

Received: 2017.04.05
Accepted: 2017.05.11
Published: 2017.07.21

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 817-821
DOI: 10.12659/AJCR.904695

Cardiac Arrest Following Drug Abuse with Intravenous Tapentadol: Case Report and Literature Review

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 32
Final Diagnosis: Cardiac arrest after intravenous tapentadol abuse
Symptoms: Headache
Medication: —
Clinical Procedure: Tapentadol drug levels in serum
Specialty: Forensic Medicine

Objective: Rare disease





Background: Tapentadol is a centrally acting opioid analgesic, with a dual mode of action, as a norepinephrine reuptake inhibitor and an agonist of the μ -opioid receptor (MOR). Tapentadol is used for the management of musculoskeletal pain, and neuropathic pain associated with diabetic peripheral neuropathy.

Case Report: A 32-year-old woman attended hospital for evaluation of an intractable headache. Computed tomography and magnetic resonance imaging of the brain were negative. She was found unresponsive in the bathroom on the day following hospital admission, and despite resuscitative measures, the patient died following cardiac arrest. Autopsy toxicology revealed significantly elevated levels of tapentadol, and bedside evidence suggested that the patient had self-administered this medication intravenously before her death.

Conclusions: We report a rare adverse effect of tapentadol causing respiratory depression leading to cardiac arrest. Medical examiners and forensic toxicologists should be aware of the toxicity of this novel opiate drug.

MeSH Keywords: Death, Sudden, Cardiac • Drug Users • Heart Arrest

Full-text PDF: <http://www.amjcaserep.com/abstract/index/idArt/904695>

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Background

Prescription opioid analgesics play an important role in pain management. Tapentadol has a dual mode of action as a norepinephrine reuptake inhibitor and an agonist of the μ -opioid receptor (MOR) that provides nociceptive and neuropathic pain relief [1].

Tapentadol is not a pro-drug and does not rely on metabolism to produce its therapeutic effects. Tapentadol is a potent opioid with no known active metabolites, and none of the metabolites contribute to its analgesic activity [2,3]. The metabolism of tapentadol is by glucuronidation to tapentadol-O-glucuronide, which conjugates with glucuronic acid to produce glucuronides and is poorly metabolized by cytochrome P3A4 (CYP3A4) and CYP2D6, which are distributed throughout the human body [2,3]. Tapentadol is prescribed for oral ingestion, and its metabolites are excreted in the urine. The maximum serum concentration is detected between 1.25 and 1.5 hours after ingestion, and its half-life is four hours [2,3].

Because tapentadol is not metabolized significantly by the CYP450 system, and it does not induce or inhibit CYP enzymes, there is limited potential for drug interactions [2,3]. Tapentadol is used for the treatment of musculoskeletal pain, and neuropathic pain associated with diabetic peripheral neuropathy [4]. Tapentadol may be selected in place of other opioid pain medications in cases of opioid-related gastrointestinal (GI) intolerance, nausea, vomiting, or itching [4]. Like tramadol, which is another dual-acting analgesic, tapentadol provides multimodal opioid as well as non-opioid analgesic benefits [4].

Case Report

A 32-year-old woman presented to the hospital emergency department complaining of severe, intractable headaches for the previous two days. She had a past medical history of migraine, anxiety disorder, and asthma. The patient stated that the headaches were throbbing in nature and felt like a tight band around her head. The patient also reported nausea and vomiting associated with these headaches but denied chest pain, palpitations, and shortness of breath, fevers, chills, dizziness, or any other complaints.

One month previously, as an outpatient, she had been prescribed tapentadol 75 mg orally every four hours for chronic pain. On this hospital admission, she was also found to be taking clorazepate, and an albuterol inhaler, as needed.

On physical examination, her body mass index was 36 kg/m². She did not appear to be in acute distress. Her vital signs were stable, and her temperature was 36.6°C. Her systolic

blood pressure was 124 mmHg with a diastolic pressure of 80 mmHg, pulse rate of 87 beats per minute, respiratory rate of 12 breaths per minute, with 98% oxygen saturation on ambient air. Her lungs were clear, with bilateral equal breath sounds. Cardiovascular examination was normal with no murmurs. Her abdomen was soft, and normal bowel sounds were present.

She was alert and oriented to person, place, and time, and exhibited no focal neurological deficit. Following consultation with a neurologist for assessment of migraine, she was admitted to a general medical ward. Computed tomography of the head showed no intracranial bleeding, no acute territorial infarct or mass lesion. Magnetic resonance imaging of the brain showed no acute intracranial hemorrhage, midline shift, or acute infarct. Her complete blood count, basic metabolic panel, and liver function tests were within normal limits.

The patient was treated with 30 mg of intravenous toradol, a non-steroidal anti-inflammatory agent, at the time of admission to the emergency department. Following neurological review, she was prescribed verapamil and divalproex sodium. The following morning, the patient was found on the floor of the hospital ward bathroom, and a rapid medical response was initiated. She was moved to the intensive care unit immediately following intubation. A nurse discovered a bottle of tapentadol containing crushed pills suspended in liquid at her bedside, together with a syringe. The patient received naloxone during resuscitation. An electrocardiogram was done immediately following the rapid response, which showed QRS duration of 74 ms and a corrected QT interval of 430 ms. Following her arrival in the intensive care unit, she went into asystole leading to cardiac arrest. Despite resuscitative measures, the patient died. Autopsy toxicology showed that the cause of death was tapentadol overdose (Table 1).

This case report describes a rare case of respiratory depression caused by intravenous tapentadol drug abuse leading to cardiac arrest in a hospitalized patient.

Discussion

Tapentadol was approved by the United States Food and Drug Administration (FDA) in November 2008 [1]. Tapentadol is indicated for the management of pain that is severe enough to require daily, continuous, long-term opioid treatment, and for pain that is opioid-responsive and for which alternative treatment options are inadequate [1]. The major concerns during tapentadol therapy are drug addiction, drug abuse, physical dependence, and withdrawal behavior [5].

Tapentadol acts by inhibiting both ascending and descending pain pathways; and inhibits the ascending pain pathway via

Table 1. Autopsy toxicology results from this case.

Tapentadol serum/plasma quantitative	99 ng/mL (cut off level <50)
Tapentadol glucuronide serum/plasma quantitative	189 ng/mL (cut off level <100)
Buprenorphine	Negative
Norbuprenorphine	Negative
Desmethyldiazepam	394 ng/mL (reference range 200–2500 ng/mL)
Acetaminophen	8 µg/mL (reference range 10–20 µg/mL)
Valproic acid	5 µg/mL (reference range 6–12 µg/mL)
Theophylline	0.8 µg/mL (reference range 5–15 µg/mL)
Opiate	Negative
Codeine	Negative
Morphine	Negative
6 acetyl morphine	Negative
Hydrocodone	Negative
Hydromorphone	Negative
Dihydrocodeine	Negative
Oxycodone	Negative
Methadone	Negative
Tramadol	Negative
Meperidine	Negative
Propoxyphene	Negative

the μ -opioid receptor (MOR) binding. Tapentadol is 18 times less potent than morphine at binding this receptor and has less potential for drug abuse. Increased norepinephrine levels are thought to modify the descending pain pathway. Tapentadol also inhibits serotonin reuptake, but its action is much weaker than selective serotonin reuptake inhibitors (SSRIs).

Tapentadol is marketed under the brand names, Nucynta, Palexia, and Tapal, and comes in two forms: an immediate release preparation, which was launched in June 2009, and an extended release form, that first became available in August 2011. The extended release tablets were manufactured partly because they are difficult to crush, for intranasal drug abuse, and difficult to solubilize, for intravenous drug abuse [6]. The use of tapentadol is associated with fewer adverse effects when compared with equivalent analgesic doses of classical opioids, an effect that may result from the fact that the analgesic pathways for this compound are only partially mediated by opioid agonist mechanisms [7].

Tramadol is a similar opioid medication to tapentadol and is also a centrally acting synthetic analgesic with combined opioid and non-opioid activities that work synergistically to produce analgesia. Both drugs have lower risks of respiratory depression, tolerance, and dependence. However, whereas tapentadol

has no active metabolites and does not require metabolic activation to exert its analgesic effects, tramadol requires metabolism by the CYP450 complex to generate its active metabolite, O-desmethyl tramadol and this is required for tramadol to be completely effective [8,9]. Tapentadol is primarily and extensively (70%) metabolized via glucuronidation by the UGT1A9 and UGT2B7 enzymes, which transform it into the following inactive metabolites: N-desmethyl tapentadol (13%), resulting from metabolism by CYP2C9 and CYP2C19, and hydroxy-tapentadol (2%), resulting from metabolism by CYP2D6 [2]. These compounds are then further metabolized by conjugation [2]. The metabolites of tapentadol do not contribute to its analgesic activity [2].

Tapentadol is rarely associated with respiratory depression leading to cardiac arrest, unlike other drugs of abuse, including cocaine, amphetamine, methamphetamine, heroin, synthetic marijuana, cyanide, ecstasy, oxycodone, and meperidine. However, common side effects of tapentadol include dizziness, drowsiness, headache, nausea, vomiting, constipation, and hypotension. Like its proto-drug, O-desmethyltramadol, tapentadol reduces the seizure threshold in patients, and so tapentadol should be used cautiously in patients with a history of seizures. Rare side effects associated with tapentadol use include anaphylaxis, angioedema, ataxia, confusion, hypotension,

decreased heart rate, delayed gastric emptying, disorientation, drug dependence, dysarthria, equilibrium disturbance, euphoria, hallucinations, hypersensitivity, hypogonadism, and drug-related hepatic disorders, but these have been reported in less than 1% of patients [10].

Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids, and serotonin syndrome has been reported during therapy with concomitant use of serotonergic agents [11]. Life-threatening or fatal respiratory depression may occur as a result of tapentadol overdose, and so close monitoring for respiratory depression is recommended, especially during treatment initiation or dose escalation. Tapentadol should not be used in patients with paralytic ileus [3]. However, no dosage adjustments are required for tapentadol when given at the same time as acetaminophen, naproxen, or acetylsalicylic acid [12].

Opioid analgesic use has been associated with QT prolongation, but this literature review showed no association of tapentadol and QT prolongation [3–13]. Cardiovascular complications such as palpitation, chest tightness, tachycardia, and ST segment elevation have recently been reported with tapentadol use, by Vachhani and colleagues [14]. A study by Dart et al. found that rates of drug abuse with intermediate release tapentadol were low during the first 24 months after its launch [15]. Published reports of lethal tapentadol overdoses include a case report by Franco et al., which describes a patient death attributed to tapentadol intoxication, possibly leading to respiratory depression, central nervous system depression, and serotonin syndrome [16]. Another published case reported by Kemp et al. described a patient death following intravenous injection of tapentadol [17]. Also, Cantrell et al. reported a case in which elevated post-mortem blood tapentadol levels were found following a patient death [18].

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Naloxone is a pure opioid antagonist that works by reversing the depression of the central nervous system and respiratory system caused by opioids, and which is included as a part of emergency overdose response kits. Naloxone is a μ -opioid receptor (MOR) inverse agonist in central nervous system. For clinically significant respiratory or circulatory depression secondary to tapentadol overdose, an opioid antagonist can be used. As the duration of opioid reversal is expected to be less than the duration of action of tapentadol, the patient should be monitored until spontaneous respiration is established. If the response is suboptimal, an additional dose of naloxone may need to be administered [19].

In the case presented in this report, samples of post-mortem blood contained elevated levels of tapentadol and crushed tapentadol pills suspended in liquid were found with the patient's possessions, all of which supported a cause of death from tapentadol drug abuse. This case report adds to the literature on the potential hazards of tapentadol overdose and drug abuse when intravenous self-administration is used.

Conclusions

Prescription opioid analgesics play an important role in the management of acute and chronic pain, with adverse effects primarily related to the central nervous system and gastrointestinal tract. The use of tapentadol for the management of pain has the advantage of tolerability, and the dual mechanism of action of tapentadol also provides analgesic benefits. However, as this case report has shown, medical examiners and forensic toxicologists should be aware that, despite its popularity as an alternative to conventional opioids, intravenous tapentadol drug abuse may cause respiratory depression leading to cardiac arrest.

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