Hypo and hyperglycemia among tramadol overdose patients in Loghman Hakim Hospital, Tehran, Iran

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Abstract: Tramadol is a synthetic and centrally active analgesic. Hypoglycemia as another possible major side effect among abusers has not been known well. Our objective is evaluation of the Blood Glucose Level (BGL) among tramadol-overdosed patients. This prospective cross-sectional study was performed from Feb to June 2013; BGL was measured at the time of admission, 8 and 12 hours later. All patients with hypoglycemia received infusion of 0.5-1gr/kg of hypertonic dextrose and their BGL was checked every hour until normal BGL. Patients' demographic, clinical and paraclinical data were collected. Totally, 128 patients with a mean (SD) age of 24.5 (6.9) years were recruited; 127 (99.2%) were male. Seizure occurred in 59.4% cases. Mean ±SD admission BGL was 94.88±21.5mg/dL. Fourteen patients experienced hypoglycemia within 12 hours period. Hyperglycemia was experienced in 8 patients (6.25%) on admission day. There was no significant relation between the dose of tramadol and BGL. In conclusion, hypoglycemia must be considered asan important side effect of tramadol-overdose. It is suggested that serial BGL monitoring in cases of Tramadol-overdose should be done for early recognition of hypoglycemia and its timely management. Also hyperglycemia may be revealed.

Keywords: Tramadol, hypoglycemia, hyperglycemia, blood glucose level.

INTRODUCTION

Tramadol is an atypical, synthetic and centrally-active analgesic by both opioid and non-opioid mechanisms, and can suppress opioid withdrawal (Duke *et al.*, 2011). Tramadol's mode of action is not fully understood, but μ-opioid receptors binding and reuptake inhibition of serotonin and nor epinephrine are two applicable complementary mechanisms in animal models (Raffa *et al.*, 1992; Gholami *et al.*, 2007). Tramadol has been marketed in Germany since 1977 and has been used in the US and Sweden since 1995 (Duke *et al.*, 2011). In Iran, tramadol was introduced as a new generic prescription drug with mild opioid properties to the Iranian Pharmaceutical market by the Office of Controlled Drugs and Substances in 1999.Studiesprior to 1994 indicated that tramadol had a low abuse potential and US Food and Drug Administration (FDA) approved it as a nonscheduled analgesic (Zabihi *et al.*, 2011).

Tramadol cannot reduce pain and also its euphoria is not as the same as an opioid compound, therefore most abusers use it concomitantly with other agents (Duke *et al.*, 2011). It has been used by Iranian physicians in the past for treatment of opioid-addicted patients, even though this is not an FDA-approved indication. Due to low efficacy and adverse effects, however, this practice has been omitted (Zabihi *et al.*, 2011).

Despite considering tramadol as a prescription only medication, easy access through Iran's retail pharmacies make it an abused substance, especially in the youth population (Iravani *et al.*, 2010).

Respiratory depression and dependency usually are observed in the use of traditional opioid receptor agonists but have not been reported in prescribed doses of tramadol (Klotz *et al.*, 2003). Overdose has been found to induce nausea, dysphoria, constipation, lethargy, seizures, confusion, gitation, hypertension, tachycardia, respiratory depression and coma. It is notable that CNS-depressant compound can exacerbate the toxic effects of tramadol (De Decker *et al.*, 2008; Mugunthan and Davoren., 2012; Talaie *et al.*,2009). It is suggested that the dose of tramadol should be decreased in patients with liver and/or renal insufficiency (Mugunthan and Davoren., 2012).

Seizure occurs rarely in therapeutic doses but is more common in patients with overdose, use of potentially epileptogenic drugs, or history of alcohol abuse (Mugunthan and Davoren, 2012; Talaie, 2009). Importantly, the occurrence of hypoglycemia as another possible major side effect among tramadol abusers has not been given sufficient attention, documented by limited

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case reports without any powerful studies being done. According to the French Pharmacovigilance (Adverse Drug Reports) database, there were reported of several hypoglycemic cases among patients who receiving tramadol (Mugunthan and Davoren, 2012). Our study's objective is evaluation of the Blood Glucose Level (BGL) among tramadol-overdosed patients.

MATERIALS AND METHODS

Study design

The research ethics committee of the Shahid Beheshti University of Medical Sciences approved the study protocol (code number =130). This prospective cross-sectional study was performed in a subject population of tramadol-overdosed patients who were admitted to Loghman-Hakim Hospital Poison Center (LHHPC) during a 4 month period from Feb to June 2013. LHHPC is a unique referral, poison control and teaching center, serving an estimated 20,000 poison patients every year. This center's daily turnover is about 80-100 patients.

Patients and methods

We included patients classified as having taken an overdose on the basis of a relative's report of ingestion, a witness of drug ingestion, finding of empty drug boxes, or a suicide note combined, with presentations related to a drug over-dose or poisoning, and available toxicology testing. Cases with exclusion criteria including existence of diabetes mellitus or co-ingestion of hypoglycemic agents (i.e. sulfonylurea), were omitted of this study. Patient data were collected in questions are as regards the ingested dose, admission symptoms (the conscious status, history of seizure, and frequency of seizures, paleness, sweating and restless) and clinical signs (heart rate, respiratory rate, body temperature, systolic and diastolic blood pressure). All examinations for this study were performed by a single physician.

Patients were maintained as nil per os (NPO) for at least 12 h while receiving non dextrose containing IV fluids. BGL was measured at the time of admission, 8, and 12 hours later by using spectrophotometer and bed-side glucometer. In cases of hypoglycemia, glucose level was checked every hour until the normal blood glucose levels were achieved. The range of BGLs was divided into hypoglycemic (<70mg/dl), normoglycemic (70-126 mg/dl), and hyperglycemic (>126mg/dl) ranges (Ousman, 2002). We categorized the patients according to their blood glucose levels in 2 groups; hypo and hyperglycemia.

All patients received medical treatment under supervision of the hospital's consultant physicians. The tramadol overdose management is mostly supportive, with exact monitoring. Treatment should include early administration of charcoal. Naloxone as an opioid antagonist known to be partly effective in tramadol toxicity reverse may cause seizure. Benzodiazepines should be administrated for seizures control. All patients with hypoglycemia received an infusion of 0.5-1g/kg of hypertonic dextrose up to obtain a normal BGL. No medications were used to control hyperglycemia (Marquardt *et al.*, 2005).

STATISTICAL ANALYSES

Statistical analyses were performed using SPSS 15.0 (SPSS Inc. Chicago, Illinois). Continuous data was represented as means with SDs (SD) and ranges. Anova test was used for comparing means among groups. Categorical variables are summarized as frequencies and percentages. Chi-square test or Fisher's exact test were used for the variables comparison. $P<0.05$ was considered as the statistically significant level.

RESULTS

Characteristic data

A total of128tramadol poisoned patients were recruited in this study, with a mean (SD) age of 24.5 (6.9) years (range: 13-55years). There were 127 (99.2%) male and only one female patient. A single acute dose of tramadol oral ingestion was recorded in all patients. The mean (SD) tramadol dose was1825.68 (2642.22)mg, (range: 100-20000 mg). Four patients had positive history of co-ingestion with other drugs or substances, which were diazepam, clomiperamin and ethanol.

At the time of entry, the mean pulse rate, respiratory rate, blood pressure (systolic and diastolic) and auxiliary temperature, of the poisoned patients were 90±16 (64-150), 16±5 (8-55), 121±18.5mm Hg(70-190),76±10.4mm Hg (60-110) and 36.9±0.18°C (36.0-37.6), respectively. With regard to symptoms of all patients 21 cases (16.4%) presented with unconsciousness; sweating, paleness and restlessness were detected in (3.9%), 9(7%) and8 (6.3%) patients, respectively. 76(59.4%) cases presented with at least one episode of seizure and 8(6.9%) had more episodes.

Blood glucose assessment

Our main outcome measure was BGL. Mean (SD) admission BGL in our study was 94.88 (21.5) mg/dL (range10-185). Seven patients (5.6%) had blood glucose under 70mg/dLat entrance and in 6 of them BGL increased to upper 70mg/dLafter 8 hours. In one patient who had a BGL of 10mg/dL, it improved to 67mg/dL after 8 hours. All got back to normal range after 12 hours. In 6 cases, blood glucose declined to lower than 70mg/dLafter 8 hours. Mean (SD) plasma blood glucose level after 8 hours was 99.25(22.3) mg/dL (range 50-208). All these 6 cases got back to normal range after 12 hours. Mean (SD) blood glucose level after 12 hours was 102.0 (26.0) mg/dL (range 25-169). Only one patient experienced hypoglycemia as 25mg/d L exactly at 12

hours. A total of 14 patients experienced hypoglycemia within a 12 hour period. Yperglycemia was experienced in 8 patients (6.25%) on admission day; none required treatment.

HbA1c was measured in six hyperglycemic patients. Mean (SD) HbA1c was 6.33(0.4) (range 6-7). There was no significant relation between the BGL and symptoms and signs except consciousness (tables 1 and 2). Also there was no statistically significant relation between the dose of tramadol and BGL.

DISCUSSION

In the present study, 85% of all patients were ≤30 years old and only one patient was female. Recently, tramadol overdose was considered as one of the most frequent causes of drug poisoning, especially among young adult malesin Tehran by Shadnia *et al* (2008).

In a few case reports, the association of hypoglycemia and tramadol overdose was recorded (Mugunthan and Davoren, 2012). Epidemiology, severity, duration, recovery, and outcome associations of hypoglycemia in tramadol poisoning patients were investigated in current study. Within 12 hours of admission, 11% of our patients experienced at least one BGL lower than 70mg/dL and 3 (2.3%) sustained at least one value lower than 40mg/dL. According to the maximum, mean, and average tramadol dose, there were no significant differences between the patients with hypoglycemia and the others. It seems that hypoglycemia severity was not independently associated with the tramadol dose. Also hypoglycemia was not t related to other complication such as seizure. The present study showed that even moderate or severe hypoglycemia is not a prognostic and predictable factor of tramadol morbidity. Also, patients who had hyperglycemia on admission did not experience an increased rate of morbidity.

Several studies have reported on the association between opioids and glucose dys regulation in both humans and laboratory animals (Faskowitz *et al.,* 2013). Cheng *et al*. (2001) studied the effect of tramadol on the plasma glucose level among diabetic rats by streptozotocin (STZ). This hypoglycemia was treated using naloxone or naloxonazinein sufficient doses to block the opioid μ-receptors. Also, glycogen synthesis can be stimulated by tramadol in hepatocytes isolated from STZ-induced diabetic rats and this effect was blocked by naloxone and naloxonazine. In addition, the levels of glucose transporter's mRNA and protein in STZ-induced diabetic rats increased after repeated treatments with tramadol. Elevated mRNA and protein levels in the liver of STZ-induced diabetic rats were reversed with repeated tramadol treatment. The conclusion was that activation of opioid μ-receptors by tramadol can increase the glucose utilization and/or decrease gluconeogenesis of hepatocytes to lower plasma glucose in diabetic rats lacking insulin. They reported a dose-dependent lowering of plasma glucose in the fasting STZ-induced diabetic rats (Cheng *et al.,* 2001).

On the contrary, we didn't find any association between the tramadol dose and severity of hypoglycemia.

Choi SB and his colleagues showed tramadol did not alter hepatic glucose output directly and suggested that hepatic glucose utilization was altered by tramadolthrough the effect on the central nervous system (Choi *et al., 2005*).

In 2006 Grandvuillemin *et al*. reported 2 cases of tramadol-induced hypoglycemia. One presented in a diabetic 8-year-old girl and the other was a nondiabetic 88-year-old woman. In both cases, hypoglycemia recovered after tramadol discontinuation (Grandvuillemin *et al.,* 2006). Thus, hypoglycemia was considered as a serious side effect of tramadol and other case reports published in diabetic and non-diabetic patients (Taugourdeau *et al.,* 2011; Jonville-Bera *et al.,* 2010).

Mugunthan *et al*. reported a 54-year-old woman who had before undergone a partial hepatectomy. She experienced a prolonged hypoglycemia attributable to acute tramadol poisoning after ingestion of 3,000 mg of tramadol. She was treated with continuous intravenous glucose infusion for 24 hours (Mugunthan and Davoren, 2012). In comparison, we had no patient with prolonged hypoglycemia and all patients recovered within 12 hours.

In addition, Martins *et al*. detected significant increase in mean+/-SD blood glucose concentrations in dogs receiving tramadol (Martins *et al.,* 2010). Some studies investigated the relation between the admission blood glucose level and clinical outcome in ill patients. Sabzghabaee *et al*. indicated a significant difference between normoglycemic and hyperglycemic patients in the severity of poisoning and clinical outcome following acute poisoning (Sabzghabaee *et al.,* 2011). However, in our study we didn't find the same relation between hyperglycemia and measured morbidities.

Strengths and Limitations

Published reports are available for hypoglycemia with tramadol, but in the literature there are few case reports of tramadol induced hypoglycemia. We provided analysis of a large group with tramadol poisoning and the incidence of hypoglycemia. However, our study had some limitations. *Despite our* relatively large *study* population, there were only 14hypoglycemic and 8 hyperglycemic patients and the number of hypoglycemia and hyperglycemia were limited to compare. In addition we didn't measure the blood glucose levels in all patients after 12 hour. Since the prolonged hypoglycemia has been reported before, this risk was not considered in our study.

Table 1: The signs of patients according to blood glucose categories

Sign	Hypoglycemia		Normoglycemia		Hyperglycemia	
	Mean	SD	Mean	SD	Mean	SD
RR	15	3	16	5	16	1
HR	99	24	90	15	89	13
SBP	119.5	23	121.4	19	121.6	12.4
DBP	77.5	11.3	76.5	10.9	76.1	7.7
T	36.94	0.16	36.97	0.19	37.03	0.12

Table 1: The symptoms of patients according to blood glucose categories

Symptom	Hypoglycemia		Normoglycemia		Hyperglycemia	
	Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Conscious	5	41.7%	84	86.6%	17	94.4%
Paleness	2	18.2%	6	6.3%	1	5.6%
Sweating	1	12.5%	3	4.2%	1	7.1%
Restless	2	28.6%	5	6.2%	1	6.7%
Seizure	9	81.8%	58	66.7%	9	56.3%

In conclusion hypoglycemia must be considered as an important side effect of tramadol -overdose. It is suggested that serial BGL monitoring in cases of Tramadol-overdose should be done for early recognition of hypoglycemia and its timely management. Also hyperglycemia may be revealed.

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REFERENCES

Cheng JT, Liu IM, Chi TC, Tzeng TF, Lu FH and Chang CJ (2001). Plasma glucose lowering effect of tramadol in streptozotocin induced diabetic Rats. *Diabetes,* **50**: 2815-2821.

Choi SB, Jang JS and Park S (2005). Tramadol enhances hepatic insulin sensitivity via enhancing insulin signaling cascade in the cerebral cortex and hypothalamus of 90% pancreatectomized rats. *Brain Research Bulletin*, **67**: 77-86.

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

Duke AN, Bigelow GE, Lanier RK and Strain EC (2011). Discriminative stimulus effects of tramadol in humans. *J. Pharmacol. Exp. Ther*., **338**: 255-262.

Faskowitz AJ, Kramskiy VN and Pasternak GW (2013). Methadone-Induced Hypoglycemia. *Cell. Mol. Neurobiol.*, **33**: 537-542.

Gholami K, Shalviri G, Zarbakhsh A, Daryabari N and Yousefian S (2007). New guideline for tramadol usage following adverse drug reactions reported to the Iranian Pharmacovigilance Center. *Pharmacoepidemiol. Drug Saf*., **16**: 229-237.

Grandvuillemin A, Jolimoy G, Authier F, Dautriche A, Duhoux F and Sgro C (2006). Tramadol-induced hypoglycemia. 2 cases. *Presse. Med.*, **35**: 1842-1844.

Iravani FS, Akhgari M, Jokar F and Bahmanabadi L (2010). Current trends in tramadol related fatalities, Tehran, Iran 2005-2008. *Subst. Use Misuse*, **45**: 2162-2171.

Jonville-Bera A, Marie A, Magba D, Gedon E and Autret-Leca E (2010). Tramadol-induced hypoglycemia in a diabetic patient. *Therapie.,* **65**: 499-500.

Klotz U (2003). Tramadol the impact of its pharmacokinetic and pharmacodynamic properties on the clinical management of pain. *Arzneimittelforschung,* **53**: 681-87.

Marquardt KA, Alsop JA and Albertson TE (2005). Tramadol exposures reported to statewide poison control system. *Ann. Pharmacother.,* **39**: 1039-1044.

Martins TL, Kahvegian MA, Noel-Morgan J, Leon-Román MA, Otsuki DA and Fantoni DT (2010). Comparison of the effects of tramadol, codeine and ketoprofen alone or in combination on postoperative pain and on concentrations of blood glucose, serum cortisol and serum interleukin-6 in dogs undergoing maxillectomy or mandibulectomy. *Am. J. Vet. Res.*, **71**: 1019-26.

Mugunthan N and Davoren P (2012). Danger of hypoglycemia due to acute tramadol poisoning. *Endocr. Pract.*, **18**: 151-152.

Ousman Y (2002). Hyperglycemia in the hospitalized patient. *Clin. Diabetes,* **20**: 147-148.

Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE and Vaught JL (1992). Opioid and nonopioid

components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. *J. Pharmacol. Exp. Ther.,* **260**: 275-328.

Sabzghabaee AM, Eizadi-Mood N, Gheshlaghi F, Adib N and Safaeian L (2011). Is there a relationship between admission blood glucose level following acute poisoning and clinical outcome? *Arch. Med. Sci.*, **7**: 81-86.

Shadnia S, Soltaninejad K, Heydari K, Sasanian G and Abdollahi M (2008). Tramadol intoxication: A review of 114 cases. *Hum. Exp. Toxicol.,* **27**: 201-205.

Talaie H, Panahandeh R, Fayaznouri M, Asadi Z and Abdollahi M (2009). Dose-independent occurrence of seizure with tramadol. *J. Med. Toxicol.*, **5**: 63-67.

Taugourdeau S, Chiche L, Rouby F, Default A, Boyer M, Castellan D, Lanfranchi MA, Bornet C, Jean R, Harlé JR, Durand JM and Jean-Pastor MJ (2011). Severe hypoglycemia induced by tramadol: Two new cases of an unlisted side effect. *Rev. Med. Interne*., **32**: 703-705.

Zabihi E, Hoseinzaadeh A, Emami M, Mardani M, Mahmoud B and Akbar MA (2011). Potential for tramadol abuse by patients visiting pharmacies in Northern Iran. *Subst. Abuse*, **5**: 11-15.