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Original Contribution

Tramadol-induced apnea

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Abstract

Background and Objectives: In contrast with other opioids, there are few cases of tramadol-related respiratory depression described in the literature, and renal impairment is a proposed risk factor. The aim of this study is to determine the prevalence of and predisposing factors for tramadol-related apnea in patients referred to our center.

Patients and Methods: All patients referred to Loghman-Hakim Hospital between February 2009 and April 2010 with pure tramadol intoxication were identified retrospectively. Data collected included the patient's age, sex, ingested dose, route of exposure, reason for poisoning (acute overdose or supratherapeutic use), previous history of suicidal attempts, previous history of drug or substance abuse (including tramadol), and clinical features on admission including seizures and apnea.

Results: We identified 525 patients with deliberate self-poisoning (359; 68.4%) or abuse (146; 27.8%), and in 114 (21.7%) of these, there was a history of tramadol abuse. Four hundred twenty-nine (81.7%) of patients had acute poisoning and were referred to hospital within 6 hours of ingestion. Nineteen patients (3.6%) experienced apnea and received respiratory support (16; 84.2%) or naloxone administration (3; 15.8%) within 24 hours of ingestion (mean, 7.7 ± 7 hours; range, 1-24 hours). The mean dose ingested by patients experiencing apnea was 2125 ± 1360 mg (range, 200-4600 mg), which was significantly higher than those who did not experience apnea, 1383 ± 1088 mg (range, 100-6000 mg), $P < .001$. One death occurred in each group, which was significant ($P < .001$). Renal impairment was not observed in any of the patients who experienced apnea.

1. Introduction

Tramadol is a widely used analgesic with a dual mechanism of action: weak agonist at the μ-opioid receptor and inhibition of serotonin and norepinephrine reuptake [1]. It is generally considered to lack the serious adverse effects of pure opioid receptor agonists, such as respiratory depression and drug dependence [2]. Although it appears be a safe and effective analgesic, adverse effects are reported particularly from abuse and intoxication [3]. Intravenous exposure to tramadol has caused apnea [4,5] and death due to nonrespiratory etiology [6,7]. In some autopsied cases associated with tramadol, the route of exposure was not clear [8-10]. In studies involving oral administration of tramadol, death was attributed to coingestion of other central nervous system depressants particularly benzodiazepines, barbiturates, and/or drugs with serotonergic effects [11-14]. Impaired clearance of the metabolite in patients with renal

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impairment has also been thought to contribute to deaths [15,16].

Tramadol was marketed in Iran in 2002 [17], and since then, its use has increased. The Iranian Ministry of Health reported that 24 million tramadol tablets (100 mg) were sold from March 21, 2004, through March 20, 2005, during an Iranian year. In the next year, sales increased to 162 million and then 350 million the following year (2006-2007), consistent with a 14.6-fold increase over 2 years [18]. Because of increasing misuse among adolescents, tramadol was classified as a controlled drug in Iran in April 2007 [19]. However, undocumented supply (eg, without a prescription) appears to be common, so these data most likely underestimate the true usage of tramadol in Iran [20].

The incidence of tramadol poisoning has also increased during this time. Interestingly, there were no reports of acute poisoning noted 2003 to 2005 [21-23]. The Iranian Pharmacovigilance Center reported 337 cases of tramadol-induced adverse drug reaction with therapeutic use, including 3 deaths from April 2002 to February 2005 [17]. A retrospective study in Tehran noted that tramadol exposure was present in more than 15% of hospitalized poisoned patients who were older than 12 years (2006 to 2007) [24]. Forensic data from Tehran show an increasing incidence of death due to tramadol, from 4 cases in 2005 to 62, 98, and 130 cases in 2006, 2007, and 2008, respectively, a 32.5 times increase in deaths [25].

Opioid agonist activity appears to be an important contributor to death from tramadol poisoning, including respiratory depression and apnea. The aim of this study was to determine the prevalence of and predisposing factors for tramadol-related apnea in poisoned patients referred to our center.

2. Patients and methods

In this retrospective study, all patients referred to Loghman-Hakim Hospital (February 2009 to April 2010) due to pure tramadol poisoning were identified via coding by medical records; patients with coingestants were excluded. Data recorded in the medical records include patient demographics, details of the exposure, clinical observations, and important complications, which include respiratory arrest and seizures. Extracted data included the patient's age, sex, number and strength of tramadol tablets, route of exposure, type of exposure (acute overdose or supratherapeutic dosing), previous history of suicidal attempts, previous history of drug or substance abuse, history of tramadol abuse, seizure and apnea occurrence, elapsed hours of intoxication/adverse effects, and length of hospitalization were recorded. All of the tramadol preparations taken by our patients are registered medical products in our country.

Data were collected by use of a predetermined questionnaire. *Apnea* was defined as sudden complete cessation of breathing and cyanosis, requiring medical intervention. Apnea could also be diagnosed in the prehospital setting from data routinely recorded by personnel of emergency medical service, which are paramedics and/or physicians who go to the scene. Because of retrospective nature and the likelihood of selection bias, details on milder forms of respiratory depression were not included in this study.

In hospital, all patients had received therapeutic interventions including standard supportive care and gut decontamination including charcoal administration when indicated. According to our hospital protocol, naloxone administration was not routinely administered for loss of consciousness in tramadol poisoning unless there was rapid progression of respiratory depression.

Statistical analysis was performed using SPSS software (SPSS, Chicago, IL). Here, continuous data were analyzed using the Student t test if the data were normally distributed (according to the Kolmogorov-Smirnov test); otherwise, the Mann-Whitney U test was used. Categorical data were compared using Pearson χ^2 test. $P < .05$ was considered to be statistically significant.

3. Results

During the 14 months encompassed by this study, nearly 32 000 patients presented to our institution, and 14 000 of these were hospitalized. We identified 732 patients (~5.4% of hospitalized patients) with a history of tramadol exposure, of which 525 reported poisoning with tramadol as the sole agent so were included in the study; see Fig. The mean age was 22.8 ± 6.9 years (range, 3-72 years), and they were predominately males (70.1%). The reason for presentation was intentional self-poisoning in 359 patients (68.4%) or abuse in 146 patients (27.8%). Eight patients (1.5%) had accidental poisoning, and data were unavailable in 12

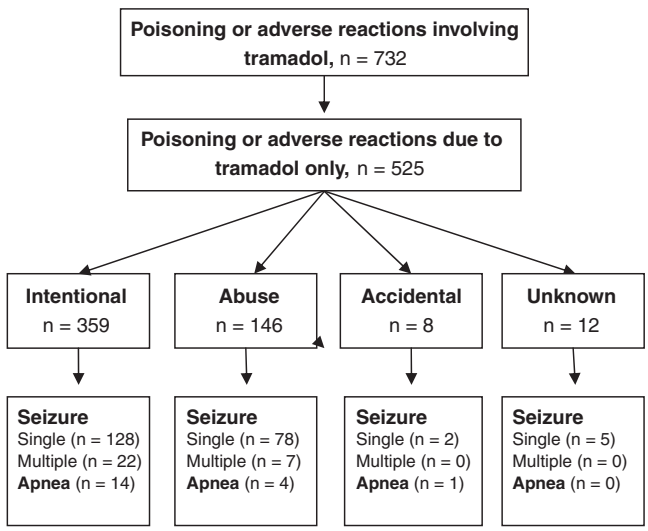

Fig. Flow chart of hospitalized tramadol-related intoxication/adverse effect in Loghman-Hakim Hospital 2010.

patients. However, there was a history of tramadol abuse in 204 patients (38.9%) and addiction history to substances in 86 patients (16.4%), whereas data were not recorded in 21 (4%) and 142 (27%) patients, respectively.

In all patients, the route of exposure was oral. Documentation was insufficient to identify patients ingesting sustained release formulation, although we anticipate that most exposures were with immediate release preparations. Two hundred sixty-four patients (50.3%) presented within 1 to 3 hours of tramadol ingestion, and 165 (31.4%) presented to hospital 3 to 6 hours postingestion.

Tonic-clonic seizures occurred in 242 patients (46.1%); there was a single episode in 213 (88.1%) patients, or they were recurrent in 29 patients (11.9%). Apnea was observed in 19 (3.6%) of patients within 24 hours of ingestion (mean, 7.7 ± 7 hours; range, 1-24) (Table 1). Treatment for apnea included intubation and ventilation in 16 patients (84.2%) or naloxone administration in the remaining 3 patients (15.8%). The minimum tramadol dose associated with apnea was only 200 mg. Regarding risk factors, none of the patients had a history of medical comorbidities or evidence of renal impairment based on routine blood tests.

The clinical characteristics of the patients with tramadol-induced apnea are compared with those without apnea in Table 2. No statistically significant differences were observed, with the exception of ingested dose and mortality.

4. Discussion

This is the first large cohort study describing an incidence of apnea in 3.6% of patients with isolated tramadol overdose. No definite risk factors for the development of apnea were identified. Although the mean dose ingested was statistically larger in those who developed apnea, a wide range of doses (as low as 200 mg) were reported. The mortality from tramadol poisoning appeared to be increased in those patients with apnea;

Table 1 Characteristics of 19 tramadol alone–induced apnea patients

N	Age (y) and sex	Elapsed hours (ingestion-admission)	Manner of ingestion	Dose (mg)	Apnea time postingestion	Naloxone administration	Seizure episodes	Addiction history	Tramadol abuser	Hospital stay (d)	Suicide history	Death
1	40M	3-6	Abuse	1000	–		Nil	Yes	Yes	24-48	Yes	Yes
2	26M	3-6	Abuse	500	1.30		Nil	Yes	Unknown	0-24	No	No
3	22F	1-3	Abuse	2000	6.00		Nil	Yes	No	0-24	No	No
4	40M	1-3	Abuse	200	1.00		Nil	Yes	Yes	0-24	Yes	No
5	22M	3-6	Self-poisoning	2700	4.00		One	Unknown	No	48-72	Yes	No
6	17F	1-3	Self-poisoning	1000	5.00		One	No	No	24-48	No	No
7	20F	1-3	Self-poisoning	3500	6.00		One	Unknown	Yes	0-24	Yes	No
8	24M	>9	Self-poisoning	1500	24.00	Yes	One	No	Yes	48-72	Yes	No
9	24M	>9	Self-poisoning	4000	12.00		One	No	Yes	0-24	No	No
10	18F	1-3	Self-poisoning	1500	14.00	Yes	Nil	No	No	48-72	No	No
11	41F	1-3	Self-poisoning	3000	5.00		Nil	No	No	0-24	No	No
12	21F	6-9	Self-poisoning	1000	11.00		Nil	No	No	0-24	Yes	No
13	29M	1-3	Self-poisoning	3000	6.00		Nil	Yes	No	0-24	No	No
14	20M	1-3	Self-poisoning	4600	8.00		Nil	No	Yes	48-72	No	No
15	17M	1-3	Self-poisoning	2000	1.00		Nil	No	Yes	0-24	No	No
16	24M	1-3	Abuse	1000	1.30		Nil	Unknown	Unknown	0-24	No	No
17	19M	>9	Self-poisoning	4000	24.00	Yes	Nil	No	No	48-72	No	No
18	23M	3-6	Self-poisoning	4000	8.00		Nil	Unknown	Yes	48-72	No	No
19	20F	1-3	Self-poisoning	1000	–		One	No	Yes	>72	Yes	No

Table 2 Comparison between the patients with tramadol alone–induced apnea and the others

Variable	Apnea patients	Other patients	*P* value (applied statistical test)
Age	24.6 (±7.6)	22.8 (±6.9)	.40 (Student *t* test)
Sex (male/female)	12/7	356/150	.50 (Pearson χ^2)
Dose ingested by the history	2184.2 (±1371)	1358.4 (±1071.8)	.001 (MWU)
History of drug or substance abuse [a] (positive/negative)	5/10	81/287	.303 (Pearson χ^2)
History of suicidal attempt (positive/negative)	7/12	133/373	.307 (Pearson χ^2)
Seizure (positive/negative)	6/13	236/270	.196 (Pearson χ^2)
Tramadol dependency [a] (positive/negative)	9/8	195/292	.197 (Pearson χ^2)
Self-poisoning (positive/negative)	14/5	345/161	.613 (Pearson χ^2)
Death (positive/negative)	1/18	1/505	.001 (Pearson χ^2)

Data are presented as mean value (±SD). Abbreviation: MWU, Mann-Whitney *U* test.
[a] Unknown or unreliable cases were deleted. Not included cigarette.

although overall numbers were low so further studies are required to confirm this association.

Tramadol is an agonist at μ-opioid receptors as well as on the noradrenergic and serotonergic systems. Cytochrome P450 (CYP) 2D6 catalyses O-demethylation of tramadol to the more active M1 (O-desmethyl tramadol) enantiomers, which have an affinity at the μ-receptor that is 200 times that of (+) tramadol. Furthermore, it has an elimination half-life of 9 hours, compared with 6 hours for tramadol, and, therefore, may accumulate with regular dosing.

There is a large interindividual variability in the enzyme activity of CYP2D6 within a population and between ethnic groups [1,26,27]. The production of M1 enantiomers can vary more than 30-fold between poor and extensive metabolizers, which, in turn, is associated with variability in the analgesic and toxic effects of tramadol [28].

Dopamine release in various regions of the central nervous system is associated with dependency. Agonists of μ-opioid receptors stimulate the release of dopamine as well as inhibiting gamma aminobutyric acid (GABA) release, which inhibits dopamine release [26,29,30]. Because tramadol and its metabolites are agonists at μ-opioid receptors, tramadol use is associated with dependence. Considering that ethnic groups from the Middle East and East Africa are more likely to be ultrarapid metabolizers compared with those from Middle Europe and North America (incidence 21%-29% vs 0.5%-1%, respectively), we expect that people in the Middle East are more susceptible to opioid effects, including dependency, seizure, sedation, and respiratory depression. The prevalence of tramadol-induced seizures in substance abusers from Mediterranean countries is 54%, which is high; here, the frequency of the CYP2D6 ultrarapid metabolizers is up to 12% of population [3,31]. Similarly, in Iran, the mortality from tramadol intoxication is largely due to seizures and is as high as 7.4% [32]; we anticipate that the frequency of ultrarapid metabolizers is similar in Iran to Mediterranean countries.

The mechanism of tramadol-induced seizures is poorly described, although high concentrations of tramadol can inhibit GABA receptors [33,34]. Inhibition of GABA receptors can potentiate the severity of seizures in animal models [34,35]. In addition, inhibition of GABA receptors by tramadol can be secondary to its opioid receptor agonist activity [34], and continuing this agonist activity on opioid receptor has been shown to evoke seizure due to inhibition of GABA pathways [36,37]. However, multiple factors may contribute to the development of seizures in patients ingesting tramadol, including an underlying seizure disorder, concomitant use of proconvulsant medications, withdrawal from ethanol or depressants of the central nervous system, or head injuries.

There are conflicting data on the proconvulsant effect of naloxone in tramadol intoxicated patients. The manufacturer's package insert cautions against using naloxone in patients with tramadol overdose because animal studies demonstrated that this increased the risk of seizures [38]. In animals poisoned by tramadol, naloxone administration increased the occurrence seizures, which was thought to be a dose-dependent effect of the (−) enantiomer [39]. Clinical experience has also shown a varying association. Naloxone administration to 8 cases with sedation and respiratory depression was followed by immediate convulsions in 1 patient [40]. We noted seizures in 1 of the 3 patients administered naloxone in our series. In a clinical study comparing the effect of 0.8 mg naloxone in tramadol overdose, compared with supportive care, seizures occurred in 28.3% vs 11.2% of patient, respectively [41]. Another study did not demonstrate a proconvulsive effect of naloxone but instead suggested that it improved clinical outcomes [42]. The association between seizures and naloxone administration in such patients is unclear and may simply reflect the exposure to tramadol. To reduce the inclusion of cases of other serotoninergic neuromuscular effects in this study, we only considered cases of generalized tonic-clonic seizures. The higher incidence of seizures noted in our series may reflect a referral bias. More research is required to clarify the relevance of animal data to human exposures.

Our study shows that oral tramadol can induce apnea from either overdose or within the therapeutic dose range. The minimum dose of tramadol that caused apnea in our study was 200 mg, and a significantly higher mean dose of

tramadol was observed in patients who developed apnea (Table 2). Administration of (+)-M1 to rats in doses greater than 2.5 mg/kg induced dose-dependent respiratory depression. In contrast, doses of (−)-M1 up to 8 mg/kg showed neither antinociception nor respiratory effects [43]. In another study, intravenous administration of 1, 2, and 4 mg/kg tramadol altered the apneic thresholds in cats, decreasing their sensitivity to carbon dioxide [44]. Oral administration of 100 mg tramadol depressed respiration in 10 healthy volunteers, by reducing the ventilatory carbon dioxide sensitivity by 30% without a change in the metabolic or arousal state. The authors suggested that the effect of 100-mg tramadol is equivalent to that of intravenous morphine 0.13 mg/kg in healthy volunteers without pain [45]. Therefore, significant opioid effects may be observed in patients administered therapeutic doses of tramadol.

To our knowledge, no clinical study evaluated the prevalence of apnea in the patients who ingested oral tramadol alone. Spiller et al [40] demonstrated respiratory depression in 2 (2%) of 87 cases ingesting tramadol alone, although the route of exposure was not mentioned.

In another prospective study on 427 cases (including some mixed overdoses), 62 (14.8%) had respiratory depression, of whom 19 (3.6%) experienced apnea. There was significant correlation between the dose of tramadol and respiratory depression [46]. Shadnia et al [47] described 2 deaths in their study, which one of them had respiratory depression. In a tramadol-induced adverse drug reaction study, 12 (4.8%) and 73 (29.3%) of 249 cases report dyspnea and convulsion, respectively. Three deaths (1.2%) suspected to be induced by tramadol [20]. In addition, there are some case reports, which describe respiratory depression by intravenous tramadol or in renal impairment patients [4,5,15].

Regarding risk factors, our study demonstrated that the occurrence of apnea was statistically independent of age, sex, history of addiction to other opioids and tramadol, the reason for poisoning, history of suicide attempt, and seizure occurrence. It is not surprising that mortality would be higher in apnea patients. We did not identify any demographic or clinical features predisposing to apnea in this study. In particular, renal impairment was not present in any of the patients who experienced apnea.

5. Conclusions

Tramadol abuse and intoxication are social and health concerns in Iran, in particular to the younger population. We observed that apnea occurs in 3.6% of cases when tramadol was the sole poison, and this may occur up to 24 hours postingestion and is not preceded by prominent central nervous system depression or seizures. The cases of apnea presented here are a fraction of the number of patients with lesser degrees of respiratory depression due to tramadol; these cases also need prompt diagnosis and treatment. Therefore, we advise that observation for at least 24 hours is required in patients presenting with tramadol poisoning. These severe manifestations of poisoning could be more common in our patients, due to ethnic susceptibility factors. Further clinical studies to measure tramadol, its metabolites, and their ratio as well as the metabolic activity of CYP2D6 may clarify the patterns of tramadol abuse observed in Iran.

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