An unexpected sudden death by oral tramadol intoxication: a case not reported earlier

Farzad Gheshlaghi[1], Nastaran Eizadi-Mood [2], Kamran Fazel[3], Mohaddaseh Behjati [4]

ABSTRACT

Background: Tramadol is a widely used centrally acting opioid analgesic and due to its ease of access in Iran as an over-the- counter drug, reported cases of intoxication are rising.

Case: A 19-year-old male who was referred to our center, Noor Hospital, Isfahan University of Medical Sciences, Isfahan, Iran, because of confusion, ataxia, agitation and an episode of seizure, followed by intentional ingestion of one hundred 100mg tablets of tramadol . On admission, he was confused, in hypotensive state, and with tachycardia. Suddenly, a generalized tonic colonic seizure occurred and resulted in cyanosis and a decrease in O2 saturation. By prompt management, he improved to some extent but unexpectedly 3 hours after admission he succumbed to cardiopulmonary arrest. Laboratory analysis, ECG, and postmortem pathology reports were normal. Semi-quantitative toxicological analysis (by Thin Layer Chromatography: TLC) was highly positive for tramadol, in all viscera, gastric contents and urine.

Conclusion: Contrary to previous beliefs, tramadol poisoning might cause sudden death even in oral form. It is not long since tramadol has become widely available as a rather safe analgesic; nevertheless, it seems that available data concerning its toxicity is limited and to assist physicians in anticipating unexpected situations in tramadol overdose, scrutiny into its side effects is mandatory.

Keywords: Heart arrest, Poisoning, Sudden death, Suicide, Tramadol

INTRODUCTION

Nowadays tramadol is widely used for the treatment of different pain disorders (1) but there is limited data available about its side-effects and manifestations in over dose cases.

CASE REPORT

A 19-year-old male who was referred to our center, Noor Hospital of Isfahan University of Medical Sciences, Isfahan, Iran, due to ingestion of one hundred 100mg tablets of tramadol.

Two hours after the intentional overdose, he experienced confusion, ataxia, and agitation. On admission (9.38 pm), he was confused and

[1,2] Department of Anesthesiology, Isfahan University of Medical Sciences, Isfahan, Iran
[1,2,3,4] Department of Poisoning Emergency, Noor Medical Center, Isfahan University of Medical Sciences, Isfahan, Iran
*Corresponding authors: Farzad Gheshlaghi, Poisoning emergency Dep., Noor medical center, Isfahan, Iran
Tel: 0311-2222127-134 , Fax: 0311-2222255
E mail: Gheshlaghi @ med.mui.ac.ir

Blood Pressure (BP): 90/50, pulse rate (PR): 140, respiratory rate: 20 and temperature: 36.8^0C. A sudden generalizedtonic colonic seizure ensued at 10.00 pm which was controlled by 10mg of intravenous diazepam. Owing to his cyanotic appearance, a decrease in O_2 saturation (35.2%), and resistant to mask ventilation, an endotracheal tube was inserted and he was transferred to the intensive care unit (ICU). The endotracheal suctioning established that gastric content aspiration had occurred. His blood sugar was 154 mg/100ml (normal range: 70-110). Due to the severe metabolic acidosis (10.03 pm: pH, 7.03; PCO_2, 44.2 mmHg; HCO_3, 13.2 mmol/l; BE, -16.2 mmol/l), sodium bicarbonate (150 mEq) accompanied by 1 liter of normal saline was infused. Then midazolam infusion set at 5 mg/hour was commenced. ECG was also normal. Thirty min after cessation of seizure, suddenly his level of consciousness increased and he extubated himself (10.54 pm); but his confusion and agitation remained unimproved. His BP was 120/75 and respiratory rate: 20, but tachycardia (PR 140) persisted. Despite midazolam infusion, his agitation got worse. At 12.20 am he was lethargic with PR=140 and BP=120/70. Physical examination was unremarkable. Finally, he became stable, but, unexpectedly, at 12.45 am about three hours after his admission, cardiopulmonary arrest took place.

Cardiopulmonary resuscitation was un-successful and the patient expired. Exploring the cause of death led to a dead end. All pre-expiration lab data including complete blood count (CBC), BUN/Creatinine, blood sodium and potassium, creatinine phosphokinase, SGOT, SGPT, alkaline phosphatase; and ECG were within the normal range. Toxicological semi-quantitative analysis (by Gas Chromatography: GC and Thin Layer Chromatography: TLC) was highly positive (+4) for tramadol in all viscera, gastric contents and urine. However blood ethanol, blood opiates, and carboxy-hemoglobin tests were negative. The pathological report for heart, liver and stomach samples were normal, yet there was congestion of blood vessels in lung alveolae.

DISCUSSION

Tramadol is an atypical weak opioid, marketed widely for the treatment of mild to moderate pain (1, 2). This centrally acting opioid analgesic (3) has low affinity for Mu receptors (4) and is a serotonin and norepinephrine reuptake inhibitor (5). This widely used novel analgesic with a favorable adverse effect profile (6), has minimal gastrointestinal or renal toxicity (7) but limited data on the spectrum of manifestations of intoxication in its overdose is available. Lethargy, nausea, tachycardia, agitation, seizure, coma, hypertension and respiratory distress are the more frequently reported symptoms (8) and they are mostly attributable to the monoamine reuptake inhibition rather than its opoid effects (8). No serious cardiovascular toxicity or arrhythmia; beyond tachycardia, have been reported (8).

Despite of the general attitude about its safety, several fatal incidents by tramadol have drawn attention toward its underestimated toxicity (9). In recent years, under the false shadow of safety, the rate of tramadol abuse is becoming disastrous (10).

Daubin C reported a 33-year-old male with assystole and refractory shock requiring extracorporeal life support caused by a combination of tramadol and some CNS depressants (9). Garrett PM described a case of acute pulmonary hypertension and right heart failure (11). Michaud et al recounted a death as a result of tramadol overdose in combination with alperazolam (12). Moore et al explored the tissue distribution of tramadol and its metabolites in overdosed patients and interestingly they came by only one death which was triggered by pure intravenous tramadol injection. The cause of death was declared sudden cardiac arrest with unknown etiology (13).

This popular analgesic with a potency of about one-tenth of codeine (14) is very rarely reported as the sole culprit (not shared, as in combination with other drugs) of deaths in overdose patients. None of these fatal outcomes were presented as sudden death; for instance

Loughrey reported a patient who died from liver failure following accidental tramadol overdose (15).

It should be mentioned that the route of tramadol administration in all reported cases was intravenous injection and none of them were intoxicated by oral ingestion.

CONCLUSION

Regarding the above mentioned particularities such as oral ingestion of the drug without any other accompanying substance and ensuing sudden death, our unfortunate patient was the first to be reported with this picture. With no previous history of any underlying medical condition, no abnormal findings in lab tests, and normal postmortem pathology report, sudden cardiac death seems to be the only fathomable cause of death.

It is not long since tramadol has become widely available as a rather safe analgesic; nevertheless, it seems that available data concerning its toxicity is limited and to assist physicians in anticipating unexpected situations in tramadol overdose, scrutiny into its side effectsis mandatory.

REFERENCES

1. Murthy BP, Skee DM, Danyluk AP, Brett V, Vorsanger GJ, Moskovitz BL. Pharmacokinetic model and simulations of dose conversion from immediate- to extended-release tramadol.Curr Med Res Opin 2007; 23(2):275-84.
2. Alemdar M, Pekdemir M, Selekler HM. Single-dose intravenous tramadol for acute migraine pain in adults: a single-blind, prospective, randomized, placebo-controlled clinical trial. Clin Ther 2007; 29(7):1441-7.
3. Raffa RB. Basic pharmacology relevant to drug abuse assessment: tramadol as example. J Clin Pharm Ther 2008; 33(2):101-8.
4. Tarkkila P, Tuominen M, Lindgren L.Comparison of respiratory effects of tramadol and pethidine. Eur J Anaesthesiol 1998; 15(1):64-8.
5. Stacey BR, Dworkin RH, Murphy K, Sharma U, Emir B, Griesing T.Pregabalin in the Treatment of Refractory Neuropathic Pain: Results of a 15-Month Open-Label Trial. Pain Med 2008; 11.
6. Ruoff GE, Rosenthal N, Jordan D, Karim R, Kamin M. Protocol CAPSS-112 Study Group. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. Clin Ther 2003; 25(4):1123-41.
7. Garcia J, Altman RD. Chronic pain states: pathophysiology and medical therapy.
Semin Arthritis Rheum 1997; 27(1):1-16.
8. Gnanadesigan N, Espinoza RT, Smith R, Israel M, Reuben DB. Interaction of serotonergic antidepressants and opioid analgesics: Is serotonin syndrome going undetected? J Am Med Dir Assoc 2005; 6(4):265-9.
9. Daubin C, Quentin C, Goullé JP, Guillotin D, Lehoux P, Lepage O, Charbonneau P. Refractory shock and asystole related to tramadol overdose. Clin Toxicol 2007; 45(8):961-4.
10. Tjäderborn M, Jönsson AK, Hägg S, Ahlner J. Fatal unintentional intoxications with tramadol during 1995-2005. Forensic Sci Int 2007; 173(2-3):107-11.
11. Garrett PM. Tramadol overdose and serotonin syndrome manifesting as acute right heart dysfunction. Anaesth Intensive Care 2004; 32(4):575-7.
12. Michaud K, Augsburger M, Romain N, Giroud C, Mangin P.Fatal overdose of tramadol and alprazolam.Forensic Sci Int 1999; 105(3):185-9.
13. Moore KA, Cina SJ, Jones R, Selby DM, Levine B, Smith ML. Tissue distribution of tramadol and metabolites in an overdose fatality.Am J Forensic Med Pathol 1999; 20(1):98-100.
14. Goldfranks. Goldfrank's Toxicologic Emergencies. In: Lewis S. Nelson. Opioids. 8th edition. McGraw-Hill, New York: 2006:606.
15. Loughrey MB, Loughrey CM, Johnston S, O'Rourke D. Fatal hepatic failure following accidental tramadol overdose. Forensic Sci Int 2003; 134(2-3):232-3.