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Short Communication

Investigation of clinical and paraclinical consequences of tramadol poisoning and related factors

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Abstract
Tramadol, is frequently misused and leading to an increase in cases of overdose and poisoning worldwide. This study aimed to investigate the clinical and paraclinical consequences of tramadol poisoning and related factors. This was a retrospective study performed on patients with acute tramadol poisoning who were referred to the Amir Al-Momenin Hospital Emergency Department, Zabol, during 2019-2020. Patients' socio-demographic information and clinical and paraclinical manifestations were collected in a predesigned checklist. Overall, 71 subjects were included in this study. The mean dose of tramadol was 640.14±521 mg. Seizures occurred in 17 subjects that were not dose-dependent. In patients who died or were in a coma, pH, bicarbonate (HCO_3), and oxygen saturation (O_2sat) levels decreased, while PCO_2 levels increased significantly ($P<0.05$). The dose of tramadol used in the poisoning of this substance played no role in the course of the disease and the prognosis of patients, but low pH, HCO_3, O_2sat, and high CO_2 pressure could be related to the outcome of these patients.
Keywords: Tramadol, Poisoning, Overdose, Seizure, Arterial blood gases

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Introduction

Tramadol is a central analgesic that works through opioid receptors and monoamine reuptake mechanisms that inhibit the reuptake of serotonin and norepinephrine and enhance the inhibitory effects of spinal pain transmission. Therefore, it is used as an analgesic to treat acute and severe pain (1,2).

Tramadol is utilized in clinical practice as an analgesic. In addition, it is used for patients in the postoperative period and in the treatment of chronic pain syndromes (3). The medication comes in several forms, including tablets, drops, capsules, suppositories, and injections, but people typically take it orally (4). Doses of 100-300 mg are prescribed as analgesics. However, at a dose of 500 mg, it increases seizures, respiratory depression, and coma, and at a dose of 3000-5000 mg, it causes death (5). The most important side effects of the drug are dependence and seizures. The common and tonic type of clonic seizure, which can occasionally be extremely long and dangerous and result in irreversible side effects, is the most typical type of seizure experienced by professional tramadol users (6).

The mechanisms of action of tramadol have not been fully elucidated, and most studies have focused on opioid receptor activation and inhibition of monoamine reuptake as tramadol mechanisms. However, many studies have shown that G-protein-coupled receptors and ion channels are targets of tramadol (7). Knowing the various side effects of tramadol poisoning and especially the various factors involved can help better predict the condition of these patients and effective preventative measures to prevent the side effects from getting worse.

Materials and Methods

This was a retrospective study conducted on patients with acute tramadol poisoning who were referred to the Amir Al-Momenin Hospital Emergency Department, Zabol, Iran, during the period between the start of January 2019 and the end of January 2020. The exclusion criteria were co-ingestion, uncertainty about the time of tramadol ingestion, intoxication with an unknown dose of tramadol, the onset of a seizure before admission to the hospital, and a past medical history of epilepsy.

The medical records were used to extract information about the patient's socio-demographic characteristics, the time and amount of the substance they ingested, the reason they became intoxicated, their pulse rate, their respiratory rate, and their body temperature. The other obtained data included their Glasgow Coma Scale readings at the time of admission, the therapeutic interventions they received,

and patients' outcomes. Laboratory findings, including pH, HCO_3, PO_2, PCO_2, O_{2sat}, blood sugar, cell blood count, and blood gas on admission time, were retrieved from patients' medical records.

The statistical procedures were performed in SPSS software (version 20). Numbers and percentages, as well as means and standard deviations, were utilized for qualitative and quantitative variables, respectively. The Chi-square test was employed for statistical comparison of qualitative variables, and a *P* of 0.05 or less was statistically significant.

Results

The mean age of the patients was 38.21 ± 11.95 years, and the youngest and oldest were 1 and 60 years old, respectively. A total of 48 (67.6%) were men and 23 (32.3%) were women.

About 40 (56.3%) patients had some form of occupation (school, work, or work practice), whereas 31 (43.7%) had no form of occupation, and only three patients (4.2%) had a history of the underlying disease.

The average dose of tramadol was 640.14 ± 521 mg, and the lowest and highest doses were 50 mg and 3,000 mg, respectively. Nearly 39 (54.95%) patients had taken a dose of tramadol above 400 mg (maximum normal dose). However, they all consumed tramadol voluntarily.

In this study, 17 (23.95%) patients also had a history of concomitant opioid use, and the lowest and highest opioids used by the patients were traditional opioids and opium, respectively.

The most commonly reported side effect was seizures, which occurred in only 17 (23.9%) patients, and 64% of them had experienced seizures only once.

Approximately 64 (90.1%) patients recovered after intensive care, while 4 (5.6%) of them died. Based on the results, 3 (8.2%) other patients also suffered from brain death and coma, which were not significantly related to the dose of tramadol (*P* = 0.407, Table 1).

Laboratory results revealed that in patients who died or were in a coma, pH, HCO_3, and O_{2sat} levels decreased, whereas PCO_2 levels represented a significant increase (Table 2).

Discussion

In this study, the average dose of tramadol was 640.14 ± 521 mg, and 39 (54.95%) of patients had taken a dose of tramadol above 400 mg (the maximum normal dose). In our study, seizures were the most commonly reported side effects, which occurred in only 17 (23.9%) patients, and 64% of them had experienced seizures only once.

Overall, 64 (90.1%) patients recovered after intensive care, whereas 4 (5.6%) of them died. Moreover, 3 (8.2%) other patients suffered from brain death and coma, which were not significantly associated with the dose of tramadol (*P* = 0.407). According to laboratory results, pH, HCO_3, and O_2sat levels decreased in patients who died or were in a coma, while PCO_2 levels increased noticeably.

Tramadol abuse and poisoning are among the most common health problems in Iran and the world (8,9).

Most patients in our study were men, and this significant increase in men's poisoning with tramadol is in line with the results of other studies. This increase in tramadol abuse in males can be justified by claims of increased sexual function and cases such as overcoming fatigue and difficulty at work (10,11). Seizures, a common complication of tramadol poisoning, were observed in 23% of patients. According to the results of studies, an increase in the frequency of seizures in tramadol abuse is more common in countries such as Iran and Egypt, where there are more illegal forms of tramadol (10). A single seizure was the most frequent one that happened in 64% of patients, while multiple seizures were observed in 36% of cases. These results contradict the findings of Taghaddosinejad et al (4), where only 15.7% of patients experienced seizures more than once. The results of this study indicated the dose of tramadol used in patients was not significantly associated with the incidence of seizures, and seizures can occur at different doses of tramadol poisoning. These results are in line with those of Habibollahi et al (12). However, Jovanović-Cupić et al (13) and Taghaddosinejad et al (4) found that tramadol-induced seizures were dose-dependent; this difference may be due to the chronic use of tramadol in patients participating in the above studies. They further reported

Table 1. Outcomes of treatment in patients based on the dose of applied tramadol

Treatment process	Dose of tramadol		*P* value
	High Dose (>400 mg)	Low Dose (<400 mg)	
Recovered	35 (89.7%)	29 (90.6%)	0.407
Coma	2 (5.1%)	0 (0%)	
Brain death	0 (0%)	1 (3.1%)	
Death	2 (5.1%)	2 (6.3%)	
Total	39 (100%)	32 (100%)	

Table 2. Outcomes of treatment in patients based on initial laboratory results

Variable	Consequences	Mean ± SD	*P* value
pH	Improved	7.30 ± 0.18	<0.001
	Coma/dead	6.98 ± 0.37	
HCO_3	Improved	22.75 ± 2.46	<0.001
	Coma/dead	18.57 ± 5.26	
PO_2	Improved	76.53 ± 17.10	0.990
	Coma/dead	76.62 ± 25.38	
PCO_2	Improved	46.23 ± 10.23	0.002
	Coma/dead	59.27 ± 7.34	
O_{2sat}	Improved	92.88 ± 4.94	<0.001
	Coma/dead	77.85 ± 8.64	
BS	Improved	106.98 ± 25.12	0.226
	Coma/dead	93.85 ± 41.90	

Note. SD: Standard deviation; HCO_3: Bicarbonate; PO_2: Partial pressure of oxygen; PCO_2: Partial pressure of carbon dioxide; O_{2sat}: Oxygen saturation; BS: Blood sugar.

that differences in the manufacturer of the drug, previous use of the drug, and race of patients can lead to this difference.

In this study, the PCO_2 level was above the normal range, especially in patients who died or were in a coma, which, as reported by numerous studies, could be attributed to tramadol-induced respiratory depression (14,15).

In our study, 23.95% of patients were simultaneously dependent on opioids, especially opium, due to the free and easy access to illegal opioids in Iran, which conforms to the results of Taghaddosinejad et al (4).

Conclusion

The results of our study demonstrated that the dose of tramadol used in poisoning with this substance had no contribution to the course of the disease or the prognosis of patients. However, it was revealed that low PH, HCO_3, O_{2sat}, and high CO_2 pressure could have been associated with the outcome of these patients.

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Authors' Contribution

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Competing Interests

None.

Ethical Approval

This study protocol was approved by the Ethics Committee of Zabol University of Medical Sciences (with code IR.ZBMU.REC.1398.185).

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