Chapter 5

Tramadol Poisoning

Omid Mehrpour, Mohammaddavood Sharifi and Nasim Zamani

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1. Introduction

Poisoning is one of the leading causes of mortality and morbidity in many countries. In 1955, poisoning was the most common cause of death in patients aged between 35 and 44 years [1]. Tramadol was first manufactured in Germany in 1970 to relieve post-surgical and chronic pains [2]. It is currently the most commonly prescribed opioid in the world [3]. According to the Australian studies, tramadol use has increased almost 10 times between 1998 and 2004 [4].

Although tramadol is very commonly prescribed, it should be administered with the consideration of the risk to benefit ratio [5]. Tramadol is one of the most common causes of poisoning in adult male patients with the previous history of drug addiction and psychological problems and suicide is the most common motivation for its use in this group of the patients [1,3,6-8]. The aim of this review is to evaluate all possible clinical manifestations and life-threatening signs/symptoms of tramadol poisoning.

2. Pharmacology

Tramadol is a synthetic analogue of codeine with central effects [2,6,9-13]. It is not an opioid derivative or non steroidal anti-inflammatory (NSAID) medication. Actually, tramadol has low affinity for opioid receptors [14,15] and has a hydrochloride structure (Figure 1) [1,16].

Tramadol is used as a racemic mixture in the treatments [15]. This mixture is a 1:1 ratio of two enantiomers with synergistic analgesic effects [17]. The (+) and (-) enantiomers weakly connect to mu opioid receptors [18]. Enantiomer (+) is the opioid part but increases serotonin release and inhibits its re-uptake, as well. Enantiomer (-) is a noradrenaline re-uptake inhibitor [17-19].

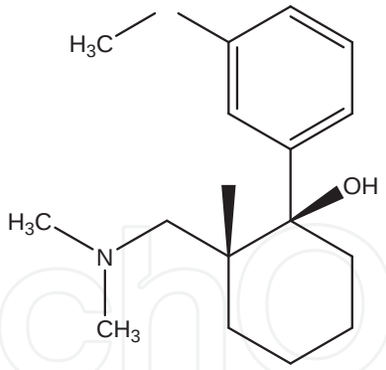

Figure 1. Tramadol structure

Most of the analgesic effects of tramadol are likely secondary to its monoaminergic central pathways [3,10,20]. Tramadol acts through some different pathways including:

a. Affecting mu receptors causing the opioid-like effects;

b. Affecting noradrenergic pathways causing inhibition of norepinephrine reuptake in central nervous system (CNS);

c. Affecting serotonergic pathways causing inhibition of serotonin reuptake in the CNS;

d. Affecting GABAergic pathways causing increased GABA neurotransmitter in the brain [2,8,13,17,21,22].

Tramadol is currently available as tablets, oral drops, solution for injection, and suppository [8] with the oral rout being the most common rout of its administration. Tramadol has a high volume of distribution (3 L/kg) [3,7]. Bioavailability of an oral dose of tramadol is 75% which can reach almost 100% with a programmed schedule [7]. The common therapeutic dose of tramadol is 50 to 100 mg (50 mg oral, 50-100 mg intramuscular [IM], and/or100 mg rectal; 1.5 mg/kg/day in a 60-kg patient) three to four times a day. Doses higher than 400 mg/day are generally not necessary [8,17,23]. However, evaluation of five rheumatologic disorder patients over 65 years of age revealed that a daily tramadol dose of 300 to 1200 mg was needed for them to relieve their pain [24].

Analgesic effects of tramadol are dose-related. The relation between serum level and analgesic effect is not the same among different people. It is estimated that the normal therapeutic serum level of tramadol and its metabolite are 0.1 to 0.3 mg/L and 0.03 to 0.04 mg/L, respectively [3,25-27]. According to the information from International Association of Forensic Toxicologists, therapeutic, toxic, and fatal levels of tramadol in adults are 0.1-0.8 mg/L, 1-2 mg/L, and over 2 mg/L, respectively [26]. Tramadol is completely and rapidly absorbed after oral use. Sustained-release tablets affect within 12 hours and their serum level peaks at 4-9 hours postingestion [6]. In the mice, tramadol is more available and effective at the final phase of the darkness and most of the mortalities happen at the mid phase of the darkness; such an effect has not been detected in human volunteers [28,29].

In postmortem evaluations using gas chromatography, tramadol level is at the most in heart, liver, peripheral blood, urine, kidney, lung, spleen, bile, and brain without any distribution into the muscles [6,25,30].

Tramadol is generally metabolized through N-demethylation, O-demethylation, glucuronidation, and/or sulfation. Metabolization of tramadol is performed by cytochrome P450 enzymes. CYP2D6 is responsible for O-demethylation while N-demethylation is done by CY2B6 and CY3A4 [6,31,32]. Tramadol can be used in renal failure although decreased doses are recommended in renal problems and liver cirrhosis [33].

In a study on six alpacas (some kind of camel), the half-life of all three metabolites of tramadol (O-, N-, and Di-desmethyltramadol) was reported to be more than the parent drug [34]. The main metabolite (O-desmethyltramadol) has a 200-time affinity for mu receptors and its analgesic effect is twice the parent medication, as well [2,15,26].

3. Tramadol toxicity

Tramadol is considered to be a safe drug. However, mortality has been reported with its use [35,36]. Toxicity can happen accidentally. Patients with the previous history of addiction are at extreme danger for such toxicity and according to FDA warnings, tramadol administration should be performed cautiously in these patients [6,37].

Toxicity of tramadol can be predicted by P450 polymorphism [38,39]. Few studies have shown the difference in the postsurgical analgesic serum levels of tramadol among people which is probably due to the genetic polymorphism in the activity of CYP2D6 [40,41]. Diversity in the response depends on the CYP2D6 genotype. Ultra-rapid metabolizers have a higher risk of tramadol toxicity with higher plasma levels of O-desmethyltramadol. They experience higher analgesic effects and nausea in comparison to the group who are extensive metabolizers [38].

4. Epidemiology of tramadol toxicity

Most of the tramadol-intoxicated patients are male (63% to 89.3%) [3,21,37,42-48] and single [1,8,21]. However, in few studies, female patients were more (55% to 59%) [49,50]. Most of the patients were in their 3rd decade of life. This is while the age range of the patients was reported to be between 5-week-old and 87-year-old in different studies [1,3,8,37,44,45,47-51]. Patients generally ingested tramadol [6,8,45,52]. Almost 51.9% to 98.7% of the patients had intentionally overdosed on tramadol; 27.8% to 29.6%, 0.87% to 3.7%, and 0.2% to 7.4% had recreationally, accidentally, or medically overdosed on tramadol, respectively [1,3,6,8,23,45].

In a recent study, university students with the previous history of cigarette smoking and consumption of addicting opioids were more prone to abuse tramadol [24]. In another study, 22.2% of the hospitalized patients had a history of admission due to tramadol overdose [3]. It has been said that in almost 90%, 7.9%, and 2.1% of the tramadol toxicities, poisoning is due

to acute, chronic, and acute on chronic overdoses [3]. Most of the patients refer within the first 6 hours postingestion [21,45,49] with a hospitalization period of 15 minutes to 21 days [8,21]. Signs/symptoms of toxicity recover within 24 hours and almost 42% of the patients will need ICU admission [49,50,53].

5. Biologic characteristics

Tramadol is used as the first-line treatment in musculoskeletal pains [15,54-57] and as an alternative treatment in osteoarthritis (OA) patients in whom NSAIDs are contraindicated or those with resistant pain to oral analgesics [58].

Tramadol analgesic effects are due to the inhibition of norepinephrine and serotonin reuptake as well as agonism of mu receptors which cause blockage of the pain impulses in the spinal cord [7,56,59]. Direct administration of tramadol on the sciatic nerve can reduce the amplitude and speed of spinal somatosensory evoked potential in the rats emphasizing the analgesic effects of tramadol on the peripheral nerves [60].

In tramadol-induced anesthesia, the patient become conscious rapidly, has amnesia during the surgery, and experiences few side effects [61]. Controlled release of tramadol through polyhydroxybutyrate (PHB) microspheres is also available which induces longer anesthesia after epidural use in comparison with tramadol alone [62].

According to a study performed on the rats, tramadol reinforces the immune system by increasing phagocytosis. Use of tramadol is therefore favored as an analgesic in immune-compromised patients [63].

6. Side effects and clinical/paraclinical findings

Tramadol is an analgesic with less side effects in comparison with other opioids [64]. It has the least gastrointestinal and renal toxicities [65]. Drug screening for opioids is generally negative in the patients with tramadol overdose [66].

In overdose, lethargy, nausea, tachycardia, agitation, seizure, coma, hypotension, hypertension, respiratory depression, dysuria, constipation, dizziness, facial paresthesia, ataxia, headache, edema, movement disorders, perspiration, blurred vision, hallucination, itching, vertigo, palpitation, hypo- and hyper-reflexia, diplopia, multi-organ failure, acute liver failure due to fulminant liver necrosis, renal failure, and urine retention have been reported [8,17,23, 48-51,64,67,68]. Dizziness, nausea, constipation, vertigo, and headache are the most common symptoms [57,69,70]. Miosis is not as common as that in toxicities with other opioids and is detected in up to one-thirds of the patients probably due to serotonin and norepinephrine reuptake inhibition [71].

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7. CNS manifestations of tramadol toxicity

The CNS manifestations are of the most common signs/symptoms of tramadol overdose ranging from CNS depression to lethargy and deep coma [6]. O-desmethyltramadol impairs consciousness and causes electrocardiographic (ECG) changes and seizure [44]. n a study by Spiller et al, significant neurologic toxicity was seen in tramadol overdose [49] which was mainly due to the monoamines reuptake inhibition [3,72].

In sub-acute and chronic toxicities, clinical manifestations are mostly behavioral disorders and seizure and may occur with doses of 25mg/kg or higher [17]. Seizure is an important problem in tramadol toxicity with its frequency being reported between 8% and 14% in different social studies and 15% to 55.3% in hospital studies. Most of the patients experience only one episode of seizure [44,47, 49,50]. Seizure is more common in young males (mean age of 22 – 39.5 y) [8,23,43,44,52]; however, some studies reported no significant difference in the frequency of seizure between different genders [3,47,72,73].

Seizure happens in less than 1% of the patients with therapeutic levels [23,74]. It seems that tramadol causes seizure in a dose-dependent manner [3,21,23] while some other studies have not confirmed this [43,44,75]. The least tramadol amount that has resulted in seizure is 100 mg. Tramadol neurotoxicity generally occurs within the first 24 hours postingestion (mainly in the first 6 hours) and seizures are usually tonic-clinic [3,6-8,11,21,23,50,75-78]. Status epilepticus has also been reported [6,11,59,76]. This shows that tramadol can cause seizure at both therapeutic and toxic levels [43,52,77,79].

Brain computed tomography (CT) of the tramadol-intoxicated patients has often been reported to be normal [43,77]. Künig and assistants reported two cases of fluctuating dizziness and cognitive problems due to long-term treatment with tramadol who recovered with cessation of the drug [80]. In a study performed to evaluate the risk of idiopathic seizure in tramadol users, only 17 cases of idiopathic seizure were found among 10917 patients, all of whom, used tramadol in combination with some other medication; it, therefore, is difficult to relate their seizure to tramadol use [71]. Seizure is less frequent in the patients who use tramadol with benzodiazepines. Psychological and somatic complications (hepatitis C and liver injury) were detected in those who had seized. Ethanol can reduce the seizure threshold in tramadol use. Seizure is also more common in younger patients who have abused tramadol for a long period of time [23].

Background seizing disorders, medications causing seizure, ethanol withdrawal, CNS depressants, or head injury can affect seizure occurrence in tramadol overdose, as well [45]. Mydriasis and tachycardia can accompany with a higher risk of seizure [44].

In a cohort study comparing 9218 tramadol users and 37232 non-users, less than 1% of the users experienced seizure after the first use. Risk of seizure was 2-to 6-fold in the patients who had background diseases or consumed other medications. The risk was also higher in those between 25 and 54 years of age, those who use tramadol for more than 4 times, or those with the history of alcohol abuse, infarction, or head injury [74].

In another study on 97 patients with seizure, electroencephalographic (EEG) evaluations were normal in seven and isolated sharp slow-wave feature of EEG was seen in one patients. Brain CT was normal in all and magnetic resonance imaging (MRI) was normal in five patients [77]. Tramadol-induced seizure can cause trauma, intra-articular dislocation, and tongue laceration [67,81,82].

In a study on 70 rats, it was revealed that tramadol could inhibit electron transfer cycle (ETC), cause ATP depletion, and disrupt the mitochondrial integrity. Apoptosis may also happen due to tramadol use [83]. In the neonates, tramadol can trigger pentylenetetrazole-induced seizure in an age-dependant manner causing fewer seizures in the neonatal period and more seizures after the lactating period [84].

Administration of tramadol hydrochloride to a zebrafish caused abnormal behaviors, reduced activity, and reduced brain and body weight. In the zebrafish brain, functional cytoskeletal proteins engaged in the energy metabolism had changed due to tramadol. Lower levels of ATP synthetase, creatine kinase, pyruvate dehydrogenase, kinase, and aldolase C could be due to the impaired production of energy because of tramadol. Weak regulation of the proteins engaged in the oxidative stress, mitochondrial functional abnormalities, and impaired production and destruction of the proteins represented the neurotoxicity of tramadol (Table 1) [85].

Authors	Publication year	Number of patients	Cause of ingestion	Sex	Co-administration or comorbidity	Dosage
Raigeret al. [139]	2012	1	Prescribed by physician	Female	History of seizure	100 mg IV
Petramfar et al.[140]	2010	106	Prescribed by physician in 18.9% Abuse in 81.1%	96% M	History of epilepsy in 13.2%, abuse of antidepressant in 5.8%, alcohol in 5.8%, opiate in 23.3%	50-1500 mg IV or oral
Mehrpour M [141]	2005	2	Prescribed by physician	F/M	_	100 mg IV

Table 1. Studies on tramadol-induced seizures

8. Cardiopulmonary effects of tramadol

Acute pulmonary hypertension and right heart failure are the uncommon presentations reported in a young tramadol-overdosed patient [86]. Cardiopulmonary arrest was reported

in some cases that had ingested more than 5 g of tramadol [8]. Higher doses of tramadol can block sodium channels and cause Brugada pattern in the ECG [11,47] which can be accompanied by ventricular dysrhythmias including ventricular fibrillation [11]. In a study on 479 tramadol-poisoned patients, up to 73% of the patients had ECG changes due to blockage of the sodium channels. Almost one-thirds of the patients had terminal 40 msec frontal plane axis deviation and one-fourth had QT prolongation (more than 0.44 sec) [47]. Some cases of right heart failure, resistant shock, asystole, hypotension (especially systolic), and sinus tachycardia have also been recorded [6,35,44,49]. Hypertension has also been reported. The least tramadol dose that has resulted in hypertension and agitation is 500 mg [49].

Eleven suspected cases of tramadol-related angioedema have been reported from Sweden. Involvement of the mouth/pharynx and upper respiratory system can progress to acute respiratory distress and airway obstruction [87]. Tramadol causes respiratory depression with less frequency in comparison with other opioids [28,57,88]. Renal failure is a probable risk factor for respiratory depression [28,89]. Tramadol overdose can cause respiratory depression; but in therapeutic oral doses, it does not cause respiratory complications. In a study on IV administration of 50 to 75 mg of tramadol, no significant changes were detected in the respiratory rate, respiratory volume per minute, and arterial PaO2 [90].

9. Hepatic system

Sixteen cases of non-fatal hepatobiliary dysfunction due to tramadol ingestion have been reported [74]. Tramadol has caused centrilobular congestion and focal necrosis of the liver cells and minimal vacuolization in the kidney tubular cells of the rats. No changes were detected in the lactate dehydrogenase, blood urea nitrogen (BUN), aspartate aminotransferase (AST), and malondialdehyde (MDA); however, alanine aminotransferase (ALT) increased significantly showing the possible hepatotoxicity of tramadol [91]. It was shown that acute or chronic toxicity did not affect liver weight or cause histopathological changes in its tissue [17,92].

In the rats, mu receptor activation increases glucose use or decreases the liver gluconeogenesis which results in the low levels of plasma glucose in diabetic rats [88,93]. It has been shown that tramadol improves the peripheral metabolism of glucose by central activation of the mu receptors. Therefore, central and peripheral metabolisms of glucose unite and cause hypoglycemia. It has also been suggested that tramadol changes the liver glucose output regulated by other organs (likely CNS) [93].

10. Gastrointestinal system

Although tramadol is fairly tolerated after ingestion, nausea and vomiting may happen in 14% to 75 % of the cases after its oral use [8,49]. Some patients discontinue tramadol consumption because of nausea and vomiting. It has been shown that slow titration decreases the frequency of tramadol discontinuation due to these complications [94].

11. Carcinogenic effects

In long-term studies on rats and mice, no tramadol-attributed carcinogenic changes were detected. Histopathologic evaluations showed increased risk of hepatic adenoma in the males and non dose-related pulmonary adenoma in females. No specific mutations or chromosomal impairments were detected in rats, mice, or hamsters due to tramadol use. In skin and eye tests, tramadol had weak corrosive effects on the white rabbits' eyes but no irritating changes on their skin [2]. Oral administration of tramadol was reported to have no carcinogenic effects on the mice and rats. No mutations or increased risk of gene toxicity were detected in human-beings, either [17].

Tramadol can cause urinary retention because of opioid agonistic effects that can increase the tonicity of the bladder sphincter [68]. Also, it was shown to have hazardous effects on the growth, survival, and reproduction system of Daphnia Magna with the most effects on the latter. Long-term exposures decreased expression of the *vtg* gene which is an important biomarker in the reproduction of the oviparous animals [64,95].

In a study by Matthiesen et al, low dose of tramadol had no effect on the fertility, giving birth, and lactation of the rats and had no teratogenic effects on the fetus [17]. These results are however in contrast to the results withdrawn by Bornas who mentioned that laboratory studies had confirmed the teratogenic effects of tramadol on the animals. Tramadol and M1 metabolite can cross the placenta easily because of their low molecular weights [55].

12. Biochemical findings of tramadol

Bleeding time (BT), clotting time (CT), prothrombin time, partial thromboplastin time, and body temperature were not affected by tramadol [17]. But, leukocytosis has been reported [44]. Tramadol overdose may result in increased creatine phosphokinase (CPK) which may be seen with or without seizure and can be accompanied by acute renal failure (Table 2) [13].

Authors	Publication year	Number of patients	Sex	Co-administration or comorbidity	Mortality	Findings	Dosage or concentration
Afshari and Ghooshkhanehee [14]	2009	Case report	male	_	_	Seizure, confusion, miosis, dramatic rise of CPK, LDH, Cr	4000 mg
Eizadi -Mood et al. [21]	2011	186	Male=76.6%	Addiction history in 41%, psychotic disorder in 30.4%, cardiac disease in	1.1%	CNS depression in 57%, bradypnea in 18%, tachycardia in	Mean dosage of 2006±7466 mg

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Authors	Publication year	Number of patients	Sex	Co-administration or comorbidity	Mortality	Findings	Dosage or concentration
				15%, renal disease and epilepsy in few patients		25%, hypertension in 6%	
Talaie et al. [43]	2009	132	Male=73.5%	_	_	Seizure in 46.2%	100-4000 mg
Hassanian-Moghaddam et al. [45]	2012	525	Male=70.1%	History of addiction In 16.4%	2.68%	Seizure in 46.1% Apnea in 3.6%	Mean dose of 1358.4±1071.8 mg
Nasif et al. [142]	2010	Case report	female	_	_	Headache, dizziness, nausea, drowsiness, visual hallucinations	500 mg
Khan et al. [143]	2010	Case report	male	_	_	Rhabdomyolysis, ARF	1000 mg
El-Hussuna et al. [144]	2010	Case report	female	_	_	Loss of consciousness, hypothermia, tachycardia, atrial fibrillation in ECG, hyperamylasemia	3750 mg
Ahmadi et al. [145]	2012	1023	Male=78.5%	26.6% with history of addiction 21.6% with coingested drugs (specially benzodiazepines)	0.97%	Seizure in 41.8% of patients	Most of patients less than 5000 mg
Pothiawala et al. [146]	2011	Case report	female	_	_	Sinus tachycardia	Cr=4 mg/L Dose=700 mg
Taromsari et al. [147]	2012	306	Male=83%	Not mentioned	0.003%	Seizure in 20.3%, agitation in 25.2% prolonged PT in 18.3%, increased ALT in 5.6%, hypotension in 10.5%, Mydriasis in 8.2%, apnea in 2.3%	Mean dose 746±453mg

Authors	Publication year	Number of patients	Sex	Co-administration or comorbidity	Mortality	Findings	Dosage or concentration
Elkalioubie et al. [148]	2011	Case report	female	_	_	Hypoglycemia hypothermia, renal and liver failure, cardiac arrest, coagulopathy	4500 mg

Table 2. Studies on patients with tramadol poisoning

13. Serotonin syndrome

Serotonin syndrome (SS) is a potentially fatal syndrome due to increased synthesis, decreased metabolism, increased release, and reuptake inhibition of serotonin or direct agonism at the serotonin receptors [5,53]. This syndrome is often due to complex interactions between the consumed medications. Three key clinical features of this syndrome include:

1. Neuromuscular hyperactivity (tremor, clonus, myoclonus, hyper-reflexia, stiffness, impaired coordination).
2. Autonomic hyperactivity (profuse sweating, fever, tachycardia, tachypnea, chills, nausea, diarrhea, vomiting).
3. Mental status changes (agitation, confusion, restlessness, hypomania and/or visual or auditory hallucinations).

The exact rate of SS is unclear but is generally not expected to occur in more than 5% of the hospitalized patients [5,44,53,96-98]. The (+) enantiomer of tramadol inhibits re-absorption of serotonin [99]. Usually, SS happens after tramadol overdose or its concurrent use with other medications especially antidepressants; however, it may happen even after a single therapeutic dose of tramadol [5,98,100].

Patients who consume mono amine oxidase (MAO) inhibitors are at the risk of development of SS [66,101]. SS has been reported after concurrent use of tramadol with serotonin reuptake inhibitors (SSRIs), venlafaxine, atypical antipsychotics, fluoxetine, sertraline, paroxetine, citalopram, fluvoxamine, moclobemide, clomipramine, mirtazapine, and tricyclic antidepressants [5,7,53,97,102].

In patients who develop lethargy, hypotension, hypoxia, agitation, tachycardia, hypertension, confusion, hyperthermia, or hyper-reflexia, diagnosis of SS should be borne in mind [7,101,103]. Treatment is conservative and includes cessation of the culpable medication as well as administration of the antiserotonergics (ciproheptadine, metisergide, propranolol, and chlorpromazine). Clinical manifestations recover within 24 hours except in those who have consumed medications with longer half-lives [5,53,97]. Up to 42% of the patients may need

ICU admission [48,53]. Pretreatment with chlordiazepoxide may prevent tramadol-induced SS [48].

14. Drug interactions

Opioids metabolized by CYP450 (including tramadol) may induce many drug-drug interactions [104]. In an Australian study, unwanted drug interactions were evaluated in 46859 patients who consumed antidepressants. In 8.1% of the patients who had experienced such complications, the most common consumed medication was tramadol (3.6%). As previously clarified, tramadol is similar to venlafaxine in structure and is believed to have antidepressant effects. Venlafaxine can even cause false positive results for tramadol in urine tests [5]. Co-administration of tramadol and antidepressants especially TCAs, SSRIs, venlafaxine, bupropion, and phenothiazines should be performed cautiously because of the increased risk of seizure [6,25,72]. Hallucinations and SS have been reported after co-administration of tramadol and SSRIs [87]. Concurrent administration of tramadol and NSAIDs can result in gastrointestinal hemorrhages due to severe platelet inhibition [105]. Fatal toxicities have been reported after tramadol-TCA overdoses [106]. It has been shown that tramadol-related mortality is more common after co-ingestion of benzodiazepines [8,26]. Co-administration of tramadol and CNS depressants, TCAs, and MAO inhibitors are therefore contraindicated [23]. Tramadol can also interact with antitumor medications. For instance, tramadol decreases the efficacy of cisplatin by affecting gap junctions [107]. In a case report, combination of paroxetine, dosulepin, and tramadol caused hallucination which improved after cessation of the medications [108].

15. Tramadol-related mortalities

Fatalities have been reported after tramadol overdose or its co-ingestion with other medications. In most cases, death occurred after ingestion of high doses within 24 hours post-ingestion with really high blood levels [70]. However, death due to tramadol overdose is rare and consists up to 1% of the hospitalized cases [1,10,44,88]. Blood levels of tramadol have been between 0.03 to 134 mg/L in different fatal cases [26,32,109,110].

The most common mechanisms of death after tramadol overdose are cardio-respiratory depression, resistant shock, asystole, and liver failure [111]. Apnea may increase the risk of tramadol intoxication-related deaths [45]. Fatal toxicity of tramadol has been reported after co-administration of other medications including propranolol, trazodone, ethanol, and especially CNS depressants including benzodiazepines, barbiturates, and serotonergic drugs [88]. M1/M2 (ODT/NDT) metabolite ratio of higher than one in biologic liquids and organs represents more sudden deaths while M1/M2 < 1 shows that death will occur at later stages after the tramadol use [32,112]. In fatal cases of tramadol, femoral blood samples are the best since they have the least redistribution changes after death [113]. Tramadol may remain undetected in muscle samples after death due to its overdose [114].

16. Miscellaneous side effects

Mannocchi and assistants reported a case of death due to tramadol and propofol due to advanced severe dyspnea [115]. A report showed nine deaths due to consumption of krypton (a plant material containing ODT and mitragynine) in whom the concentration of ODT was between 0.4 to 4.3 μg/g [116]. Another study reported death due o tramadol because of respiratory depression accompanying GABA A and GABA B1 alpha1 over-expression in the ambiguus nucleus and medulla oblongata solitary. (Table 3) [117].

Author	Publication year	Number of patients	Cause of ingestion	Cause of death	Co-administration or comorbidity	Dosage or concentration(C)
Barbera et al. [32]	2013	Case report	Suicide	Respiratory depression and cardiac arrest	Carbamazepine	C= 61.83 mg/l
De Decker et al. [88]	2007	Case report	Intentional overdose	Asystole and multiple organ failure	Munchausen's syndrome, benzodiazepine	C=8 mg/L
Solarino et al. [149]	2009	Case report	Suicide	Cardiorespiratory failure	Nicotine, diphenhydramine	C= 6.6 mg/L
Ripple et al. [150]	2000	Case report	Prescribing multiple drugs	Seizure activity	Alcohol, venlafaxine, trazodone, quetiapine, lithium, acetaminophen	C= 0.7 mg/L
Gheshlaghi et al. [151]	2009	Case report	Suicide	Cardiopulmonary arrest	_	Dose=1000 mg
Häkkinen et al. [152]	2012	117	Accidental in 54.8% Suicide in 31.3% Unclear 13.9%	Not mentioned	Other opioids detected in 18.8% Benzodiazepines in 85.5% and alcohol in 14.5%	Median concentration of 5.3 mg/L
Randall and Crane et al. [153]	2014	127	Suicide in 38% Accidental in 27% Unknown in 35%	Mostly multi organ or liver failure and aspiration pneumonia	Other drug/ medicine in 49%, alcohol in 36%	C= 1.85-88.8 mg/L

Table 3. Studies on deaths related to tramadol poisoning

17. Toxicity in children

Accidental ingestion of tramadol is well tolerated by children [50,71,111]. Side effects of tramadol seem to be more common but milder in children. Vomiting is especially common in them [118]. Riedel and Stockhausen reported that tramadol could cross the blood brain barrier (BBB) in children and suppress the brain [119]. Rectal administration of tramadol resulted in severe CNS depression in a 5-week-old infant which was explained to be due to the decreased kinetic elimination and increased permeability of the BBB [51]. Mazor et al. reported two cases of tramadol toxicity with abnormal neurological findings (both seizures and seizure-like activities) in children [9]. Seizure has been reported after accidental ingestion of 4 mg/kg of tramadol in children [23].

Short-term use of tramadol in lactating mother is not dangerous [120] and the risk of neonatal dependency is low.

Tramadol can cause SS without the effect of any other medication while in the adults the risk is increased if a SSRI is also taken [40]. In an 8-month-old infant with SS, the cause of hospital presentation was epistaxis. Sinus tachycardia, hyperthermia, hypertension, agitation, drowsiness, and hyper-reflexia of the lower extremities occurred within the first 24 hours after ingestion of 200 mg of tramadol. Neurologic and cardiovascular effects recovered in two days. The infant was discharged after five days in good condition [121].

18. Treatment

Treatment should focus on conservative approaches including maintenance of airway, breathing, and circulation, oxygen therapy, fluid resuscitation, and diazepam administration to control agitation and seizure [6,14,36]. Patients should be monitored for increased CPK and possible acute renal failure that may happen within the next two days [6,14]. Hemodialysis should be considered in cases with acute renal failure and severe creatinine increase [14]. They may need intubation and ICU admission. Gastrointestinal decontamination should be performed in the patients who have referred within the first two hours post-ingestion and have no contraindications [8,49,50].

In severe toxicities due to ingestion of large amounts of sustained-release drug, multiple dose activated charcoal should be considered if no contraindication exists [6,122]. In cases with resistant shock or asystole, extracorporeal methods may be needed [6,35]. Treatment of liver failure is conservative, as well, and urgent liver transplantation is not feasible in many cases [18]. Intubation/ventilation and administration of naloxone are the treatments for tramadol-induced apnea [45]. In severe cases who have not even seized, experimental therapy with diazepam can be performed which can be of help in mild undiagnosed SS [6,44]. Treatment of SS in also conservative and includes withdrawal of the culpable drug and external cooling. Up to 42% of the patients may need ICU and most of them recover within 12-24 hours [70].

In a clinical study on 122 patients, naloxone administration could induce seizure in tramadol-intoxicated patients [75]. Therefore, naloxone should not routinely be administered to treat

decreased level of consciousness in tramadol toxicity unless respiratory depression has developed [21,45]. Seizures due to tramadol do not respond to naloxone but improve with administration of benzodiazepines. Naloxone can be considered for treatment of post-seizure complaints [123].

Shadnia et al suggested that because of the low risk of multiple seizures in tramadol toxicity, anticonvulsant treatment should not be routinely given even in those with initial seizures [52]. Stoops et al evaluated naltrexone and showed that it could reverse the opioid-induced effects such as miosis; but, increased the serotonergic and adrenergic effects such as mydriasis [56].

Intravenous lipid emulsion (ILE) can reduce mortality due to acute toxicity of tramadol in rabbits, but increasing the ILE dose may cause reverse effects. In a study on 30 rabbis, ILE reduced tramadol-induced tachycardia when administered within 30 minutes of poisoning and showed positive effects on normalizing mean arterial pressure and diastolic blood pressure but it did not have major effect on systolic blood pressure. Intralipid also prevented tramadol-related seizures in low doses and reduced the frequency of increased CPK with higher doses [124].

19. Dependency and withdrawal

Although tramadol has less side effects, addicting capacity, and respiratory depression power in comparison with other opioids, many cases of dependency, abuse, intentional overdose, or poisoning have been reported following its use [20,27,48,56,70,113,125,126]. Tramadol withdrawal lasts longer compared with other opioids [111]. Where ultrarapid metabolizers are high in number, people are expected to have a higher risk of dependency to tramadol [127].

Tramadol is as potent as heroin to cause euphoria [2,55,112]. Withdrawal occurs after rapid abrupt discontinuation of tramadol with clinical manifestations including abdominal cramps, anxiety, skeletal pain, depression, diarrhea, goose flesh, insomnia, lacrimation, nausea, restlessness, rhinorrhea, and sweating. The manifestations may sometimes be atypical and include hallucination, paranoia, panic attack, confusion, and atypical sensational experiences such as paresthesia, itching, tingling, delusion, depersonalization, derealization, and tinnitus [22,55].

Tramadol dependency happens faster in those who abuse it with other analgesics or ethanol [55]. Clinical therapeutic doses of tramadol may affect psychomotor and physiologic capacities of the patients who recreationally abuse it [128].

Tramadol abuse in pregnancy may cause preterm labor and withdrawal manifestations in the newborn baby depending on the age of pregnancy, time elapsed since the beginning of tramadol use, dose of tramadol, CYP450 D2 polymorphism, development of the liver conjugation, and renal function of both mother and baby. Attempts have been performed to treat this syndrome in neonates using clonidine alone or in combination with the thin opioid tinctures, chloral hydrate, benzodiazepines, and methadone [55]. In a study on patients with chronic non-cancer pain, it was shown that the frequency of abuse and dependency on tramadol and NSAIDs were the same and significantly less than hydrocodone [129].

20. Conclusion

Weak opioids such as tramadol can be used in the treatment of reumatologic pains after development of complications following use of NSAIDs or if they are unable to alleviate the patients' pain [130]. It is less dangerous to the organs in comparison with selective and nonselective NSAIDs and very powerful in the treatment of chronic pains [131]. Tramadol can also be used in moderate to severe toothaches alone or in combination with acetaminophen or codeine [132,133]. In opioid-addicted patients, tramadol can be used for the treatment of withdrawal pain [68]. Tramadol in combination with paracetamol has a fair efficacy, immunity, and acceptance rate by the patients without development of dependency syndrome [131,134,135].

Complications can be decreased by adding tramadol to the controlled medications [136]. Monitoring of the liver function especially when the maximum daily doses are given is mandatory. Also, because of drug-drug interactions and differences in the individual metabolism and the chance of dependency, tramadol administration should be controlled by the treating physician. If the patient is an opioid-addict, tramadol should not be administered unless absolutely indicated [137,138].

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Author details

Omid Mehrpour[1*], Mohammaddavood Sharifi[2] and Nasim Zamani[3]

*Address all correspondence to: omid.mehrpour@yahoo.com

1 Medical Toxicology and Drug Abuse Research Center, Birjand University of Medical Sciences, Birjand, Iran

2 Department of Emergency medicine, Mashhad University of Medical Sciences, Iran

3 Department of Clinical Toxicology, Loghman Hakim Hospital, Shahid Behehshti University of Medical Sciences, Tehran, Iran

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