Tramadol abuse: A Case Report

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ABSTRACT

Introduction: Tramadol is a weak opioid analgesic that is commonly prescribed for moderate to severe pain. At therapeutic doses, it has less potential to cause respiratory depression, constipation and dependence relative to morphine which is the classic opioid analgesic. Tramadol dependence can occur at high doses and at therapeutic doses when used for prolonged periods of time (weeks to months). In recent times, cases of tramadol abuse and dependence have been on the increase globally. In Nigeria, the alarming number of cases of tramadol abuse led to the ban of the 225mg and higher doses which were commonly abused in 2018. Diagnosis of tramadol abuse may be misleading due to its mixed receptor activity leading to atypical presentations.

Materials and Methods: We report a case of a 25-year old university student who presented to our clinic with withdrawal symptoms from four years of tramadol abuse.

Results: Although naloxone is a recognized opioid antagonist and may be useful in acute toxicity, management is mainly supportive.

Conclusion:

Advocating for continuous awareness programmes is imperative. Also, institutions should put in place procedures to identify students who are potential drug abusers or currently on drugs. In addition, there is the need to establish rehabilitation centers to properly manage those already dependent.

Key words:

Tramadol, Naloxone

INTRODUCTION

Tramadol abuse is associated with high morbidity and mortality if untreated. In Nigeria, the use and abuse of psychoactive substances have become problems of national public health significance with variable medical, psychosocial and economic consequences. [1 – 3] Studies in Nigeria indicate that, the use of tramadol cuts across all parts of the country with an increasing prevalence. In Kano, Northern Nigeria, a cross sectional study amongst commercial bus drivers reported that 80.6% of respondents misused tramadol. [4] Another cross-sectional study among 'Almajiris', in Borno, Northern Nigeria, reported a 7% prevalence of tramadol misuse. [5] In Owerri, South East Nigeria, a survey of the use of psychoactive substances amongst university students indicated that 53.4% admitted to the use of tramadol. [6] In a case report from the Niger Delta University Teaching Hospital (NDUTH) in 2017, tramadol misuse was common among young males in the Niger Delta region. [7] A cross-sectional study among secondary school students in south west Nigeria on substance abuse showed that, tramadol was the most commonly abused substance apart from alcohol. [8] In one study, the major reasons for tramadol abuse among the study participants were: (i) for the relief of tiredness or fatigue, which could be accounted for by the occupational composition of the subjects (unskilled workers), (ii) the prolongation of time of sexual intercourse, and (iii) the control of the compulsive urge or craving for the drug which is attributable to the addictive potential of the drug. [9, 10]

Tramadol is a synthetic opioid analgesic. It acts centrally to modulate the descending pain pathways through the binding of its active M1 metabolite O-desmethyltramadol to μ-opioid receptors and also, the inhibition of the reuptake of norepinephrine and serotonin. Tramadol also consists of two enantiomers, (+)– tramadol, which preferentially inhibits serotonin uptake and (-)- tramadol, which is the potent inhibitor of norepinephrine reuptake. [11 – 13] It is used for the treatment of moderate to severe pain. There are two forms of tramadol available, the immediate release form and the extended release form. The commoner form is the immediate release with a dose of 50 -100mg every four to six hours with or without food. The maximum daily dose should not exceed 400mg with adult therapeutic blood levels of 0.1–0.8mg/L. [14] Like every opioid the principle of starting low and going slow applies. Increments in the doses are advisably done with three-day intervals. Tramadol is considered a controlled drug in most parts of the world but its available over and off the counter. [15]

Diagnosis of tramadol abuse/ withdrawal is mainly clinical. Symptoms could be typical or atypical. Typical symptoms include diarrhea, epiphora, insomnia, abdominal pain, bone pain, anxiety, nausea, agitation, depression and diarrhea. Atypical symptoms include severe anxiety, panic attacks, delusion, paresthesia, numbness, burning sensations, tinnitus, visual and auditory hallucinations.

We report an atypical withdrawal symptom of tramadol abuse for four years.

CASE REPORT

A 25-year old male university student was referred to us from the family medicine clinic with complaints of recurrent generalized body weakness and burning sensations in the feet which had been occurring for a period of nine months. He was apparently well until nine months prior to presentation when he started experiencing the above symptoms. The generalized body weakness was associated with non-specific generalized headaches with no neurological deficits. There was also a positive history of fainting attacks especially when rising from a sitting

position, no breathlessness, cough, palpitations, exertional dyspnea, orthopnea or paroxysmal nocturnal dyspnea. There was a history of anorexia and weight loss over the period, however, there was no cough, fever, drenching night sweats, polyuria, polydipsia, polyphagia, cold nor heat intolerance.

The patient also complained of burning sensations in the eyes and feet over the period. The burning sensation was worse in the feet during walking with no associated history of gait abnormality. The burning sensations in the eyes were not associated with discharge, redness, tearing, grittiness, nor trauma. There was insomnia, restlessness, loss of attention and concentration during conversations which affected his academic performance. There were no seizures, irrational behavior nor slurred speech. He also complained of vague abdominal pain that was not associated with abdominal swelling, hematemesis, melena, pruritus, jaundice nor pale bulky stools. There was a positive history of tramadol use for pleasure at a dose of at least 400mg daily for the past four years which he tried stopping nine months prior to presentation. However, he realized that during the period of generalized body weakness he regained strength whenever he took tramadol.There were moments when he had to take about a 1g of tramadol to relieve him of the generalized weakness. There was a history of alcohol use (about nine units per week) but he did not smoke any substance. There was a history of multiple unprotected sexual exposure with multiple sexual partners. He had no surgeries or blood transfusions in the past.

On physical examination, he was alert, afebrile (Temperature -36.3^{o}C), not pale, anicteric, acyanosed, not dehydrated, no peripheral lymphadenopathy, digital clubbing, pedal edema, joint deformity nor palmoplantar rash. He had no tattoos or injection marks. His neurological exam was essentially normal. His pulse was 80bpm, regular with good volume. Blood pressure values recorded were 100/70mmHg and 90/70mmHg both sitting and standing respectively. Examination of the precordium and all other systemic examinations were normal.

Laboratory investigations which included: full blood count, erythrocyte sedimentation rate, renal function test, serum magnesium, urinalysis, vitamin b12 assay, fasting blood sugar, hepatitis B surface antigen, antibodies to hepatitis C virus, human immunodeficiency virus (HIV) and venereal disease research laboratory screen for syphilis were all normal.

We made a diagnosis of peripheral neuropathy and other withdrawal symptoms secondary to tramadol abuse. Psychotherapy was prescribed for him with tablet pregabalin 75mg daily and tablet neurovite forte twice daily. He was then reviewed a week after.

At review, his symptoms of generalized body weakness and the burning sensation in the eyes and feet had improved. He complained of burning epigastric pain with associated tightness with meals. A further assessment of dyspepsia also secondary to tramadol abuse was made. He was given suspension gestid (an antacid) 10mls thrice daily, tablet acetaminophen 1g thrice daily, psychotherapy done and was scheduled for review the following week.

On the second review, he complained of insomnia, suprapubic pain with no associated fever, urgency, hematuria or hesitancy. He had suprapubic tenderness on examination, however, urinalysis done was normal. Urine for microscopy, culture and sensitivity was taken and sent to the lab. Tablet ciprofloxacin 500mg twice daily for five days, amitriptyline 25mg nocte, tab pregabalin 75mg daily and psychotherapy were prescribed for him. He was then scheduled for a two-week review.

On his third review, which was four weeks after the initial visit, he complained of persistent insomnia but his other symptoms had improved. He had not used tramadol since he started attending our clinic. Urine microscopy, culture and sensitivity came out to be normal. He had

psychotherapy. Prescription for tab bromazepam 3mg nocte for one week, tablet triptizol 25mg nocte, tab pregabalin 75mg daily, tab vitamin b complex one tab thrice daily for two weeks was made and he was scheduled for review in another two weeks.

However, the patient defaulted from clinic and only presented two months after the last review with largely the same complaints having resulted to further abuse of tramadol. Psychotherapy was done. He was then recommenced on tablet pregabalin 75mg daily and tablet neurovite forte twice daily for two weeks and scheduled for follow-up visits. So far, patient seems to have improved but the major problem is getting him off the drug completely.

DISCUSSION

Tramadol is a centrally acting analgesic with multimodal sites of action. It has two enantiomers, (+)– tramadol, which preferentially inhibits serotonin uptake and (-)-tramadol, which is the potent inhibitor of norepinephrine reuptake, while its metabolite O-desmethyltramadol acts on the μ-opioid receptor. Its analgesic potency is said to be about a tenth that of morphine but equipotent to codeine. [6] Tramadol is used to treat both acute and chronic pain of moderate to severe intensity. Tramadol monotherapy does not usually provide adequate analgesia. [16] In chronic non-cancer pain, there is little evidence for the use of tramadol for more than three months. [16, 17]

Ordinarily, tramadol is considered to be a relatively safe analgesic. The common adverse reactions to tramadol therapy are nausea, dizziness, and vomiting, particularly at the start of the therapy. Tramadol is contra-indicated, however, in patients with diminished respiratory function and in patients on monoamine oxidase inhibitors. [18] It is generally considered as a medicinal drug with a low potential for dependence relative to morphine. Nevertheless, tramadol dependence may occur when used for prolonged periods of time (more than several weeks to months). [19] Dependence on tramadol may occur when used within the recommended dose range, especially when used at supra-therapeutic doses. In many individuals with tramadol dependence, a substance abuse history is found. [16] [20] However, there are few recorded cases of individuals with no previous history of substance abuse. [21]

The therapeutic dosage of Tramadol is 50-100mg every four to six hours with a maximum dose of 400mg. It is recommended that, for higher therapeutic doses, titration be done over a period of about 10 – 16 days for the commoner immediate release formulation. [16] Tramadol has a high oral bioavailability (70 – 80%) that can increase to 90 – 100% with repeated dosage. Thus, the difference between the oral and parenteral dose administration is not significant. [22] The volume of distribution of tramadol is about 2.6 – 2.9L/kg bodyweight following a 100mg intravenous dose. Plasma protein binding is approximately 20%. Tramadol is metabolized extensively in the liver by demethylation, oxidation and conjugation by cytochrome p450 2D6 and 3A4 enzymes mainly. Following oral tramadol administration, 90% is eliminated in urine (30% unchanged and the remaining 60% in the form of free and conjugated metabolites) and the remaining 10% in faeces. [16]

Adverse effects of tramadol are multisystemic, with the likelihood of adverse effects increasing with increasing doses. [23] [24] The effects on the central nervous system include: agitation, dizziness, headache, drowsiness, insomnia, paresthesia, restlessness, depression, ataxia, anxiety, euphoria and depersonalization. Flushing, orthostatic hypotension, chest pain and hypertension are known cardiovascular effects. Skin manifestations of

toxicity may be pruritus or diaphoresis. The gastrointestinal effects are constipation, nausea, vomiting, dyspepsia and xerostomia. On the neuromuscular and skeletal system, it causes weakness. The unwanted effects in the genitourinary include: urinary frequency, urinary retention, urinary tract infection, pelvic pain and menopausal symptoms. In the respiratory system, cough, sneezing, pharyngitis, rhinorrhea and respiratory depression are observed in supratherapeutic and lethal doses.

Diagnosis of tramadol abuse or overdose is mainly clinical in resource poor settings. A good history with empty sachets or containers of tramadol makes the diagnosis more likely. In our case report, the atypical symptom of burning sensation in the feet was a chief complaint. After ruling out possible causes, we were convinced his symptom was due to tramadol abuse. When available, toxicology screens with blood levels >2mg/L of tramadol is significant. 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 levels between 1–2mg/L and lethal concentrations being higher than 2mg/L.

Treating tramadol overdose is majorly with supportive therapy and close monitoring. This proved beneficial in our patient. Where available, patients can be admitted into rehabilitation wards for specialized round-the-clock care. Outpatient care with close monitoring is also effective, which we employed in our case. If victims present within one to two hours following oral ingestion, activated charcoal can be used. Naloxone, an opioid antagonist is only partially effective in tramadol toxicity because of the weak opioid effect of tramadol and the other significant mode of action via the inhibition of serotonin and norepinephrine reuptake receptors. Seizures from either naloxone use or tramadol toxicity can be effectively managed with benzodiazepines. In a case report reviewing five cases of tramadol abuse in the Niger Delta region, it was demonstrated that supportive therapy was effective in the management of tramadol abuse or related toxicities. [7]

The presentation of tramadol toxicity may be similar to that of serotonin syndrome which may include neuromuscular hyperactivity (myoclonus and hyperreflexia), autonomic hyperactivity (tachycardia and pyrexia) and altered mentation (usually agitation, excitement, and later confusion). [25 26] This is due to the inhibition of serotonin reuptake. It is important for clinicians to remember to not prescribe tramadol together with medications like Selective Serotonin Reuptake Inhibitors (SSRIs) e.g. fluoxetine, Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) e.g. duloxetine, Monoamine Oxidase Inhibitors (MAOIs) e.g. selegiline, Tricyclic Antidepressants (TCAs) e.g. amitriptyline, triptans e.g. sumatriptan and lithium since these can increase the occurrence of serotonin syndrome.

Effective national control programs have been shown to reduce the prevalence of tramadol abuse in different countries. Zhang et al [27] studied tramadol dependence in users without a history of substance abuse. According to the authors, tramadol has been a drug of abuse ever since its introduction in China as a non-controlled analgesic medicine. After placing under national control in 2007, tramadol use among drug abusers declined from 13.3% in 2009 to 3.4% in 2011. [27] This shows that with effective national control programmes, the ever-growing menace of tramadol abuse and related morbidity and mortality can be reduced.

CONCLUSION /RECOMMENDATION

In summary, tramadol, a central-acting analgesic is gaining popularity globally due to its abuse and dependence contrary to the literature assertion that it has low risk of dependence compared to morphine. Its

imperative for the clinician to know the variable presentations of tramadol misuse and to be able to manage effectively the toxicity-related symptoms when encountered. Supportive therapy remains the mainstay of treatment for tramadol toxicity. There is a need for further studies to determine if the prevalence of this menace is reducing or increasing in Nigeria despite the recent ban on the illicit formulations and availability of the drug in the country. Measures should also be put in place to identify at an early stage especially among youths, potential drug abusers and how best those who are already addicted to the drug can be best managed.

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