cannabinoid. The increased in U.LAP and U.NAG levels in G_3 were insignificant when compared with those in G_1 and G_2. This suggestion is supported by the results of the present study (Table 3) which showed a positive correlation between U.THC and U.LAP in G_3 and report of renal biopsy that heavy marijuana use caused an acute tubular necrosis (DeDecker, et al., 2008).

The effects of cannabis depend upon the dose received, the mode of administration, the user's prior experience with cannabis, any concurrent drug use, the user's expectations, attitudes towards the effect of cannabis, their mood state and the social setting in which it is used (MacPhee, et al., 1999).

Albumin is the major plasma protein, and protein uptake is via a constitutive reabsorption pathway in the proximal tubule cells (Christensen, et al., 2007**).** The structural and functional changes to the proximal tubule cells are a key contributing factor to the development of excessive albumin loss in urine (albuminuria). Albumin present in the urine is often the first indicator of glomerular damage (Thrailkill, et al., 2009) and a decline in renal function.

Limitation of our study is that the number of participants classified as addicted was quite small. It was reported that both younger age and high doses were identified as risk factors for addiction (Edlund, et al., 2007 and Wasan, et al., 2007) and therefore the addicted out patients might have been reluctant to participate in the study realizing that they had addiction problems .

Conclusions

Tramadol addiction may affect only the function and structure of proximal tubules, although U.Tr level showed no correlation with any of the measured urinary parameters of proximal tubules. Cannabinoid use in combination with tramadol addiction may cause glomerular damage and increase the proximal tubular dysfunction which caused by tramadol addiction and this may be due to the synergetic effect of cannabinoid to tramadol. Therefore, another group of cannabis alone should be included to best analyze more accurately the synergistic effect of tramadol and cannabis. Also, the effect of longer addiction duration on the function and structure of both the glomeruli and proximal tubules needs further study.

Acknowledgement

The corresponding author Prof. IAM El-Safty would like to acknowledge the financial support provided by Ain-Shams University, Dr. Haytham Hassan and Dr. Rehab Naguib for drafting the questionnaire and physical examination as well as interviewing the participants.

References

Agurell S, Halldin M, Lindgren JE, Ohlsson A , Widman M , Gillespie H. **1986**. Pharmacokinetics and metabolism of delta-1-tetrahydrocannabinoids with emphasis on man. Pharmacol Rev; 38: 21-43.

Atici S, Cinel I, Cinel L, Doruk N , Eskandari G , Oral U. **2005**. Liver and kidney toxicity in chronic use of opioids: An experimental long term treatment model. J Biosci; 30: 245-252.

Bachs L, Morland H. **2001**. Acute cardiovascular fatalities following cannabis use. Forensic Sci Int; 124: 200-203.

Bohatyrewicz M, Urasinska E, Rozanski J, Ciechanowski K. **2007**. Membranous glomerulonephritis may be associated with heavy marijuana abuse. Transplant Proc; 39: 3054-3056.

Christensen E, Birn H, Rippe B, Maunsbach AB. **2007**. Controversies in nephrology: renal albumin handling, facts, and artifacts! Kidney Int; 72: 1192-1194.

Cicero TJ, Adams EH, Geller A, Inciardi JA , Munoz A , Schnoll SH , et al. **1999**. A post-marketing surveillance program to monitor Ultram (tramadol hydrochloride) abuse in the United States. Drug Alcohol Depend; 57: 7-22.

DeDecker K, Cordonnier J, Jacobs W, Coucke V , Schepens P , Jorens PG. **2008**. Fatal intoxication due to tramadol alone: case report and review of the literature. Forensic Sci Int; 175: 79-82.

Degenhardt L, Black E, Breen C, Bruno R, Kinner S, Roxburgh A, et al. **2006**.Trends in morphine prescriptions, illicit morphine use and associated harms among regular injecting drug users in Australia. Drug Alcohol Rev; 25:403-412.

Edlund MJ, Steffick D, Hudson T, Harris KM, Sullivan M. **2007**. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain;129: 355-362.

El-Akabawi AS. **2001**. Drug abuse in the arab world: a country profile of Egypt. In: Okasha A and Maj M, editors. Images in Psychiatry-An Arab Perspective. World Psychiatric Association Series. p. 143-150.

El-Sohly M. **2002**. Chemical constituents of cannabis. In: Grotenhermen F and Russo E, editors. Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential. Binghamton, NY: The Haworth Press In;. p. 27-36.

Grond S, Sablotzki A. **2004**. Clinical pharmacology of tramadol. Clin Pharmacokinet; 43: 879-923.

Gutustein HB and Akil H. **2001**. Opioid analgesics. In: Hardman JG and Linobird LE, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. New York: McGraw-Hill;. 10th ed. p. 569-620.

Guxens M, Nebot M, Ariza C, Ochoa D. **2007**. Factors associated with the onset of cannabis use: a systematic review of cohort studies. Gac Saint; 21: 252-260.

Jjaderborn M, Jonsson AK, Ahlner J, Hagg S. **2009**. Tramadol dependence: a survey of spontaneously repeated cases in Sweeden. Pharmacoepidemiol Drug Saf; 18: 1192-1198.

Jung K. **1991**. Enzyme activities in urine. How should we express their excretion? Eur J Clin Chem Clin Biochem; 29: 725-729.

Kimmel PL, Alam S, Lew SQ. **2001**. Renal disease in patients with substance abuse. In: Schena FP editor. Nephrology. London: McGraw-Hill;. p. 237-243.

Kitahara M, Kojima K, Hanada M, Kuriyama Y, Ohmura A. **2009**. Effectiveness of oral tramadol hydrochloride for chronic non-malignant pain. Masui; 58: 971-975.

Knisely JS, Campbell ED, Dawson KS, Schnoll SH. **2002**. Tramadol post-marketing surveillance in Health care professionals. Drug Alcohol Depend; 68: 15-22.

Lambrecht GL, Malbrain ML, Coremans P, Verbist L, Verhaegen H. **1995**. Acute renal infarction and heavy marijuana smoking. Nephron; 70: 494-496.

Lanier RK, Lofwall MR, Mintzer MZ, Bigelow GE, Strain EC. **2010**. Physical dependence potential of daily tramadol dosing in humans. Psychopharmacology; 211: 457-466.

LeGuen PY, Gestin S, Plat E, Quehe P , Bressollette L. **2011**. Renal and spleen infarction after massive consumption of cannabis and cocaine in a young man. J Mal Vas; 36: 41-44 (article in French).

Lemann J Jr, Dowmans BT. **1987**. Proteinuria in health and disease assessed by measuring the urinary protein/ creatinine ratio. Clin Chem; 33: 297-9.

Leppert W, Mikolajczak P. **2011**. Analgesic effects and assays of controlled-release tramadol and O-desmethyltramadol in cancer patients with pain. Curr Pharmaceut Biotechnol; 12: 306-12.

Li C, Chen HF. **2011**. 1158 cases report of heroin dependence. Med J Chinese People's Health; 23: 595-6.

Liu CJ, Qi L, Yang J. **2011**. Survey of tramadol addiction in drug treatment agencies in Ningxia

province. J Ningxia Medical University, 33: 67-9.

MacPhee D. **1999**. Effects of marijuana on cell nuclei: a review of the literature relating to the genotoxicity of cannabis. In: Kalant H, Corrigal W, Hall W, Smart R, editors. The health effects of cannabis. Toronto Center for Addiction and Mental Health. 1st edn. p. 293-300.

Miranda HF, Pinardi G. **1998**. Antinociception, tolerance and physical dependence comparison between morphine and tramadol. Pharmacol Biochem Behav; 61: 357-360.

Mueller PW, Lash LH, Price RG, Stolte H, Gelpi E , Maack T. **1997**. Urinary biomarkers to detect significant effects of environmental and occupational exposure to nephrotoxins. I. case of cannabis poisoning. Toxicol Lett; 5: 279-281.

Thrailkill KM, Nimmo T, Bunn RC, Cockrell GE, Moreau CS, Mackintosh S, et al. **2009**. Microalbuminuria in type I diabetes is associated with enhanced excretion of the endocytic multiligand receptors megalin and cubilin. Diabetes Care; 32: 1266-1268.

Wall ME, Sadler BM, Brine D, Harold T, Perez-Reyes M. **1983**. Metabolism, disposition, and kinetics of delta-9-tetrahydrocannabinol in men and women. Clin Pharmacol Ther; 34: 352-363.

Wasan AD, Butler SF, Budman SH, Benoit C, Fernandez K, Jamison RN. **2007**. Psychiatric history and psychologic adjustment as risk factors for aberrant drug-related behavior among patients with chronic pain. Clin J Pain; 23(4):307-15.

Categories of tests for detecting effects of nephrotoxins. Ren Fail; 19: 505-521.

Musso CG, Oreopoulos DG. **2011**. Aging and physiological changes of the kidneys including changes in glomerular filtration rate. Nephron Physiol; 119 (Suppl. 1): 1-5.

Pertwee RG. **2008**. Ligands that target cannabinoid receptors in the brain: from THC to anandamide and beyond. Addict Biol; 13: 147-159.

Sommer GL, Schmid R, Lubec G. **1985**. Drug addicts and renal lesions. Drug Alcohol Depend; 16: 287-9.

Tewari SN, Sharma JD. 1980. Detecton of delata-9-tetrahydrocannabinol in the organs of a suspected

Woolerton J, Jury DR, Dunn PJ, Speed JF. **1987**. Urine albumin/creatinine ratio and clinical correlates in a diabetic population. NZ Med J; 100: 130-4.

Wu WN, McKnown LA, Liao S. **2002**. Metabolism of the analgesic drug ULTRAM (tramadol hydrochloride) in human: API-MS and MS/ MS characterization of metabolites. Xenobiotica; 32: 411-425.

Yassa HA, Dawood AA, Shehata MM, Abdel-Hady RH, Abdel-Aal KM. **2010**. Subchronic toxicity of cannabis leaves on male albino rats. Hum Exp Toxicol; 29: 37-47.

Zuppi C, Baroni S, Scribano D, DiSalvo S, Musumeci V. **1995**. Choice of the time for urine collection for detecting early kidney abnormalities in hypertensives. Annals Chin Biochem; 32: 373-8.

دراسة أولية بين مدمنين مصريين علي التقييم البولي للتسمم الكلوي قبل الأكلينيكي للترامادول منفرداً واتحاده مع القنب

أبراهيم الصفتي[١] ، أميمة الجمل[٢] ، أحمد شومان[٣] ، جمال ماضي[٤] ، أماني هارون[٢] ، هشام صادق[٢]، محمد العشماوي.[٥]

[١]قسم الكيمياء كلية التربية، [٢]مركز الأدمان والأمراض النفسية، [٣]قسم طب المجتمع والبيئة وطب الصناعات، [٤]قسم الباطنة وأمراض الكلي كلية الطب جامعة عين شمس، [٥]قسم الكيمياء كلية العلوم جامعة بورسعيد.

أظهرت حيوانات التجارب ودراسات ما بعد وفاة الإنسان لتأثيرات الترامادول والقنب علي وظائف الكُلي وجود تغييرات هستوباثولوجية في الكُبيبات الكلوية وكذلك الأنابيب الملتفة التالية لهذه الكُبيبات. وتهدف هذه الدراسة إلي دراسة التأثير المبكر لإدمان الترامادول منفرداً ومتحداً مع أدمان القنب علي وظيفة وتركيب الأجزاء الكلوية السابق ذكرها.

وقد شملت الدراسة ٧٢ فردا من الذكور تم تقسيمهم كالآتي : المجموعة الضابطة (G_1) وتتكون من ٢٣ فرداً لم يتعاطوا أي من الترامادول أو القنب والمجموعة (G_2) وتتكون من ٢١ فرداً من مدمني الترامادول والمجموعة (G_3) وتتكون من ٢٨ فرداً من مدمني الترامادول بالإضافة إلي إدمان القنب.

تم جمع عينات البول من المشاركين لقياس المؤشرات البولية الآتية في كل عينة : البروتين الكلي (U.TP)، الميكروألبومين (U.μalb)، ألفا -١- ميكروجلوبيولين (U.α_1M)، ليوسين أمينوبيتيديز (U.LAP)، إن – أسيتيل – بيتا – دي – جلوكوزآمينيديز (U.NAG). كذلك تم قياس تركيز الترامادول بالبول (U.Tr) في عينات (G_2) و (G_3) ومستوي دلتا-٩-تتراهيدروكانابينول (U.THC) بالبول في عينات (G_3).

وقد أظهرت النتائج أن مستويات (U.α_1M)، (U.LAP) و (U.NAG) في (G_2) أعلي من مثيلاتها في (G_1) ولكن الفرق بينهم لم يكن ذو دلالة إحصائية. كذلك وجد أن مستوي المؤشرات البولية في (G_3) أعلي من مثيلاتها في (G_1) و (G_2) وكانت الفروق أيضاً غير ذات دلالة إحصائية. كذلك أظهرت النتائج وجود ارتباط ذات دلالة إحصائية بين المستوي البولي لـ (U.THC) والمستوي البولي لكلاً من (U.α_1M) و (U.LAP) في (G_3) بينما لا يوجد مثل هذا الارتباط بين المستوي البولي لـ (U.Tr) وأي من المؤشرات البولية في (G_2) و (G_3).

ولذلك فإن إدمان الترامادول قد يؤثر فقط علي الأنابيب الملتفة التالية للكبيبات بينما إدمان الترامادول مع إدمان القنب قد يسبب خلل وظيفي للكبيبات مع زيادة الخلل الوظيفي للأنابيب الملتفة التالية للكبيبات عما يسببه إدمان الترامادول فقط. وبالتالي فإن الجمع بين الترامادول والقنب قد يكون أكثر سّمية علي الكُلي من الترامادول فقط. وهذه الدراسة تقييم للتأثير الكلوي قبل الإكلينيكي للترامادول والقنب وتشير إلي وجود ارتباط بين زيادة الإفراز البولي لكل من (U.α_1M) و (U.LAP) مع (U.THC) وكذلك تقترح وجود تآزر من القنب للترامادول.