CASE REPORT

Tramadol Overdose: A Case Report *

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ABSTRACT

Tramadol, a commonly prescribed opioid analgesic, is considered to have a low abuse potential and devoid of side effects like drug dependence. Very few fatalities due to isolated tramadol overdose, either intentional or accidental, have been reported so far. We report a case of a 27-year-old female with isolated tramadol overdose, having a peripheral blood tramadol concentration of 4mg/L, which is exceeding the lethal blood concentration of 2mg/L. This is the first report of a patient in Singapore who survived tramadol overdose despite having a lethal blood concentration. Physicians should be aware that patients with tramadol overdose may only present with signs related to isolated Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) properties and not always associated with the features of classical opioid overdose. Some patients might exhibit a certain degree of tolerance to the drug after prolonged prior exposure to the medication, and this tolerance could extend beyond the therapeutic range. It also emphasises the need for physicians to be more cautious while prescribing tramadol to their patients.

Keywords: isolated, opioid, poisoning, tolerance, tramadol

INTRODUCTION

Tramadol is a centrally acting, synthetic opioid analgesic agent. It exerts its analgesic effect by inhibiting the re-uptake of norepinephrine and serotonin and also by weak opioid receptor agonism, mechanisms that are due to tramadol and its active metabolite O-desmethyltramadol. Tramadol also consists of 2 enantiomers, (+)– tramadol, which preferentially inhibits serotonin uptake and (-)- tramadol, which is the potent inhibitor of nonepinephrine reuptake[1,2]. It is used for the treatment of moderate to severe pain. Tramadol dosage should be adjusted according to the severity of pain. The total daily dose should not exceed 400mg with adult therapeutic blood levels of 0.1–0.8mg/L[3]. We report a case study of an adult female with tramadol overdose having a lethal blood concentration and who survived with no serious adverse effects.

CASE HISTORY

A 27-year-old female was brought by the paramedics to the emergency department at 8:27am. She was found by her parents shrieking in her room around 7:00am and they found the patient confused and unable to recognise them. Paramedics found 3 strips of tramadol and a total of 14 empty blisters at the scene, giving an approximate dose of 700mg exposure. On arrival in the Emergency Department, the patient was alert and rational but had no recollection of the preceeding events. She had a background history of suffering from headache intermittently for the past 3 years. She had consulted a general practitioner a few times over the last year for complaints of headache and was prescribed tramadol. She had been taking 2–6 tablets of tramadol per day as needed over the last year. She had a persistent left-sided headache that night which was unrelieved despite taking a regular dose of tramadol as prescribed. She only

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remembered that she took more than the usual number of tablets of tramadol but was unable to quantify the exact number. The exact time of consumption of tablets was unknown. She had no nausea or vomiting and there was no photophobia or any focal weakness. She denied any suicidal ideation and no other concomitant drug ingestion. She has a history of chronic smoking of 20 cigarettes per day.

On examination, the patient was alert. She was tachycardic with a heart rate of 142 beats per minute and her respiratory rate was 18 per minute. Her initial temperature was 36.5ºC and the blood pressure was 130/82mmHg and remained stable throughout. The patient's oxygen saturation on room air was 100%. The pupils were 1.5mm in size bilaterally and reactive to light. She had tremors of both hands. There was no thyroid swelling or bruit. Her skin colour was normal with a good capillary refill and there was no sweating or dryness of oral mucosa. Her neurologic examination was normal with normal deep tendon reflexes and no rigidity or clonus was noted. Rest of the systemic examination was normal. Electrocardiogram showed sinus tachycardia with a normal QRS/QTc duration. Laboratory investigations which included full blood count, urea and electrolytes, blood sugar level, liver function tests and thyroid function tests were normal. D-dimer, salicylate and paracetamol levels were normal. CT scan of the brain was done which was unremarkable. Toxicological sample was collected and sent to the laboratory for analysis. Patient was given activated charcoal, started on intravenous normal saline and admitted to the general ward of Internal Medicine department for observation and further management. The toxicological analysis of blood reported a tramadol level of 4mg/L, with the therapeutic range of 0.1–0.84 mg/L. No other drugs were detected in the toxicological screen.

In view of the persistent tachycardia, a cardiology consultation was sought and patient was scheduled for a 2-D echocardiogram. Despite the lethal tramadol concentration, the patient was asymptomatic and not in cardio-respiratory distress. Patient was monitored closely for deterioration and provided supportive care.

Despite having persistent tachycardia of 110 beats per minute, patient decided to discharge against medical advice 1 day post-admission. She was advised about the need for further assessment and the risks involved with early discharge. She was evaluated by a psychiatrist to be competent to sign discharge papers against medical advice. Based on the National Electronic Medical Record System, the patient has not presented for follow-up or subsequent admission to any other public hospital in Singapore since then.

DISCUSSION

Tramadol is a commonly used opioid for the management of moderate to severe pain. Therapeutic dosage is 50–100mg every 4–6 hours, to a maximum recommended dose of 400mg/day. In therapeutic dosage, it is rapidly and almost completely absorbed with a peak blood concentration within 2 hours. The volume of distribution is 3L/kg with a 20% plasma protein binding. Tramadol and its metabolites are mainly excreted via the kidneys with the mean elimination half-life of about 5 hours. This elimination is prolonged to about 6–9 hours in the elderly and in patients with renal or hepatic impairment. Following a 100mg dose, a peak plasma concentration of about 0.3mg/L is seen 2 hours post dose. Peak plasma concentrations following chronic 400mg/day dose were approximately 0.6mg/L.

Tramadol is less likely to cause adverse effects like drug dependence and respiratory depression[4,5]. When compared with other opioids, the abuse potential of tramadol is considered low[6,7]. Hence, tramadol is a non-scheduled opioid available for clinical use. Despite this, it can induce physical and psychological dependence. Subjects with a history of substance abuse are at higher risk[8]. But, the dependence is not limited to those patients with a prior history of opioid dependence or substance abuse. This has led to increasing incidence of tramadol related fatalities in case reports and post-marketing surveillance reports.

When taken in overdose it is known to be associated with significant morbidity and mortality. Moreover, fatal intoxications with tramadol may also occur unintentionally. The most common symptoms of tramadol overdose are central nervous system (CNS) depression, nausea and vomiting, tachycardia and seizures[9]. Higher doses can be associated with classic opioid toxicity features of coma, respiratory depression and cardiovascular collapse.

Tramadol overdose might also present with features of the serotonin syndrome due to the Serotonin-Norepinephrine Reuptake Inhibitor (SNRI) properties of the drug, which may include neuromuscular hyperactivity (myoclonus and hyperreflexia), autonomic hyperactivity (tachycardia and pyrexia) and altered mental state (usually agitation, excitement and later confusion)[10,11]. A prospective multicentre evaluation of tramadol exposure suggested that much of the toxicity in tramadol overdose can be attributed to the monoamine uptake inhibition rather than its opioid effects and agitation, tachycardia, confusion and hypertension suggest a possible mild serotonin syndrome[12].

Drugs that interact with tramadol leading to increased likelihood of serotonin syndrome include medications like Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), Monoamine Oxidase Inhibitors (MAOIs), Tricyclic Antidepressants (TCAs), triptans and lithium. Some common SSRIs are paroxetine (Paxil), fluoxetine (Prozac) and sertraline (Zoloft). Common SNRIs include duloxetine (Cymbalta) and venlafaxine (Effexor). Triptans that are commonly prescribed are sumatriptan (Imitrex), almotriptan (Axert) and eletriptan (Relpax).

No laboratory diagnostic tests exist for detection of serotonin syndrome presently, and the diagnosis is based on clinical symptomatology and a high index of suspicion[13]. Sternbach's Criteria and Hunter Serotonin Toxicity Criteria are commonly used. Moreover, there are no studies to show that the severity of clinical manifestations of serotonin syndrome correlate well with the level of serotonin or tramadol in the blood.

Tramadol overdose has been one of the most frequent causes of drug poisoning in the recent years, especially in young adult males with a history of substance abuse and mental disorders[14]. According to the data of the International Association of Forensic Toxicologists, therapeutic blood levels in adults range from 0.1–0.8 mg/L, toxic level was between 1–2mg/L and lethal concentration was higher than 2mg/L[15].

The treatment of tramadol overdose is mainly supportive, with careful monitoring. Symptom onset is rapid, requiring administration of activated charcoal within 1–2 hours of ingestion. Naloxone, an opioid antagonist, is only partially effective in reversing tramadol toxicity and can cause seizures. Seizures should be controlled with benzodiazepines. Symptoms will generally resolve within 24 hours of admission. Accidental ingestion in children is generally well tolerated, causing primarily sedation. Treatment should include early administration of charcoal and supportive care[9]. The usual causes of death related to tramadol ingestion, either alone or in combination with other drugs, include cardio-respiratory depression, refractory shock, asystole and even severe hepatic failure.

As concluded by previous reports, tramadol overdose, especially when taken in combination with other CNS depressants such as benzodiazepines, can cause death even at low doses[3,16,17]. There is another case report illustrating that tramadol overdose in combination with CNS depressants may cause refractory shock and asystole[18]. However, a report of 4 post-mortem cases in which tramadol was identified failed to attribute any of the deaths to tramadol intoxication alone[19].

Very few fatalities due to isolated tramadol overdose, either intentional or accidental, have been reported so far. Acute ingestion of an estimated 5.5gm of tramadol by a 36-year-old HIV positive male caused coma, respiratory depression and tachycardia and it was successfully treated with a 16-hour naloxone infusion[20]. Tramadol does not appear to exhibit significant and consistent post-mortem distribution; heart/peripheral blood concentration ratios in 6 deaths averaged 1.1 (range, 0.6–1.4)21. Death with tramadol has been reported in a 6-month-old child with a blood concentration of 2mg/L[22]. A 5-month-old infant admitted with seizures, impaired consciousness and a serum tramadol level of 0.56mg/L was believed to be a victim of deliberate overdosage[23]. A case of suicide by tramadol overdose with a blood concentration of 13mg/L[24], a tramadol overdose fatality with a blood concentration of 15.1mg/L[1], and another case of fatal intoxication in an adult with tramadol alone with a blood tramadol concentration of 9.6mg/L[25] have been reported. There are 2 cases of tramadol overdose causing acute liver failure finally leading to death[26,27]. In the case reported by Loughrey *et al*, death due to acute liver failure occurred at a blood tramadol concentration of 3.7 mg/L, though much higher than the normal therapeutic range, but still

much lower than the levels reported with other fatal tramadol overdoses. A patient attempting suicide by ingestion of 4,000mg of tramadol survived but no tramadol levels were reported in the study[28]. Thus, it is rare to attribute death to tramadol poisoning alone[20,27].

Tramadol is increasingly being prescribed as an analgesic in Singapore. According to our knowledge and based on the literature review till date, this is the first report in Singapore where a patient presented with isolated tramadol overdose and survived despite having blood concentrations of 4mg/L, which are higher than the accepted lethal concentration. Moreover, the patient only manifested the features of the serotonin syndrome due to SNRI properties i.e. early phase of agitation/excitement and confusion, tachycardia and tremors.

Although tramadol toxicity may occur following intentional or accidental ingestion of the drug, fatality may not occur in all the cases. There might be a possibility of individual variation and some patients might exhibit a certain degree of tolerance to the drug after chronic ingestion or prolonged prior exposure to the medication, and this tolerance could extend beyond the therapeutic range, as in our case. Also, a review by Clarkson *et al* revealed that blood drug concentrations in many tramadol related deaths exceeded the therapeutic serum range, but they overlapped with the range identified in living subjects arrested for impaired driving. They suggested caution in the interpretation of blood tramadol concentration outside of the recognised therapeutic range[29].

CONCLUSION

In summary, with the increasing use of tramadol for pain control, it is important for physicians to be aware of its potentially lethal side effects, particularly if consumed or prescribed in inappropriately large doses, or when it interacts with other medications. Although lower as compared to other opioids, tramadol has a potential for physical and psychological dependence. Physicians should be aware that patients with tramadol overdose may only present with signs and symptoms related to isolated SNRI properties, and not always associated with the features of classical opioid overdose. It also emphasises the need for physicians to be more cautious while prescribing tramadol to their patients.

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