SOCIO-DEMOGRAPHIC PATTERN OF TRAMADOL INTOXICATED PATIENTS AND THE CORRELATION BETWEEN HEPATO-RENAL BIOMARKER LEVELS WITH THE INGESTED DOSES AND LAG TIMES: A PROSPECTIVE CONTROLLED STUDY AT BENHA POISON CONTROL UNIT, QALYUBIA, EGYPT

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ABSTRACT

Tramadol, a synthetic opioid derivative of codeine, is an extensively prescribed analgesic as it is considered a safe and effective drug. However, tramadol poisoning is increasingly reported and becoming a serious health problem worldwide, including Egypt. Despite this, the likelihood of tramadol-induced hepato-renal complications is infrequently studied. This prospective study was conducted over a six-month (January-June-2015) to describe socio-demographic and drug exposure patterns beside assessment of hepato-renal functions (AST = aspartate amino transferase, ALT = alanine amino transferase, ALP = alkaline phosphatase, TBL = total bilirubin, BUN = blood urea nitrogen, and CRE = creatinine) among tramadol poisoned patients who were admitted to Benha Poison Control Unit, Qalyubia, Egypt. Ninety-five patients in tramadol-intoxicated group (TI-GP) and twenty-five volunteers in the healthy-control group (HC-GP) fulfilled the inclusion criteria. For poisoning severity, clinical picture of the patients were categorized into group-I (G-I; mild), group-II (G-II; moderate), and group-III (G-III; severe). Most patients experienced minor clinical manifestations and listed in G-I. In TI-GP, the majority of cases were males (73; 76.84%) in the third decade of life with a mean age of 28.06±0.85-year, unmarried (45; 47.37%), urban residents (68; 71.58%) with sufficient financial resources (72; 75.79%), highly educated (61; 64.21%), and unemployed (39; 41.05%), whereas, the drug exposure data featured predominance of home incidence (77; 81.05), oral route only (95; 100%), accidental manner (82; 86.32%) with abusive history (71; 74.74%), a mean ingested dose of 1258.68±57.71-mg, and a mean lag time of 6.57±0.56-hour. The mean ingested dose and lag time estimates of G-III demonstrated significant increases as compared to TI-GP, G-I, and G-II. All hepato-renal biomarkers of TI-GP, some in G-I (ALP, TBL, and CRE), G-II, and G-III showed significant elevations compared to HC-GP. Additionally, all biomarker levels (except TBL; insignificant) of G-I as well as some variables of G-II (AST, ALP, BUN, and CRE) and G-III (ALT, ALP, TBL, and CRE) were significantly decreased and increased, respectively, when compared with TI-GP. Whereas, all biomarker levels of G-II (except TBL; insignificant) and G-III demonstrated significant rises as matching G-I and dissimilar statistical results when compared with each other (significant rise of AST in G-II and ALT in G-III). All biomarkers showed positive correlation with the alleged ingested doses and lag times. Tramadol wide popularity, high consumption prevalence, and poisoning incidences, particularly among young Egyptian adults, is potentially growing socially

hazardous phenomenon that has detrimental effects on hepato-renal functions in a dose-and time-dependent manner and should be considered during patients' monitoring in overdosed situations for early detection of subclinical or serious organs damage.

INTRODUCTION

Tramadol hydrochloride, an atypical synthetic opioid member of the aminocyclohexanol group, is a centrally acting analgesic compound that was initially synthesized in 1962 and marketed in Germen since 1977 **(Marquardt et al., 2005; De Decker et al., 2008; Leppert, 2009)** and has been launched in Egypt since 1995 **(Fawzi, 2011).** Tramadol produces its antinociceptive effects by acting as a weak μ-opioid receptor agonist in addition to blocking of norepinephrine and serotonin reuptake at spinal and supraspinal neurons **(Grond and Sablotzki, 2004; Leppert, 2009).**

It is globally sold and extensively prescribed in clinical practice to manage moderate to severe pain associated with various acute or chronic conditions such as surgical operations, cancer, osteoarthritis, polyneuropathy, and diabetic neuropathy **(Klotz, 2003; Grond and Sablotzki, 2004)** and its recommended therapeutic daily doses ranged from 50 to 100 mg every 4-6-hour (maximum 400 mg/day) **(Grond and Sablotzki, 2004; Jovanović-Cupić et al., 2006)**. In Egypt, the wide range of tramadol consumption has been contributed greatly to its popularity as a remedy to obviate rapid ejaculation, prolong intercourse duration, and augment sexual enjoyment, especially among youth and middle aged people **(Salem et al., 2008).**

It is considered a safe drug devoid of many serious hazards of traditional opioids **(Elkalioubie et al., 2011)** and the most common adverse events seen with intentional or unintentional tramadol exposure are drowsiness, nausea, vomiting, restlessness, headache, constipation **(Marquardt et al., 2005)**, seizures **(Talaie et al., 2009; Farajidana et al., 2012),** and minimal respiratory depression **(Elkalioubie et al., 2011; Hassanian-Moghaddam et al., 2013).** Nevertheless, enormous availability and utilization of tramadol has been accompanied by significant increases in its overdose and poisoning worldwide that account for many rare, life-threatening complications including loss of consciousness, recurrent seizures, serotonin syndrome, refractory shock, cardiovascular failure, and even death **(Marquardt et al., 2005; Daubin et al., 2007; De Decker et al., 2008; Shadnia et al., 2008; Tashakori and Afshari, 2010; Farajidana et al., 2012; Shadnia et al., 2012; Rahimi et al., 2014).** Also, tramadol toxicity is of great interest in Egypt **(Ezzeldin et al., 2014; Ghoneim et al., 2014; Mohamed et al., 2015)** and there are also growing distressing clinical evidences of tramadol related abuse **(Fawzi, 2011; Abbas et al., 2013; Loffredo et al., 2015)** and intoxication **(El Masry and Tawfik, 2013; Fouad et al., 2015)**, which may lead to many health and social problematic consequences among the Egyptian people **(Fawzi, 2011; Bassiony et al., 2015)**.

Information regarding the hazardous effect of tramadol on human liver and kidney functions is scarce and variable. Ortho-McNeil

Pharmaceuticals, Inc. **(Ortho-McNeil Inc, 2008; Ortho-McNeil-Janssen Inc, 2014),** the manufacturer of Ultram©, Tramadol Hydrochloride, has listed hepatitis, liver failure, elevated liver enzymes, and creatinine increase as possible adverse events in the enclosed pamphlet of regular tramadol and indexed hepato-biliary disorders such as cholelithiasis and cholecystitis in the product datasheet of extended release tablets. Few studies showed variable effects of tramadol on hepato-renal functions. Significant and insignificant changes of enzymes were respectively recorded in 65 and 137 Egyptian patients suffering from tramadol poisoning **(Fouad et al., 2015)** and significant elevation of the total bilirubin level only was also documented by **Rahimi et al. (2014)**. In like manner, tramadol was responsible for the incidence of acute renal failure in many cases **(Afshari et al., 2008; Afshari R and Ghooshkhanehee, 2009)**. Similarly, organ dysfunctions have been reported in several patients received other opioid substances structurally related to tramadol like morphine **(Glare et al., 2002)**, dextropropoxyphene **(Gaubert et al., 2009)**, or buprenorphine **(Zuin et al., 2009)**.

Based on these findings, the present study was designed to identify the socio-demographic and drug exposure characteristics beside assessment of the hepato-renal functions and correlate these biochemical parameters with alleged doses taken and lag times among acute tramadol poisoned patients only.

SUBJECTS & METHODS:

This prospective controlled study was carried out over a period of 6 months from the 1st of January to 31th June, 2015 at Benha poison control unit (BPCU), Benha University Hospitals, Qalyubia, Egypt, after approval from the research ethics committee of Benha Faculty of Medicine, Benha University, Egypt. All selected patients with acute tramadol ingestion only that fulfilled the inclusion criteria as well as healthy volunteer persons were enrolled in the current study after completing an informed verbal consent. Initially, all patients were rapidly stabilized, evaluated clinically with special examination of the liver and kidney, blood sampled, and managed.

Inclusion criteria involved: all survived and consented individuals with a history of acute tramadol exposure, clinical manifestations of toxicity especially gastrointestinal and central nervous system disturbances, positive urinary tramadol test, and negative hepatitis test. Exclusion criteria included: all patients with co-ingestion, vague history of alleged dose and lag time, previous history of renal and/or hepatic impairment, different ailments such as viral infections, immune mediated diseases, and neuromuscular disorders or other chronic diseases as well as deceased cases, non cooperative patients who refused to participate in the study, and any patient with a poor correlation between his/her laboratory findings, history of tramadol ingestion, and clinical manifestations when all matched together.

All participated individuals were divided into tramadol intoxicated group (TI-GP) and healthy control group (HC-GP). The subjects of HC-GP were randomly chosen from the surrounding community and kindly accepted to be included in this study. They had not

any neuromuscular disorders or chronic disease with normal cardio-pulmonary and hepato-renal systems on clinical examination and did not receive any drug during the last 2 weeks.

The clinical severity of each enrolled case in TI-GP was estimated according to the Poisoning Severity Score (PSS) criteria of the European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) **(Persson et al., 1998).** The patients were graded into 3 groups as follows: G-I: representing mild intoxicated cases with minimal and self-limited clinical manifestations (such as vomiting, diarrhea, abdominal pain, coughing, mild dyspnoea and wheezes, drowsiness, vertigo, tinnitus, ataxia, restlessness, mild extrapyramidal symptoms, isolated extrasystoles, and mild and transient hypo/hypertension), G-II: involving moderate intoxicated patients with more pronounced and prolonged systemic manifestations as infrequent seizure, but not life-threatening, and G-III: containing severely intoxicated individuals with life-threatening manifestations, significant disability as coma.

Prior to beginning the study, all proposed procedures were explained to the volunteers, patients, or relatives. Socio-demographic data of the gender, age, marital status, residency, income levels, educational standards, and occupational status besides drug exposure profile of the poisoning scene location, route of exposure, circumstantial evidence, history of previous drug and recent tramadol abuse, dosage intake, and the interval duration between exposure and blood sampling (lag time) were registered. The alleged dose taken of tramadol was inquired from the patients (when they are fully alert) or their relative or friends via taking a full detailed history with particular focus on its generic or brand names, form type, color, strip packaging shape, contents, amount, and concentration; besides, persons may bring tramadol strips to the hospital. The dose was calculated by multiplying the number of tablets or capsules by their concentrations and expressed as milligrams.

All participants voided urine samples in a clean plastic container for preliminary qualitative detection of tramadol and its principal metabolites in urine using DIMA® Tramadol (TML) dipstick strips (Dima Gesellschaft für Diagnostika mbH, Germany), which is a competitive immunochromatographic assay method that has a specific cutoff level of 100 ng/ml. Also, the Spectrum HBsAg/HCV Ab Rapid Test-Cassette (Egyptian Company for Biotechnology, Egypt), a chromatographic immunoassay technique, was used for the qualitative detection of Hepatitis B surface antigen and anti-Hepatitis C virus antibodies for all subjects.

Laboratory investigations of the liver and kidney enzyme activities from each volunteer and patient (after stabilization of any life-threatening conditions and before therapy initiation) were assayed colorimetrically according to the methods described inside the manufacturer's instructions of the supplied commercial diagnostic kits and the collected serum samples were used for measurement of following: aspartate amino transferase (AST) and alanine amino transferase (ALT) **(Reitman and Frankel, 1957),** alkaline phosphatase (ALP) **(Tietz et al., 1983),** and total bilirubin (TBL)

(Walters and Gerade, 1970) as well as blood urea nitrogen (BUN) **(Patton and Crouch, 1977)** and creatinine (CRE) **(Fabiny and Ertingshausen, 1971)**.

The collected data were defined, coded and analyzed using the statistical package of social science (SPSS) software package version 16. Comparisons between mean values were checked by one-way analysis of variance (ANOVA) followed by Fisher's Least Significant Difference (LSD) for post hoc analysis. Values were expressed as mean ± standard error (mean ± SE). Biochemical parameters of all groups were also correlated with administered doses and lag times using Pearson's coefficient analysis. A statistically significant difference was considered when the level of $p< 0.05$.

RESULTS

During the 6-month period of this study, exactly 95 patients were represented in the tramadol intoxicated group (TI-GP) and a total of 25 healthy subjects that matched as closely as possible with the TI-GP and served as a healthy control group (HC-GP).

Table (1) displays the socio-demographic profile of TI-GP. Of the total intoxicated patients, the vast majority of cases experienced minor toxic manifestations as listed in G-I followed by those in G-II (with infrequent seizures) and G-III (with coma), respectively, the total percentage and gender ratio of poisoned males dominated that of females, a non-significant alternations in the mean ages were noticed when TI-GP, G-I, G-II, and G-III compared together with males being insignificantly younger than females, and poisoning events predominantly encountered in the age bracket between 21-30 years. In the same way, unmarried patients from urban areas with both high economical (from inheritance or belonging to wealthy families) and educational levels (undergraduate or graduated from a university) and unemployed were most frequently reported.

Table (2) illustrates toxicological data of the patients. Of the all cases, the incidence of poisoning mainly occurred at home through oral route only, accidental exposure with history of drug abuse were largely reported, tramadol at doses of ≤1000 mg were considerably consumed with the largest dosage intake seen in G-III, and the majority had a lag time of less than 6 hours duration that was markedly delayed in G-III. The mean dosage ingestion and lag time estimates of G-I delineated significant decrease when compared with TI-GP, G-II, and G-III, whereas those of G-III demonstrated a significant increases as compared to the TI-GP, G-I, and G-II, which suggesting a strong correlation between poisoning severity grades with the alleged ingested doses and lag times.

Table (3) illustrates different liver and kidney biochemical changes after acute tramadol exposure in TI-GP, G-I, G-II, and G-III as compared to HC-GP and each others. Statistical comparison between the mean estimates of the all liver parameters in TI-GP and only ALP and TBL in G-I as well as all biomarkers in G-II and G-III revealed significant elevations when compared with that of HC-GP values. The remaining AST and ALT variables of G-I addressed insignificant increase when compared with their corresponding figures in HC-GP.

On the other side, the mean levels of AST, ALT, and ALP in G-I were significantly low, while AST and ALP in G-II as well as ALT, ALP, and TBL in G-III were statistically high when facing their comparable rates in TI-GP. Although, the mean levels of the remaining tests were inferior in G-I (TBL) and superior in G-II (ALT and TBL) as well as in G-III (AST), however, these slight changes scored insignificant distinction when compared with their symmetrical amounts of TI-GP. Likewise, the examined mean data of AST, ALT, and ALP in G-II and all assayed elements in G-III witnessed significant rising as opposed to their identical items in G-I. The mean grade of TBL in G-II was minimally raised, but displayed a non-significant disparity in contrast to G-I standard. Moreover, in G-II, the mean values of AST and ALT were significantly high and low, respectively, while the marginally decreased ALP and TBL depicted non-significant discrepancies when matched to those of G-III.

A statistically significant increase in the mean kidney biomarker levels of TI-GP, only serum CRE of G-I (non-significant rise of BUN), and all analyzed variables of G-II and G-III were manifested when all categories facing HC-GP averages. Furthermore, the mean serum levels of kidney enzymes in the three groups versus TI-GP declared significant reduction in G-I and significant expansion in G-II, however, results of G-III sequentially showed insignificant and significant increases in BUN and CRE levels. Likewise, the assayed mean values of kidney biomarkers were significantly elevated in G-II and G-III opposed to G-I. Otherwise, the slightly elevated mean levels of BUN and CRE in G-II showed non-significant differences when confronting G-III.

Table (4) shows correlation of various biochemical parameters in all groups with alleged ingested doses and lag times. The calculated scores of all biochemical parameters showed moderate to strong, statistically significant positive correlations with the alleged doses of tramadol ingested and lag times, which indicating dose- and time-dependent effects of tramadol on hepato-renal functions.

Table (1): Socio-demographic profile of TI-GP, G-I, G-II, and G-III.

Parameters	Number (%)[@]			
	TI-GP (n=95)	**G-I (n=60)**	**G-II (n=24)**	**G-III (n=11)**
PSS grading	95 (100)	60 (63.16; 100)	24 (25.26; 100)	11 (11.58; 100)
Gender				
Male	73 (76.84)	45 (47.37; 75)	19 (20; 79.17)	9 (9.47; 81.82)
Female	22 (23.16)	15 (15.79; 25)	5 (5.26; 20.83)	2 (2.11; 18.18)
Ratio	3.32:1	3:1	3.8:1	4.5:1
Gender/Age				
Overall Mean ± SE	28.06±0.85	26.8±1.03[$]	30.48±1.82[$]	29.72±2.45[$]
Male Mean ± SE	27.57±10	26.25±1.25[$]	30.02±2.04[$]	28.99±2.87[$]
Female Mean ± SE	29.71±1.57	28.44±1.73[$]	32.2±4.41[$]	33±4.67[$]
Age bracket (Years)				
<20	19 (20)	17 (17.89; 28.33)	2 (2.11; 8.33)	0 (0; 0)
21-30	40 (42.11)	22 (23.16; 36.67)	11 (11.58; 45.83)	7 (7.37; 63.64)

31-40	28 (29.47)	18 (18.95; 30.00)	7 (7.37; 29.17)	3 (3.16; 27.27)
41-50	7 (7.37)	3 (3.16; 5.00)	3 (3.16; 12.50)	1 (1.05; 9.09)
51-60	1 (1.05)	0 (0; 0)	1 (1.05; 4.17)	0 (0; 0)
Range	15-52	15-50	18-52	20-48
Marital status				
Unmarried	55 (57.89)	37 (38.95; 61.67)	15 (15.79; 62.50)	3 (3.16; 27.27)
Male	45 (47.37)	34 (35.79; 56.67)	9 (9.47; 37.50)	2 (2.11; 18.18)
Female	10 (10.53)	3 (3.16; 5.00)	6 (6.32; 25)	1 (1.05; 9.09)
Married	40 (42.11)	23 (24.21; 38.33)	9 (9.47; 37.50)	8 (8.42; 72.73)
Male	28 (29.47)	13 (13.68; 21.67)	8 (8.42; 33.33)	7 (7.37; 63.64)
Female	12 (12.63)	10 (10.53; 16.67)	1 (1.05; 4.17)	1 (1.05; 9.09)
Residence				
Urban	68 (71.58)	46 (48.42; 76.67)	16 (16.84; 66.67)	6 (6.32; 54.55)
Rural	27 (28.42)	14 (14.74; 23.33)	8 (8.42; 33.33)	5 (5.26; 45.45)
Income				
High[#]	72 (75.79)	50 (52.63; 83.33)	13 (13.68; 54.17)	9 (9.47; 81.82)
Low	23 (24.21)	10 (10.53; 16.67)	11 (11.58; 45.83)	2 (2.11; 18.18)
Education				
Illiterate	6 (6.32)	1 (1.05; 1.67)	2 (2.11; 8.33)	3 (3.16; 27.27)
School degree	28 (29.47)	18 (18.95; 30)	7 (7.37; 29.17)	3 (3.16; 27.27)
University degree	61 (64.21)	41 (43.16; 68.33)	15 (15.79; 62.50)	5 (5.26; 45.45)
Job				
Unemployed	39 (41.05)	18 (18.95; 30)	14 (14.74; 58.33)	7 (7.37; 63.64)
Students	22 (23.16)	16 (16.84; 26.67)	6 (6.32; 25.00)	0 (0; 0)
Driver	19 (20)	19 (20; 31.67)	0 (0; 0)	0 (0; 0)
Worker	10 (10.53)	4 (4.21; 6.67)	2 (2.11; 8.33)	4 (4.21; 36.36)
Employed	5 (5.26)	3 (3.16; 5)	2 (2.11; 8.33)	0 (0; 0)

%=Percentage; @=Percentage result as compared to TI-GP and per categorical group, respectively; TI-GP=Tramadol intoxicated group; G=Group; n=Number of cases; PSS=Poisoning Severity Score; <=less than; SE=Standard error; #=Undergraduate or graduated from a university; $=No significant difference when compared with TI-GP as well as each other. The level of significance is set at P<0.05.

N.B. Healthy control group involved 25 persons (mean age: 25.69±1.52, range: 17-45 years, males: 17; 68%, females: 8; 32%).

Table (2): Drug exposure profile of TI-GP, G-I, G-II, and G-III.

Parameters	Number (%)[@]			
	TI-GP (n=95)	G-I (n=60)	G-II (n=24)	G-III (n=11)
Poisoning scene location				
Home	77 (81.05)	57 (60; 95)	13 (13.68; 54.17)	7 (7.37; 63.64)
Other places	18 (18.95)	3 (3.16; 5)	11 (11.58; 45.83)	4 (4.21; 36.36)
Route of exposure				
Ingestion[©]	95 (100)			
Circumstances of poisoning				
Suicidal	13 (13.68)	7 (7.37; 11.67)	3 (3.16; 12.50)	1 (1.05; 9.09)
Accidental	82 (86.32)	53 (55.79; 88.33)	21 (22.11; 87.50)	10 (10.53; 90.91)
History of abuse				
Yes[&]	71 (74.74)	45 (47.37; 75)	18 (18.95; 75)	8 (8.42; 72.73)
No	24 (25.26)	15 (15.79; 25)	6 (6.32; 25)	3 (3.16; 27.27)
Dosage range (mg)				
≤1000	46 (48.42)	42 (44.21; 70)	4 (4.21; 16.67)	0 (0; 0)
>1000-≤2000	34 (35.79)	18 (18.95; 30)	14 (14.74; 58.33)	2 (2.11; 18.18)
>2000-≤2500	15 (15.79)	0 (0; 0)	6 (6.32; 25)	9 (9.47; 81.82)
Range	600-2500	600-1150	900-2200	1850-2500
Mean ± SE	1258.68±57.71	908.75±18.72	1653.13±93.71	2306.82±66.15
P Value				
TI-GP vs all groups		0.000[*] (↓)	0.000[*] (↑)	0.000[*] (↑)
G-I vs G-II and III			0.000[*] (↑)	0.000[*] (↑)
G-II vs G-III				0.000[*] (↑)
Lag times (hours)				
<6	59 (62.11)	53 (55.79; 88.33)	6 (6.32; 25.00)	0 (0; 0)
6-12	23 (24.21)	7 (7.37; 11.67)	15 (15.79; 62.50)	1 (1.05; 9.09)
13-18	10 (10.53)	0 (0; 0)	3 (3.16; 12.50)	7 (7.37; 63.64)
19-24	3 (3.16)	0 (0; 0)	0 (0; 0)	3 (3.16; 27.27)
Range	1-24	1-12	1-18	6-24
Mean ± SE	6.57±0.56	3.58±0.29	8.88±0.73	17.81±1.04
P-value				
TI-GP vs all groups		0.000[*] (↓)	0.021[*] (↑)	0.000[*] (↑)
G-I vs G-II and III			0.000[*] (↑)	0.000[*] (↑)
G-II vs G-III				0.000[*] (↑)

TI-GP=Tramadol intoxicated group; G=Group; vs=Versus; ©=Tablets or Capsules; mg=Milligram; %=Percentage; @=Percentage result as compared to TI-GP and per categorical group, respectively; n=Number of cases; ≤=Less than or equal to; >=Greater than; SE=Standard error; P= Probability; <=less than; *=Significant difference, ↓=Decrease; ↑=Increase. The level of significance is set at P<0.05.

&=Patients were on substance abuse for about one and half years before they recently shifted to tramadol abuse for about 7 months (range=4-7 months).

Table (3): Liver and kidney biomarkers changes in TI-GP (n=95), G-I (n=60), G-II (n=24), and G-III (n=11) as compared to HC-GP (n=25) and each other.

Groups	Assayed parameters					
	AST (U/L)	ALT (U/L)	ALP (U/L)	TBL (mg/dl)	BUN (mg/dl)	CRE (mg/dl)
HC-GP						
Mean ± SE	23.72±0.95	28.20±1.02	80.76±3.32	0.66±0.04	18.76±0.65	0.92±0.03
Range	15-32	19-35	55-110	0.25-0.98	11-22	0.65-1.19
TI-GP vs HC-GP						
Mean ± SE	42.06±2.90	44.49±2.94	113.44±4.03	1.06±0.05	23.10±0.79	1.40±0.05
Range	15-142	18-161	55-222	0.33-2.75	12.30-55.40	0.72-2.60
Changes %	+77.32	+57.77	+40.47	+60.61	+23.13	+52.17
P-value	0.001*	0.003*	0.000*	0.000*	0.006*	0.000*
G-I Vs HC-GP						
Mean ± SE	28.90±1.38	34.18±1.63	97.53±3.24	0.95±0.05	20.34±0.57	1.16±0.04
Range	15-60	18-70	55-140	0.33-1.76	12.30-27.40	0.72-1.85
Changes %	+21.84	+21.21	+20.77	+43.94	+8.42	+26.09
P-value	0.356NS	0.294NS	0.044*	0.012*	0.341NS	0.007*
G-II vs HC-GP						
Mean ± SE	73.38±7.57	47.13±4.65	136.33±7.55	1.17±0.14	28.54±2.21	1.84±0.08
Range	25-142	20-93	58-189	0.39-2.28	13.60-55.40	1.28-2.50
Changes %	+209.36	+67.13	+68.81	+77.27	+52.13	+100
P-value	0.000*	0.006*	0.000*	0.000*	0.000*	0.000*
G-III vs HC-GP						
Mean ± SE	45.55±4.72	95.00±13.83	150.27±17.44	1.43±0.18	26.32±2.01	1.76±0.14
Range	29-77	39-161	67-222	0.68-2.75	14.50-36.70	1.18-2.60
Changes %	+92.03	+236.88	+86.07	+116.67	+40.30	+91.30
P-value	0.011*	0.000*	0.000*	0.000*	0.003*	0.000*
G-I vs TI-GP						
Changes %	-31.29	-23.17	-14.03	-10.38	-11.95	-17.14
P-value	0.001*	0.010*	0.006*	0.178NS	0.017*	0.000*
G-II vs TI-GP						
Changes %	+74.47	+5.93	+20.18	+10.38	+23.55	+31.43
P-value	0.000*	0.631NS	0.004*	0.352NS	0.001*	0.000*
G-III vs TI-GP						
Changes %	+8.30	+113.53	+32.47	+34.91	+13.94	+25.71
P-value	0.643NS	0.000*	0.001*	0.019*	0.147NS	0.004*
G-I vs G-II						
Changes %	+153.91	+37.89	+39.78	+23.16	+40.31	+58.62
P-value	0.000*	0.026*	0.000*	0.073NS	0.000*	0.000*
G-I vs G-III						
Changes %	+57.61	+177.94	+54.08	+50.53	+29.40	+51.72
P-value	0.032*	0.000*	0.000*	0.003*	0.009*	0.000*
G-II vs G-III						
Changes %	+61.10	–50.39	–9.28	–18.18	+8.43	+4.55
P-value	0.001*	0.000*	0.272NS	0.141NS	0.380NS	0.538NS

AST=Aspartate aminotransferase; ALT=Alanine transaminase; ALP=Alkaline phosphatase; TBL=Total bilirubin; BUN=Blood urea nitrogen, CRE=Creatinine; HC-GP=Healthy control group; TI-GP=Tramadol intoxicated group; G=Group; vs=Versus; P=Probability; *=Significant difference; NS=No significant difference; –=Decrease; +=Increase; SE=Standard error; n=Number of cases; %=Percentage. The level of significance is set at P<0.05.

Table (4): Pearson's correlation analysis of various biomarkers in TI-GP and the three groups with alleged ingested doses and lag times among tramadol intoxicated cases

Parameters	Alleged Ingested Doses				Lag Times			
	TI-GP (n=95)	G-I (n=60)	G-II (n=24)	G-III (n=11)	TI-GP (n=95)	G-I (n=60)	G-II (n=24)	G-III (n=11)
AST								
r-value	0.671@	0.779$	0.745@	0.742@	0.579@	0.767$	0.741@	0.842$
P-value	0.000	0.000	0.000	0.009	0.000	0.000	0.000	0.001
ALT								
r-value	0.788$	0.781$	0.840$	0.819$	0.857$	0.872$	0.880$	0.726@
P-value	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.011
ALP								
r-value	0.757$	0.714@	0.856$	0.842$	0.750@	0.784$	0.788$	0.660@
P-value	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.027
TBL								
r-value	0.597@	0.723@	0.769$	0.771$	0.640@	0.734@	0.813$	0.786$
P-value	0.000	0.000	0.000	0.005	0.000	0.000	0.000	0.004
BUN								
r-value	0.693@	0.762$	0.817$	0.906$	0.646@	0.615@	0.869$	0.897$
P-value	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
CRE								
r-value	0.796$	0.716@	0.830$	0.806$	0.744@	0.639@	0.770$	0.849$
P-value	0.000	0.000	0.000	0.003	0.000	0.000	0.000	0.001

AST=Aspartate aminotransferase; ALT=Alanine transaminase; ALP=Alkaline phosphatase; TBL=Total bilirubin; BUN=Blood urea nitrogen, CRE=Creatinine; HC-GP=Health control group; TI-GP=Tramadol intoxicated group; G=Group; n=Number of cases; r=Correlation coefficient; P=Probability; @=Moderate positive correlation; $=Strong positive correlation. The level of significance is set at P<0.05.

DISCUSSION

The 31st annual report of the American Association of Poison Control Centers in 2013 revealed a total of 13,086 cases of tramadol toxicity with 6,534 single substance exposures **(Mowry et al., 2014)**. The Poison Control Center of Ain Shams University in Egypt also recorded an alarming number of tramadol intoxicated cases amounting to 1595 in the year 2011 compared to 760 cases in 2010 and 386 cases in 2009 **(El Masry and Tawfik, 2013)**.

Regarding the poisoning severity score of this work, the main bulk of

the victims experienced mild toxic manifestations. Similarly, minor effects **(Marquardt et al., 2005)** besides stable vital signs and conscious level **(Rahimi et al., 2014)** were commonly reported in tramadol overdosed individuals. This can be explained by the fact that tramadol is relatively safe drug with few serious adverse effects **(Klotz, 2003)** or due to considerable inter-individual disparity in relation to its metabolism **(Shadnia et al., 2008)**. The higher percentage of seizure than a deep coma statue in this study is mainly consistent with prior reports **(Shadnia et al., 2008; Taghaddosinejad et al., 2011; Shadnia et al., 2012; Rahimi et al., 2014).** This may be due to prolonged and severe synergistic interactions of tramadol enantiomers and their metabolites on the central nervous system or variable degree of drug dependency and tolerance between persons **(Grond and Sablotzki, 2004)**.

The results of the collected socio-demographic data of the instant study are greatly in agreement with the results of other published studies, whereas, the main bulk of patients were predominantly males **(Shadnia et al., 2008; Tashakori et al., 2010)**, within the third decade of life **(Shadnia et al., 2008; Taghaddosinejad et al., 2011; Shadnia et al., 2012; Rahimi et al., 2014),** chiefly unmarried **(Shadnia et al., 2008; Shadnia et al., 2012; Zhang and Liu, 2013)**, largely urban residents **(Fawzi, 2011)** with sufficient income backup **(Hanson and Chen, 2007)**, highly educated **(Zhang and Liu, 2013)**, and mainly unemployed **(Fawzi, 2011).** Generally, men are more subjected to substantial amount of stressful life events than women alongside with strong concepts that tramadol can effectively alleviate psychosocial problems emerging from lack of marriage or unemployment; hence, affected individuals may administer larger doses of the drug to overcome these difficulties or escape reality.

On the other hand, several articles of tramadol toxicity showed different socio-demographic aspects **(Marquardt et al., 2005; Talaie et al., 2009; Fawzi, 2011; Abbas et al., 2013; Zhang and Liu, 2013),** which disagree completely with the present findings. These discrepancies could be due to transposition of socio-epidemiological characters of tramadol between different regions in Egypt as well as other countries. In Egypt, recent up-scheduling, low ordinary pharmacy stocks, reduced illegal smuggling and transactions, and diminished black-market supplies of tramadol may efficiently controlled its availability and lead to a dramatic increase of its price.

The outcomes of drug exposure pattern in the current survey are markedly in alignment with formerly data of other investigators who authenticated that the peak rate of tramadol exposure occurs in the patients' homes **(Karbakhsh and Zandi, 2008),** by entire oral route only **(Taghaddosinejad et al., 2011; Farajidana et al., 2012; Shadnia et al., 2012; Rahimi et al., 2014)**, by an accidental mode **(Tashakori and Afshari, 2010; Fawzi, 2011)** especially among abusers **(Fawzi, 2011; Taghaddosinejad et al., 2011; Farajidana et al., 2012; Zhang and Liu, 2013),** and by ingestion of less than 1000-mg **(Jovanović-Cupić et al., 2006; Talaie et al., 2009)** with a

mean lag time of less than 6 hours **(Shadnia et al., 2008; Taghaddosinejad et al., 2011; Farajidana et al., 2012; Hassanian-Moghaddam et al., 2013)**. Drug-related overdoses are more likely to occur in domestic places possibly due to individual behaviors (most safe and preferred place for recreational setting away from law enforcement officials). Fundamental oral route of tramadol is probably due to the tremendous spread of tablet and capsule preparations in pharmacies **(Shadnia et al., 2012)**, being rapidly and completely absorbed **(Grond S and Sablotzki, 2004),** or confined dispersion of the injectable form to particular pharmacies and hospitals **(Taghaddosinejad et al., 2011)**. Lack of patients' knowledge and experience about the safe use and toxic effects of tramadol may be responsible for increasing its accidental overdose mode. Predisposing factors that may contribute to wide popularity and abuse of tramadol include purchasing ability without prescription from the black market **(Shadnia et al., 2012)**, unscheduled status in some nations **(Grond and Sablotzki, 2004)**, and lack of availability of other legal opioids **(Taghaddosinejad et al., 2011).** Common factors that might affect patients' hospital arrival include referral distance, availability of aid during the incident, and the onset of appearance of toxic signs and symptoms.

On the other side, other researchers had reported different results **(Marquardt et al., 2005; Shadnia et al., 2008; Fawzi, 2011; Farajidana et al., 2012; Shadnia et al., 2012; Rahimi et al., 2014; Randall and Crane, 2014),** which are incompatible with the consequences of the existing research. These divergences might be linked to cultural norms and inexperience in consuming the drug between affected persons.

In this study, tramadol induced alterations of hepato-renal functions as manifested by significant elevations of the values of overall assayed enzymes in TI-GP when compared with HC-GP levels. Also, biochemical changes of the tested parameters were more prominent in G-II and G-III than G-I displaying a dose-dependent behavior of tramadol on the studied organs. Hepato-renal enzyme activities were significantly increased by tramadol in a dose- and time-dependent manner as assessed by Pearson's correlation analysis.

Tramadol-induced hepatic, renal, and/or hepato-renal toxicity has been reported in a few isolated cases and many literatures. Multiple organ dysfunction and considerable deterioration in hepatic and/or renal enzyme activities with remarkably high blood drug concentrations had been documented after lethal exposure to tramadol **(Loughrey et al., 2003; De Decker et al., 2008; Wang et al., 2009; Randall and Crane, 2014).** Likewise, sixteen patients of benign hepatobiliary dysfunction were reported to the Medicines Control Agency as mentioned by **Loughrey et al. (2003)**. The former investigators comprehensively reviewed concentrations of tramadol and its metabolites in blood and various tissues in post-mortem or near-fatal cases and speculated that massive ingestion of tramadol may lead to fatal complications and irreversible organ(s) damage. Furthermore, biochemical findings of acute hepatic and/or renal

injury were demonstrated in some cases with tramadol-related life-threatening conditions **(Daubin et al., 2007; El-Hussuna et al., 2010; Tashakori and Afshari, 2010; Yousef Khan et al., 2010; Elkalioubie et al., 2011).** The previous authors just recorded these abnormalities without commenting on these results. Tramadol-induced hepatic injury is confirmed by the presence of congestion and edema by CT scan **(El-Hussuna et al., 2010)** as well as steatosis, fulminant centrilobular necrosis, and congestion during histopathological examination of liver specimens **(Musshoff and Madea, 2001; Loughrey et al., 2003; De Decker et al., 2008; Wang et al., 2009; Mannocchi et al., 2013).**

On the contrary, routine laboratory investigations of liver and/or kidney profiles were within normal ranges in tramadol poisoned cases **(Clarot et al., 2003; Udy et al., 2005; Agrawal et al., 2009; Xiong et al., 2011; Lota et al., 2012; Ghosh et al., 2013; Hassanian-Moghaddam et al., 2013; King et al., 2013).** However, the prior articles focused on tramadol associated adverse effects such as respiratory impairment, drug interaction, metabolic disturbance, and neurological disorders rather than discussing the findings of hepato-renal disorders.

Tramadol-induced hepatotoxicity and/or nephrotoxicity, especially with large doses, have been demonstrated in rats **(Ezzeldin et al., 2014; Elkhateeb et al., 2015),** but not observed in sheep **(Dehkordi et al., 2012)** and rabbits **(Udegbunam et al., 2015).** These paradoxical findings may be due to variation in route of administration, dosage regimen, duration of the study, and experimental models between these studies.

Previous clinical **(Afshari and Ghooshkhanehee, 2009; Liu et al., 2009; Elkalioubie et al., 2011)** and experimental **(Ezzeldin et al., 2014; Mohamed et al., 2015)** studies demonstrated a strong correlation between ingested doses and lag times and tramadol-induced hepato-renal injury, which support the results of the present work. The apparent elimination half-life of tramadol is prolonged and its level increased for several hours, probably due to combined renal and hepatic dysfunction, which may explain the consequences of severe overdoses **(Elkalioubie et al., 2011).**

The pathogenic mechanism(s) of tramadol-induced impairment of hepato-renal functions may be explained by multi-factorial processes. In overdose events, excessive production of the more potent and toxic metabolite mono-O-desmethyltramadol with subsequent higher blood concentrations, significant accumulation in the human bile, liver, and kidney, and fundamental excretion via the urinary system may cause direct cellular injury leading to hepato-renal damage **(Singhal et al., 1998; Grond and Sablotzki, 2004; Kirchheiner et al., 2008; Musshoff and Madea, 2001; Barbera et al., 2013; Mannocchi et al., 2013).** Additionally, tramadol related complications such as shock, hypoxia, ischemia, or rhabdomyolysis may contribute to organ disorders **(Afshari et al., 2008; De Decker et al., 2008; Wang et al., 2009; Randall and Crane, 2014).** Moreover, tramadol associated hyperammonemia, lactic acidosis, and steatosis **(De**

Decker et al., 2008) as well as tissues oxidative stress in laboratory animal are features directly correlated with cellular mitochondrial injury and depletion of adenosine triphosphate production due to excessive generation of reactive oxygen species, lipid peroxidation, and inhibition of glutathione peroxidase activity **(Ghoneim et al., 2014; Elkhateeb et al., 2015; Mohamed et al., 2015).**

In addition, other studies pointed out that opioid compounds are likely to cause cytotoxicity and may impair organ functions via their toxic reactive metabolites **(Nagamatsu et al., 1985; Nagamatsu et al., 1986; Jairaj et al., 2003),** reduction of intracellular glutathione, glycogen, and albumin contents **(Ponsoda et al., 1991; Gómez-Lechón et al., 1987-1988),** depletion of cellular protein thiol contents, inhibition of β-oxidation, and uncoupled oxidative phosphorylation **(Berson et al., 2001),** inhibition of antioxidant enzyme activities **(William et al., 1991),** oxidative injury **(Bellomo and Orrenius, 1985),** or disturbance of calcium ions homeostasis **(Singh et al., 2011).**

Finally, results of the current work may disagree with other several studies because of variability in: socio-cultural behavior between regions, pharmacokinetics and pharmacodynamics response to the drug among inter-population, inter-individual, and racial, genetic polymorphic enzymes for drug metabolism, drug forms and availability, dosage taken (therapeutic or toxic; single or repeated), route of administration (oral or injection), and duration of exposure (short or long-term).

This study does have some limitations. The BPCU does not receive all tramadol poisoned cases, as many cases may be managed in nearby hospitals or private clinics, so this hospital-based study may not reflect the exact incidence of tramadol exposure in the region. Suicide and abuse are legal offence in Egypt, thus patients or relatives might deny drug intake to avoid legal repercussions leading to underestimations of its records. As well, diagnosis of co-ingestions and history of organs' premorbid conditions are provided by the patients or relatives. Another bias includes inability to measure the blood concentrations of tramadol. Yet, strength points of the study involve the relatively sufficient number of the studied patients and particular assessment of the hazardous effects of acute tramadol ingestion on hepato-renal functions wherein results from poisoned patients compared with that of the healthy control persons.

In conclusion, acute tramadol poisoning is a growing serious problematic phenomenon and a potential hazard to the Egyptian society due to the wide popularity of the drug that plays a pivotal role in promoting its massive abuse. The majority of cases had minor clinical manifestations and the prevalence of poisoning was common among young adult males that being unmarried and urbanized, with sufficient pocket money, and highly educated, but unemployed. The drug profile revealed a predominance of poisoning at home by oral route only, accidental manner that closely related to drug abuse (acute on top of chronic), and dosage ingestion as well as delayed hospital arrival among comatose patients. The total values of all assayed enzymes in

the poisoned patients were significantly elevated when compared with that of control and biochemical changes were markedly altered in patients with seizures and coma than those with mild toxicity. Tramadol induced perturbation of hepato-renal functions in a dose-and time-dependent manner. So, measurement of these enzymes will be helpful for early identification of patients with subclinical organ injuries before the development of serious or permanent damage. Enlightenment for awareness of people about the serious complications of tramadol as well as implementation of more restricted regulations, especially by agencies responsible for controlled substances abuse, to prevent its abuse potentiality and limiting its access and distribution are necessary.

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الملخص العربى

النمط الإجتماعى والديموغرافى لحالات التسمم بالترامادول والعلاقة بين مستويات الدلائل الحيوية للكبد والكلى مع الجرعات المتناولة والفترات الزمنية الفاصلة : دراسة مستقبلية بوحدة بنها لعلاج حالات التسمم – القليوبية – مصر

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الترامادول ، أحد مُخلِقات الأفيون المشتقة من الكودايين ، يوصف طبيا على نطاق واسع كمسكن للآلام نظرا لكونه عقار آمن وفعال. إلا أنّ ، تقارير التسمم بالترامادول على نحو متزايد وأصبحت مشكلة صحية خطيرة في جميع أنحاء العالم ، بما في ذلك مصر. على الرغم من هذا ، احتمالية حدوث مضاعفات كبدية - كلوية ناجمة عن الترامادول قَلّمَا ما تمت درستها. أجريت هذه الدراسة المستقبلية على مدى ستة أشهر (يناير- يونيو- 2015) لوصف الأنماط الإجتماعية والديموغرافية وخصائص التعرض للعقار بجانب تقييم الوظائف الكبدية – الكلوية (أسبرتات أمينو ترانسفيراز ، ألانين أمينو ترانسفيريز ، الفسفاتاز القلوية، البيليروبين الكلي ، نيتروجين يوريا الدم ، و الكرياتينين) فى حالات التسمم بالترامادول التى أدخلت وحدة بنها لعلاج السموم ، القليوبية ، مصر.
خمسة وتسعين حالة تسمم بالترامادول (مجموعة الترامادول) و خمسة وعشرين متطوعا (المجموعة الضابطة) حققوا معايير الاشتمال. بالنسبة لشدة التسمم ، صنفت الأعراض السريرية للحالات إلى المجموعة الأولى (طفيفة) ، المجموعة الثانية (متوسطة) ، المجموعة الثالثة (شديدة). الأعراض السريرية كانت طفيفة فى معظم الحالات وأدرجت في المجموعة الأولى. بالنسبة لمجموعة الترامادول ، كانت معظم الحالات من الذكور (73؛ 76.84٪) في العقد الثالث من العمر مع متوسط العمر من 28.06 ± 0.85 عام ، غير متزوجون (45 ؛ 47.37٪) ، من سكان الحضر (68 ؛ 71.58٪) معها ما يكفي من الموارد المالية (72 ؛ 75.79٪) ، ذات تعليما عاليا (61 ؛ 64.21٪) ، وعاطلين عن العمل (39 ؛ 41.05٪) ، في حين أن بيانات التعرض للعقار أظهرت غالبية الإصابة بالمنزل (77 ؛ 81.05٪) ، عن طريق الفم فقط (95 ؛ 100٪) ، بطريقة عرضية (82 ؛ 86.32٪) وتاريخ سابق من إدمان العقاقير (71 ؛ 74.74٪) ، كان متوسط الجرعات المتناولة 1258.68 ± 57.71 ملجرام ، و متوسط الفترة الزمنية الفاصلة 6.75 ± 0.56 ساعة. أظهر متوسط الجرعة المتناولة و الفترة الزمنية الفاصلة بللمجموعة الثالثة زيادة ذات دلالة إحصائية بالمقارنة مع مجموعة الترامادول ، المجموعة الأولى ، والمجموعة الثانية.
أظهرت جميع الدلائل الحيوية للكبد والكلى لمجموعة الترامادول ، فقط البعض في المجموعة الأولى (الفسفاتاز ، البيليروبين ، و الكرياتينين) والمجموعة الثانية ، والمجموعة الثالثة زيادة ذات دلالة إحصائية عند مقارنتهم بالمجموعة الضابطة. بالإضافة إلى ذلك ، أظهرت جميع مستويات الدلائل الحيوية للمجموعة الأولى (ما عدا البيليروبين) وكذلك بعض المتغيرات بالمجموعة الثانية (الأسبرتات ، الفسفاتاز ، اليوريا ، و الكرياتينين) والمجموعة الثالثة (الألانين ، الفسفاتاز ، البيليروبين ، الكرياتينين) على التوالى ، نقصان و زيادة ذات دلالة إحصائية عند مقارنتهم بمجموعة الترامادول. بينما ، أظهرت جميع مستويات الدلائل الحيوية للمجموعة الثانية (ما عدا البيليروبين) والمجموعة الثالثة زيادة ذات دلالة إحصائية عند مقارنتهم بالمجموعة الأولى ونتائج إحصائية متباينة بالمقارنة مع بعضهم البعض (زيادة ذات دلالة إحصائية بأسبرتات المجموعة الثانية و ألانين المجموعة الثالثة).
شعبية الترامادول الواسعة ، وانتشار الاستهلاك العالي ، وحوادث التسمم ، خاصة بين الشباب المصري البالغ ، يحتمل أن تنامي ظاهرة إجتماعية خطرة التي لها آثار ضارة على الوظائف الكبدية والكلوية بطريقة تعتمد على الجرعة والوقت والتى ينبغي أخذها بعين الإعتبار خلال متابعة حالات التسمم بالجرعات الزائدة للكشف المبكر عن إصابة أعضاء الجسم بالأعراض المستترة سريريا أو الخطيرة.