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Tramadol-Induced Liver and Kidney Toxicity among Abusers in Gaza Strip, Palestine

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Abstract

Tramadol, a centrally acting analgesic opioid, is considered to have a low abuse potential and is devoid of side effects like drug dependence, liver and kidney toxicity.. The present study was conducted to assess the tramadol addiction effects on both liver and kidney functions among tramadol abusers. A total of 50 male individuals with a tramadol abuse problem were referred to psychiatric clinics in Gaza Strip, along with an age matched normal control. An informed consent was obtained, a questionnaire was filled, blood samples were collected, serum was separated, and tested serologically to detect antibodies to hepatitis A virus, the presence of hepatitis B surface antigen, and IgM antibodies to hepatitis A virus. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) activities, bilirubin, creatinine, uric acid and blood urea nitrogen (BUN) levels were measured in the serum. Serum ALT, AST and LDH levels were significantly higher in abuser group compared to the control group. Serum ALP, direct bilirubin, total bilirubin, BUN, uric acid and creatinine levels significantly increased in the abusers that were addicted to tramadol for more than 5 years. Our results point out the risk of increased hepatic and renal damage due to a long-term use of tramadol. Although opioids are reported to be effective in pain management, their toxic effects should be kept in mind during the chronic usage. In addition, measures to control the spread of tramadol abuse should be implemented.

Keywords: Tramadol addiction, Liver toxicity, Kidney toxicity, Gaza Strip, Palestine.

1. Introduction

Tramadol (Tramal TM) is a centrally acting synthetic opioid analgesic agent, used parenterally and orally for the treatment of moderate to severe pain. The mechanism of its analgesic action is complex. Most reports suggest that the analgesic activity and other clinical effects of tramadol are a result of opioid and non-opioid mechanisms. Tramadol binds to the μ-opioid receptor, although much more weakly than morphine. It also inhibits the neuronal reuptake of norepinephrine and serotonin as do the antidepressant drugs such as amitriptyline and desimpramine (Raffa *et al.,* 1992; Raffa, 1996; Dayer *et al.,* 1997; More *et al.,* 1999; Grond and Sablotzki, 2004; Gillman, 2005).

Tramadol has a high oral bioavailability in the range of 70- 80%. Peak blood levels are reached in about 2 hours after an oral dose. It is metabolized in the liver by the cytochrome p450 and by-products are excreted through the kidney. Its biotransformation occurs in the liver and results in O-desmethyl-tramadol, which itself is an active substance and 2 to 4 times more potent than tramadol (Subrahmanyam *et al.,* 2001; Wu *et al.,* 2001; Tao *et al.,* 2002; Wu *et al.,* 2002; Halling *et al.,* 2008). Further, biotransformation results in inactive metabolites, which are excreted by kidneys (Lee *et al.,* 1993; Matthiessen *et al.,* 1998).

Tramadol has a dose-dependent analgesic efficacy that lies between that of codeine and morphine, with a parenteral potency comparable to that of pethidine, i.e., about 10- 20 % of the standard morphine (Wilder-Smith *et al.,* 1999; Pang *et al.,* 2003). A long-term of tramadol administration for management of pain, as well as its use as an acceptable alternative for persons with drug-seeking behavior is controversial. However, the tramadol's effects at a cellular level are not clearly understood (Brena and Sander, 1991; McCarberg and Barkin, 2001; Atici, 2005).

The adverse effects associated with the medicine used in clinics constitute a serious problem for patients and health care providers (Asis *et al.,* 2009). It has been estimated that about 10% of drugs are associated with severe, undesirable side effects (Hussaini and Farrington, 2007; Shi *et al.,* 2010). However, this number is probably underestimated, given that drug-induced adverse effects are difficult to detect due to pre-existing medical conditions, multiple drug usage, and lack of diagnostic standards (Asis *et al.,* 2009).

The central role of liver and kidney in detoxification and drug metabolism increases the risks of toxic injury. Almost certainly, every drug has been associated with hepatotoxicity due to the essential role of the liver in drug

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metabolism (Poppers, 1980; Tolman, 1998). Metabolites of the drugs that are excreted from kidneys may also cause a cellular damage leading to a kidney dysfunction and may have a higher activity and/or a greater toxicity than the original drug (Singhal *et al.,* 1998).

Tramadol is considered to have a low abuse potential and is devoid of side effects, like drug-dependence. A tramadol overdose may lead to a Central Nervous System (CNS) depression, nausea and vomiting, tachycardia, seizures, coma, respiratory depression and cardiovascular collapse (Jones, 2005; Chandrasekaran, 2007). Very few fatalities have been reported so far (Pothiawala *et al.,* 2011). Therefore, a tramadol dosage should be adjusted according to the pain severity. The total daily dose should not exceed 400mg in adult therapeutic blood levels of 0.1–0.8 mg/L (Clarot *et al*., 2003).

Unfortunately, the unregulated access of tramadol to Gaza Strip leads to the misuse of the drug and this is considered a serious problem that may have a negative impact on liver and kidneys among users. A cross-sectional prospective study was conducted to assess the liver and kidney functions among chronic users of tramadol in Gaza Strip. In addition, an investigation of the possible causes of tramadol abuse was attempted.

2. Materials and Methods

2.1. . Study Population

The present study is analytical and descriptive. A total of 50 male individuals with tramadol abuse problems, ranging from 15 to 35 years old, were referred between September 2013 to June 2014 to psychiatric clinics in Gaza Strip. A normal control group with matching age and sex was also included, with the condition that they did not take any medication, and did not suffer from any chronic diseases. All the selected abusers were free of chronic diseases, such as diabetes mellitus, hypertension, heart diseases and kidney or liver failure; all had a history of addiction.

The purpose and the procedures of the present study were explained to all participants. An informed consent was obtained, a questionnaire filled, and a blood sample was collected. Helsinki ethical committee in Gaza Strip approved of this study.

2.2. Sample Collection

Blood samples were collected into plain tubes, and then the specimens were transported within one hour to the Clinical Chemistry Laboratory of the Faculty of Health Sciences, Islamic University - Gaza. Blood samples were centrifuged at 4000 rpm for 10 minutes, serum was separated immediately. All blood specimens were tested serologically to detect antibodies to hepatitis C virus (HCV), the presence of hepatitis B surface antigen (HbsAg), and IgM antibodies to hepatitis A virus (HAV) by enzyme linked immunosorbent assay (ELISA) (CTK Biotech Inc, San Diego). Then, biochemical tests were performed within two hours.

2.3. Biochemical Analysis

Levels of Serum enzymes Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) activities, bilirubin, creatinine, uric acid and blood urea nitrogen (BUN) were determined in the serum using (BioSystem, Barcelona) protocols. Data entry and analysis were done using Statistical Package for Social Sciences (SPSS version 20) software. Comparisons were made using Chi-square test and t-test. A *P*-value of < 0.05 was considered indicative of a statistically significant difference.

3. Results

3.1. Description of Study Subjects

A total of 100 specimens (50 tramadol abusers who are admitted to psychiatric clinics in Gaza Strip and 50, of matching age and sex, as control) were included in the study. 28 (56%) of the abusers were from the age group of 21-25 years old, followed by the age group of 26-30 (24%), the age group of 31-35 (12%) and the age group of 15-20 (8%) (Figure 1). All abusers were male.

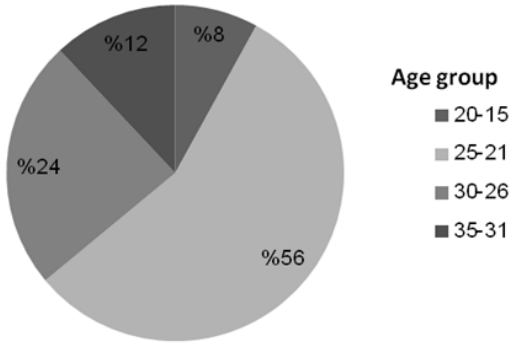

Figure 1. Abusers distribution by age

Twenty-five (50%) of the patients were at the secondary educational level, 27 (54%) of the patients were single. The addiction profile for the patients showed that the average addiction period was 4 years (ranging from 0.5 to 15 years). Most of the patients, 33, (66%) were addicted to a tramadol dose of more than 500 mg and 17 (34%) were addicted to a tramadol dose of less than 500 mg (Table 1) with an average intake of 5 times per day. 48 (96%) of the patients were smokers. Patients selected were free of any abnormalities that may introduce abnormal results in liver and kidney function tests; any patient with positive HAV, HBV, or HCV tests was excluded. None of the patients had a chronic disease such as diabetes, hypertension, heart, and kidney or liver diseases.

Table 1. Tramadol dose intake among patients (N=50)

Daily dose	Frequency	Percent
Less than 500 mg	17	34.0
500-1000 mg	13	26.0
1001-1500 mg	7	14.0
1501-2000 mg	5	10.0
More than 2000 mg	8	16.0

3.2. Liver Function Tests

Liver toxicity does not solely occur by drug metabolites that accumulate due to over dosage (Singhal *et al.*, 1998); it can also occur through viral infection. In the present study, all patients were tested for hepatitis viruses (HAV, HBV, and HCV) and only those with negative results were included in the study.

With regard to liver function tests, ALT results were significantly higher at *p*-value of less than 0.05 in tramadol abusers (72%) against the control group (0%) (Figure 2A).

About 50% of the tramadol abusers showed abnormal AST and LDH results in comparison with the control group that scored only 16% (Figures 2B and 2D). ALP, direct billirubin, and total bilirubin results showed no significant difference between the two groups. When the addiction period was considered in comparing the results, it was found that 4% of the "more than 5 years tramadol abusers" showed an abnormal result against a 100% normal result among the control group (Figure 2C).

3.3. Kidney Function Tests

During the vital role of kidney in blood clearance from toxic compounds, some of these compounds, such as drug metabolites, may cause a cellular damage, leading to a kidney dysfunction (Singhal *et al.*, 1998).

Kidney function was evaluated among the tramadol addicts and the results showed that a low percentage of the abusers (ranging from 6% -10%) had abnormal BUN and Uric acid value. Those patients were categorized as chronic addicts for more than five years (Figure 3 A and B); this indicates that the long-term tramadol addiction may cause kidney injury. The creatinine levels showed no significance differences among abusers and controls.

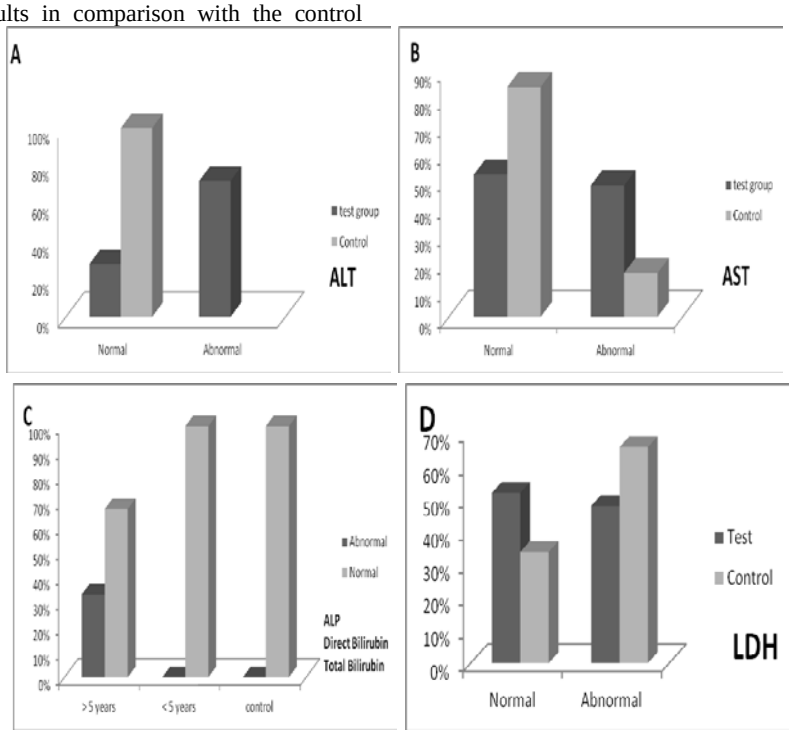

Figure 2. Liver enzymes results in patients and control serum. At $P < 0.05$ patients showed significant higher ALT results (A) , AST results (B). ALP, Direct bilirubin and Total bilirubin and bilirubin was only elevated in patients addicted to tramadol more than 5 years (C). Data significantly showed high levels of LDH among patients at $P < 0.05$ (D).

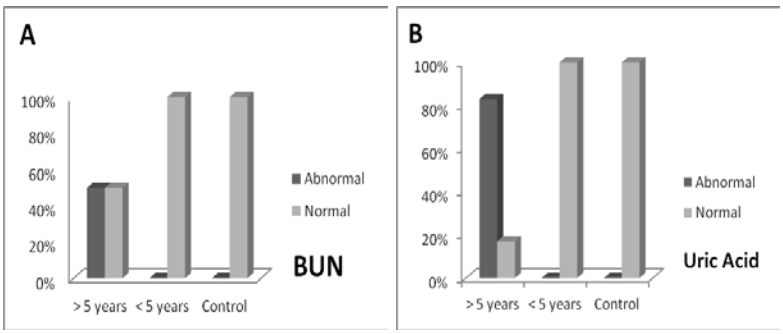

Figure 3. Kidney function tests results in patients and control serum. At $P < 0.05$ patients with long term of addiction had abnormal BUN results (A), uric acid results (B).

4. Discussion

Tramadol overdosing has been one of the most frequent causes of drug poisoning in the recent years, especially in young adult males with a history of substance abuse and mental disorders (Shadina *et al.*, 2008). When overdosed, it is, as believed, associated with significant morbidity and mortality (Jones, 2005; and Chandrasekaran, 2007). The present is the first study that attempts to assess the effects of tramadol addiction on liver and kidney functions among the chronic users of tramadol in young adults of Gaza Strip.

The hepatic function in drug metabolism involves converting drugs and other compounds into products that are more easily excreted (Coughtrie *et al.*, 1989; Milne *et al.*, 1997; Tolman, 1998). Metabolites may have a higher activity and/ or a greater toxicity than the original drug. These metabolites, excreted via kidneys, may also cause a cellular damage and, thus, a kidney dysfunction (Singhal *et al.*, 1998). The liver and kidney are responsible for the tramadol metabolism and excretion and the high risk of hepatotoxicity and nephrotoxicity (Wu *et al.*, 2001; Jansen, 2005).

In the present study, tramadol abusers' personal data showed that about 56% of the abusers were 21 to 25 years old, and 50% did not go to college. This age is particularly critical, especially with the difficult socioeconomic status along with a life of hardship and unemployment. Another key factor that could contribute to the use of tramadol and other drugs by young adults is the absence of awareness of the hazardous effects of such drugs and also to the relatively easy accessibility. This is in agreement with a study performed in Iran, showing that the majority of people seeking tramadol from pharmacies are adolescents/ young adults taking tramadol orally, with the criteria for drug addiction (Zabihi *et al.*, 2011). Most of patients, 33 (66%), were addicted to a tramadol dose of more than 500mg by means of opioid overdose according to previous published data that considered the total daily dose should not exceed 400mg for adult therapeutic blood levels of 0.1–0.8mg/L (Clarot *et al*., 2003)

The liver function was evaluated through measuring Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) activities and serum bilirubin. The results showed a significantly higher ALT result among tramadol abusers compared with the control group. About 50% of the tramadol abusers (> 5 years abuse) showed abnormal AST and LDH results; and this is in agreement with the findings of a study carried out by Panchenko *et al.* (1999). A significant increase in the level of ALT and AST was reported among rats that received 40 and 80 mg/kg of tramadol with a pronounced effect caused by the large dose and the duration of drug administration (El-Gaafarawi, 2006). Those findings were similar to previous studies conducted on long-term tramadol treated mice (Borzelleca *et al.*, 1994; Aitic *et al*., 2005; Elyazji *et al.*, 2013; Rukhshanda *et al.*, 2014).

ALP and billirubin results showed no significant difference between tramadol abuser and control groups except for the chronic abusers (more than 5 years) who showed abnormal levels. This indicates that the long-term use of tramadol intake is more harmful to liver and causes a serious cellular toxicity and a liver failure. Previous histopathological studies indicated the necrosis, vacuolization, central vein dilation, hemorrhage, cytolysis and complete cell membrane degeneration in hepatocytes in tramadol long-term treated mice (Aitic *et al.*, 2005; Rukhshanda *et al.*, 2014).

Moreover, the results of the kidney function tests showed an increase in BUN, uric acid and creatinine levels in samples obtained from the-more-than-5-years tramadol abuser. This suggests that the long-term use of tramadol has negative impacts on kidney functionality. This result is in accordance with Aitic *et al.* (2005) who reported an increase in BUN and creatinine levels in rats with long-term tramadol receiving; others studies reached similar results (Borzelleca *et al.*, 1994; Aitic *et al.*, 2005; Elyazji *et al.*, 2013; Rukhshanda *et al.*, 2014).

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