Abstract. – Background and Objectives: To determine the prevalence, type and site of the injuries due to tramadol-induced seizures in the patients who had referred after its overdose or use of its therapeutic dose.

Material and Methods: All patients referring to Loghman Hakim Poison Hospital (February 2009 to April 2010) due to tramadol-induced seizures were included. The patients’ data including age, gender, ingested dose by history, route of exposure, manner of poisoning, previous history of suicidal attempts, previous history of drug or substance abuse, history of tramadol abuse, type of the seizure, number of episodes of seizure before presentation or after admission, site of the trauma, and type of injury were recorded.

Results: A total of 232 patients were included in the study. Of them, 185 (79.7%) had referred within the first 6 hours after ingestion. The mean dose ingested by the history was 1416±1124 mg. History of tramadol abuse was positive in 114 (49.1%) patients. Seizure episodes had occurred once in 207 (89.2%), twice in 21 (9.1%), and three times in 4 (1.7%) patients. The prevalence of trauma was 24.6% (in 57 patients) with the most frequent site of trauma to the face (9.5%) followed by shoulder (4.3%), head (3%), trunk (1.7%), and upper extremities (1.3%). No statistically significant difference was found between patients with and without trauma associated with tramadol-induced seizures in terms of age, gender, ingested dose by history, positive history of addiction to other opioids, and number of episodes of seizure.

Conclusions: The only serious injury associated with this type of seizure was the head injury, present in approximately 1% of the patients.

Key Words: Tramadol, Seizure, Trauma, Type of injury.

Introduction

Tramadol is an analgesic with dual mechanism of action: induction of weak agonist effects at the µ opioid receptor and inhibition of serotonin and norepinephrine reuptake. It is one of the most widely used analgesics due to its multimodal analgesic mechanisms.

One of the complications of the tramadol use is the seizure which is most often generalized tonic-clonic. Attention to seizure-associated trauma is very important. However, evaluation of the prevalence of trauma has not been performed in the patients who refer with seizures after tramadol overdose or as a side effect following the use of a therapeutic dose of it. The aim of this study was to determine the prevalence, type and site of the injuries due to tramadol-induced seizures in the patients who had referred after its overdose or use of its therapeutic dose.

Materials and Methods

In this retrospective study, all patients with tramadol-induced seizures referring to Loghman Hakim Poison Hospital in Tehran, Iran between February 2009 and April 2010 were evaluated. Medical charts of all the admitted patients who had experienced seizures before presentation or after admission due to either tramadol overdose or as a side effect of its therapeutic use were identified using diagnosis code through the computer search from all those patients who had referred with tramadol toxicity. The diagnosis of seizures before hospital presentation had been confirmed by an accurate medical history taken from the people accompanying the patient or the
report of the personnel of Emergency Medical Service. Since the diagnosis of seizure types except tonic-clonic type is very difficult for the people other than the medical staff, it can be concluded that all seizures reported before the hospital presentation had been of the tonic-clonic type.

The patients with co-ingestion of other drugs and those with previous history of convulsive disorders were excluded. The patients’ data including age, gender, ingested dose by history, route of exposure, manner of poisoning, previous history of suicidal attempts, previous history of drug or substance abuse, history of tramadol abuse, type of the seizure, number of episodes of seizures before presentation or after admission, site of the trauma, and type of the injury were extracted from the medical charts and entered into the abstraction forms. All patients had received therapeutic interventions including gut decontamination and standard supportive care when indicated.

**Statistical Analysis**

To compare the patients with and without trauma associated with tramadol-induced seizure, statistical analysis was done using SPSS software, version 17 (SPSS Inc., Chicago, IL, USA) and application of Kolmogorov-Smirnov, Mann-Whitney U-test, Pearson’s chi square or Fisher’s exact test, and Student’s t-test. A p value less than 0.05 was considered to be statistically significant.

**Results**

A total of 232 patients with tramadol-induced seizures met our inclusion criteria and were entered into the study. Of them, 197 (84.9%) were male and 35 (15.1%) were female. Mean age of the patients was 23±6 years old (range: 3 to 60 years). In all patients, the route of exposure was oral. A total of 101 (43.5%) patients had referred within the first one to three hours post-ingestion; 84 (36.2%) had referred within 3 to 6 hours post-ingestion and 185 patients (79.7%) had referred within the first 6 hours after ingestion). The mean dose ingested by the history was 1416±1124 mg (range: 100 to 6000 mg). Two patients (16 years and 34 years) had convulsed with 100 mg of tramadol. Additionally, a 3-year-old and a 12-year-old had developed seizure after ingestion of 150 mg and 100 mg of tramadol, respectively. History of tramadol abuse was present in 114 (49.1%) patients. Forty-eight (20.7%) patients were addicted to opioids other than tramadol. Sixty-three (27.2%) had the previous history of suicide attempts. A total of 141 (60.8%) patients had ingested tramadol to suicide; 84 (36.2%) had been intoxicated as a side effect of drug abuse; 5 (2.2%) had ingested it for therapeutic purposes, and 2 (0.9%) had mistakenly taken the medication. The type of seizure was reported to be tonic-clonic in all cases including those who had experienced seizures after admission. Seizures episodes before presentation or in the course of hospital stay had occurred once in 207 (89.2%), twice in 21 (9.1%), and three times in 4 (1.7%) patients.

The prevalence of trauma was 24.6% (in 57 patients). Frequent sites of trauma included face (9.5%), shoulder (4.3%), head (3%), trunk (1.7%), and upper extremities (1.3%). Frequency of the types of injuries associated with tramadol-induced seizures is shown in Figure 1. Comparison of the clinical characteristics of the patients with tramadol-induced seizures with and without trauma is presented in Table I. As shown in this table, no statistically significant difference was found between the clinical characteristics of these two groups.

**Discussion**

It has been stated that tramadol is one of the most widely used analgesics worldwide. Seizures due to tramadol use may occur in both overdose and within therapeutic dose range. It has been shown that the appearance of seizures with tramadol is not dose dependent, as in our study, in which the minimum dose of tramadol that caused seizure was 100 mg. To our knowledge, no study has been performed to evaluate the prevalence of trauma in the patients who overdose on tramadol or refer with seizures induced by the use of its therapeutic doses. The present study shows that the prevalence of trauma in patients with tramadol-induced seizures is approximately 25% with the most common site of trauma to the face. The most common type of trauma was the abrasion, and the most uncommon types of injury were burning and head injuries. Furthermore, our study demonstrated that the occurrence of trauma was statistically independent of age, gender, ingested dose by history, positive history of addiction to other opioids, and
number of episodes of seizures. Since the seizure due to tramadol use is generalized tonic-clonic,
our study is maybe comparable with the only re-
view article on the accidents and injuries in pa-
tients with epilepsy. The Author had shown that
most of the injuries associated with epilepsy
were minor with its most common types to be
contusion and laceration followed by abrasions.
He had mentioned burning as the least common
type of injury. We observed that subarachnoid
hemorrhage and skull fracture were the most un-
common injuries, as well as burning. This shows
a different trend of frequency compared with the
above mentioned study.

Conclusions

According to our findings, although seizure-re-
lated traumas in tramadol use occur in about 25% of the cases, the related injuries are in most cases
not serious. The only serious injury associated with
this type of seizure is head injury which is present
in approximately 1% of the patients.

Table I. Comparison between the patients with tramadol-induced seizure with and without trauma.

<table>
<thead>
<tr>
<th></th>
<th>Traumatic patients</th>
<th>Non-traumatic patients</th>
<th>p value (applied statistical test)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (years)</td>
<td>23.5 (± 5)</td>
<td>22.5 (± 6)</td>
<td>0.25 (Student’s t-test)</td>
</tr>
<tr>
<td><strong>Gender (Male/Female)</strong></td>
<td>46/11</td>
<td>151/24</td>
<td>0.31 (P chi²)</td>
</tr>
<tr>
<td><strong>Dose ingested by the history</strong></td>
<td>1468.5 (± 1136)</td>
<td>1399.5 (± 1123.5)</td>
<td>0.53 (MWU)</td>
</tr>
<tr>
<td><strong>History of drug or substance abuse</strong></td>
<td>11/23</td>
<td>37/89</td>
<td>0.74 (P chi²)</td>
</tr>
<tr>
<td><strong>Episodes of seizure(s)</strong> (once/twice or more)</td>
<td>52/5</td>
<td>155/20</td>
<td>0.57 (Fisher’s exact test)</td>
</tr>
</tbody>
</table>

MWU: Mann-Whitney U-test, P chi²: Pearson’s chi square test, *None of the p values were significant (< 0.05), Data are presented as mean value (± standard deviation).
References

2) Raffa RB, Stone DJ Jr. Unexceptional seizure potential of tramadol or its enantiomers or metabolites in mice. J Pharmacol Exp Ther 2008; 325: 500-506.