IJPT
1735-2657/12/111-6-9
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 11: 6-9, 2012

ORIGINAL ARTICLE

Seizurogenic Effects of Low-dose Naloxone in Tramadol Overdose

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Received April 2, 2011; Revised September 25, 2011; Accepted October 11, 2011

This paper is available online at *http://ijpt.iums.ac.ir*

ABSTRACT

Tramadol is used in treatment of moderate to severe pain. Nowadays tramadol overdose is one of the common emergencies. Naloxone is an antagonist which is used as a first step of treatment in these patients. This study was designed to evaluate the seizurogenic effects of naloxone in tramadol overdose. A number of 124 patients with the diagnosis of tramadol overdose were divided to receive low-doses of intravenous naloxone (0.8 mg, case group) or just supportive cares (control group). All patients in case and control groups were observed by a single emergency resident and fallowed for 1.5 hours to document the happening of seizures. In the naloxone group, incidence of seizure was higher than in control group. The possibility of seizure occurrence was significantly higher in naloxone group than the control group (p<0.05). In conclusion, naloxone induced a seizurogenic effect in patients with tramadol overdose. This finding could be considered in the management of patients with tramadol overdose.

Keywords: *Tramadol overdoses, Naloxone, Seizure*

Tramadol is a centrally-acting analgesic commonly used in the treatment of moderate to severe pain. Tramadol produces its anti-noceptive and analgesic effects via opioid and non-opioid mechanisms. The opioid component involves low affinity to μ-opioid receptors and the non-opioid component inhibits the reuptake of serotonin and norepinephrine neurotransmitters [1]. Initially this new opioid painkiller medication was introduced as having safe and low abuse liability and widely used throughout the word. However, after a while, it was revealed that this agent has significant risks when overdose occurs. Nowadays, tramadol abuse has become a common medical emergency. The US Food and Drug Administration (FDA) MEDWATCH system has received hundreds of reports of tramadol-associated abuse, dependence, and withdrawal [2]. Among opioids listed in the 2001 and 2002 annual reports of the American Association of Poison Control Centres Toxic Exposure Surveillance System, tramadol was ranked second to oxycodone in number of exposure cases [3].

As one possible method for reducing drug-related deaths caused by opioid overdose, two significant adverse reactions which known to potentially occur with tramadol - seizures and serotonin syndrome- could dramatically be controlled by naloxone. Therefore, most guidelines for treatment of opioid overdose recommend short-acting opioid antagonist naloxone as the first step of treatment after supportive care [4]. Naloxone, is a phenanthrene compound structurally related to morphine. It was the first opiate receptor antagonist introduced in clinical practice [5] and has been widely used to antagonize the effects of opiate drugs. Indeed, most of biological effects of the analgesics have been long classified as opiate or non-opiate depending on whether or not they were reversed by naloxone [6].

Despite all advantages of naloxone, recent data showed serious adverse effects including several instances of seizures following naloxone administration [7]. Although the seizurogenic effects of low-dose naloxone in tramadol overdose has been reported rarely, but it could increase the mortality in patient whose in risk of seizure. This study was designed to evaluate the

Table 1. Demographic characteristics of 124 patients with tramadol overdose

Variable	Case* (N = 62)	Control** (N = 62)	*p* value
Age(year)	26.33	29.46	0.5
Male	59	55	0.18
Female	3	7	—
Single	35	27	0.15
Married	27	35	—

p value less than 0.05 considered significant

*The Cases received low-doses of naloxone, **The Controls received just supportive care.

role of naloxone in inducing seizure among patients with tramadol overdose.

METHODS AND MATERIALS

This study was conducted over a 12-month period from July 2008 to July 2009 in our University Hospital. One hundred twenty-four patients (age range: 17-58 years) of both genders with the diagnosis of tramadol overdose were allocated by randomization list to receive supportive care and low-doses of naloxone (case group) or just supportive care (control group). Participants were equally divided in two groups (case and control). Exclusion criteria consisted of being pregnant, those overdoses with multi-drug abuse and risk factors of seizure including electrolytes imbalance, low blood sugar or abnormal blood urea nitrogen (BUN) and creatinine. The patients in case group, in addition to usual supportive cares received 0.8 mg single dose intravenous (IV) naloxone. The patients in control group just received supportive care. The tramadol concentration were estimated with urine analysis on admission in the emergency ward using gas chromatography-mass spectrometry and it was considered positive if it showed high peak of tramadol of magnitude greater than the therapeutic range (0.1 to 0.3 mg/L).

All patients in case and control groups were observed by a single emergency resident and fallowed for 1.5 hours to document the happening of seizure. This short period was selected due to the short half-life of naloxone. The diagnosis of seizure was based on the onset of jerky movements of whole body, tonic and colonic spasms and convulsions which recorded as qualitative measures of experimental seizure activity.

All patients prognosis were observed in Emergency Department, and in case of occurring a life-threatening problem such as respiratory apnea or significant decrease in the level of consciousness, the patient were dropped out from the study and received advanced life support, naloxone, etc. They were discharged from the hospital after 24 hours if they were alert and cooperative. The study was undertaken after obtaining institutional ethics committee approval and subjects were enrolled only after obtaining informed coasted from the subjects.

Statistical analyses were performed with SPSS 16.0 Software for Windows. Demographic data, doses of drug and time of hospital referral after drug abuse were compared between case and control groups using the student t-test. Nominal data like gender, marital status or history of seizure were compared between groups using the chi-square or Fisher's exact test. Logistic regression was used to determine the effects of different past medical history of drugs and diseases on the outcomes. Data were presented as mean, median value of 25%-75% SD. All *p* values are two tailed. The $p<0.05$ was taken as statistically significant.

RESULTS

The study involved 124 patients, with 62 patients in each group with a mean (SD) age of 27 (3) years. Table 1 demonstrates demographic characteristics of the studied population. There were no significant differences between the two groups with regard to demographic data like age, gender and marital status. No patient was dropped out from the study. The doses

Table 2. Comparison of past medical history of the patients with tramadol overdose between the two studied groups (N = 124)

	Case† (N = 62)	Control†† (N = 62)	*p* value
Former drug overdose	24	34	0.07
Former tramadol overdose	8	7	0.78
History of seizure	3	5	0.71
CNS[1] disease	3	5	0.38
Alcoholism	0	1	1.00
Cigarette smoking	52	45	0.12

[1]Central Nervous System

†The Cases received low-doses of naloxone, ††The Controls received just supportive care.

p value less than 0.05 considered significant.

Table 3. Clinical outcomes of the patients with tramadol overdose between the two studied groups (N = 124)

	Case† (n = 62) N (%)	Control†† (n = 62) N (%)	*p* value
Seizure	15 (24%)	6 (9%)	0.02**
Serotonin Syndrome	0 (0%)	0 (0%)	0.83
Apnea	6 (9.6%)	4 (6.4%)	0.52
Loss of consciousness	12 (19.3%)	4 (6.4%)	0.2

†The Cases received low-doses of naloxone, ††The Controls received just supportive care.

***p* value less than 0.05 considered significant.

of tramadol abuse and the time of presentation to the hospital were significantly different between the two studied groups ($p<0.05$).

The history of alcoholism and smoking, central nervous system (CNS) disorders, history of previous tramadol or non-tramadol drug abuses and tramadol overdoses or tramadol- induced seizures were not significantly different between case and control groups ($p>0.05$) (Table 2). We evaluated the possible effect of all past medical events which may induce seizures. The only variable which significantly contributed in inducing seizures was previous tramadol overdose ($p<0.05$).

In both groups, symptoms reported with overdose were: lethargy 26 (30%), nausea 12 (14%), tachycardia 11 (13%), agitation 9 (10%), seizures 7 (8%), 4 each (5%) of coma and hypertension, and respiratory depression 2 (2%).

Clinical outcomes between case and control groups were followed during the hospitalization period (7 days in mean). In the naloxone group, incidence of seizure was significantly higher than in control group (15 patients in naloxone group vs. 6 patients in control group; $p<0.05$). But, there was no significant difference in other clinical outcomes such as loss of consciousness, serotonin syndrome or respiratory apnea between cases and controls (Table 3).

DISCUSSION

In the present study, we found that low doses of naloxone could increase the risk of seizure in patients with tramadol overdose. However, the history of previous tramadol overdose could have a coefficient effect on the side effect of naloxone. Although tramadol is a novel analgesic possessing which is used in the management of moderate to severe pain, there are some studies on the adverse effects of toxicity in overdoses due to different mechanisms like opioid-dependent gamma-aminobutyric acid inhibitory pathway [8] or histamine (H1 receptor) involvement [9] which could cause tramadol-induced seizures [10]. Furthermore, opioid antagonist naloxone which is recommended for taramdol overdose has controversial effects. Some studies indicated that administration of naloxone markedly attenuate this tramadol-induced potentiating of seizurogenic activity [11]. But on the other hand, other studies indicate that naloxone markedly increased colonic seizure [12] and even some of them showed that naloxone did not modify the reaction of tramadol seizurogenic effects [13]. Different susceptibility in some especial groups and studies could happen by the different personality characteristics like age and race. In addition, with regard to abuse and/or overdose, neurotoxicity of tramadol is speculated to be related to the reuptake inhibition of serotonin and norepinephrine rather than its opioid effects. Patients will be at risk of seizure as an adverse effect itself [14] and naloxone seizurogenic effect could put them in a worse condition.

It may be concluded that naloxone induced a seizurogenic effect in patients with tramadol overdose in Iranian young patients. With respect to high risk of seizure further experimentation may be useful to determine the mechanism of naloxone effect on tramadol overdose and other related biochemical changes occurring in the CNS and thus resulting in seizurogenic effects of naloxone especially in tramadol overdoses patients. Consequently, the therapeutic effect of naloxone in tramadol overdoses patients is still controversial. Our study sample was too small to certify the point. We also were not able completely to match the case and control groups in dosage abused and time of referral to hospital after intoxication and couldn't set the study as a randomized trial which were limitations of this study. But as a conclusion, we recommend until the certain general opinion on this issue, clinicians prescribe the naloxone with caution and only in special clinical indications like respiratory apnea.

ACKNOWLEGDEMENTS

The authors are grateful to Farzan Institute of Education and Technology for support and institutional facilities.

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