Türk Psikiyatri Dergisi 2024;35(3):245–247
https://doi.org/10.5080/u26711

Loss of Consciousness After Naltrexone Implantation: A Case Report

Oğuzhan DOĞAN[1]

ABSTRACT

Naltrexone is an μ opioid receptor antagonist that is used in alcohol and opiate use disorder. Naltrexone does not constitute tolerance and dependence, and cessation of the drug does not cause withdrawal symptoms. Sustained release form of naltrexone has been developed due to patient compliance issues. There is currently only one sustained-release form available in Turkey, which is inserted subcutaneously.

In this case report, we present, a probable serious side effect of sustained release naltrexone implant. A 36 years old male with alcohol use disorder, developed a sudden clouding of consciousness one hour after the naltrexone implant application followed by anterograde amnesia in the next 8-10 hours. We were not able to detect any medical or neurological reasons for the altered mental status but after the removal of the naltrexone implant, the symptoms improved. To the best of our knowledge, this is the first case to report clouding of consciousness and anterograde amnesia after naltrexone implantation.

Keywords: Naltrexone Implant, Side Effect, Alcohol Use Disorder, Lethargy, Consciousness

INTRODUCTION

Naltrexone is a competitive antagonist of μ opioid receptors in the central nervous system with a similar effect on kappa receptors in the brain and spinal cord, but also has partial agonist activity showing little or no activity at delta receptors in the spinal cord and peripheral nervous system (Daniel Sudakin. 2015). Brain imaging studies have shown that 95% of cerebral μ opioid receptors are blocked after a standard oral dose of 50 mg of naltrexone in humans (Weertss et al. 2018). Oral naltrexone has been used for many years to treat opioid addiction and was approved by the FDA (Food and Drug Administration) in 1984 for the treatment of Alcohol Use Disorder. Naltrexone reduces mesolimbic opioidergic activity and thus modulates the rewarding effects of alcohol through dopamine and reduces alcohol consumption (Volpicelli et al. 1992). A number of extended-release implants have been developed for use in alcohol and opioid addiction to overcome the problems associated with poor adherence to treatment with oral naltrexone (Kimberly et al. 2011). Implantable and oral doses of naltrexone are generally well tolerated. Common side effects are headache, insomnia, depression, fatigue, nausea, vomiting, diarrhea, high blood pressure, increased liver enzymes, cough, bronchitis, pneumonia, widespread rash and wound infections (Ak ve Gürel 2020, Krupitsky ve ark. 2019). In the literature review, no confusion and anterograde amnesia were found in the side effect profile of the naltrexone molecule. Confusion and anterograde amnesia, which started one hour after the naltrexone implant was inserted, lasted about 8-10 hours and resolved 8-10 hours after the removal of the implant and the results were discussed in our case.

CASE

The 36-year-old male patient has never married and lived in the same house with his mother, father and older brother. He made a living by working as a barber and fishing. He started using cannabis (delta-9-tetrahydrocannabinol) for the first time at the age of 14, ecstasy (3,4-methylene dioxy methamphetamine) and intravenous heroin (diacetyl morphine) for about 5 years without interruption. He spent 6 years in prison. The patient managed to stay clean for 4 years after his discharge. However, he started to use alcohol heavily and regularly 3 years ago. He has been drinking an average of 1000 mL of raki (home-made) every day for the

Received: 16.06.2021, **Accepted:** 30.06.2022, **Available Online Date:** 21.11.2023

[1]Psychiatrist, Mersin Toros State Hospital, AMATEM Bl., Mersin.

e-mail: doganodo@hotmail.com

last year. The patient, whose alcohol use started to affect his social and professional functionality, applied to our clinic for treatment. His consciousness was full in his mental state examination and speech was clear and purposeful. His mood was euthymic, his affection status was appropriate and associations were regular. He had no perception disorder, no delusion in his thought content, he had thoughts related to the difficulties he experienced due to alcohol use. Based on the frequency of withdrawal symptoms, development of tolerance, and deterioration of social and occupational functionality, the patient was admitted to the ward with the diagnosis of Alcohol Use Disorder according to DSM-5 criteria. The patient's treatment was updated by adding diazepam 5 mg 2*1 olanzapine 10 mg 1x1 to the previously taken clomipramine 75 mg 2x1 and amlodipine 10 mg/day treatment for hypertension, and vitamin replacement was perfomed. The patient's Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) score was followed, and the washout period was recorded without any problems. White blood cell was 11.83 (4.5-11.5 10^9/L), C-reaktive protein (CRP): was 8.74 (0-8), Anti-streptolysis-o (ASO): was 388 (0-200) in the examinations performed during his hospitalization. Hepatitis markers were negative, free T3, free T4, TSH, biochemistry tests, vitamin B12 and folate levels were within the normal range. The COVID-19 Polymerase Chain Reaction (PCR) test was reported as negative. The dose of diazepam that the patient was taking was continued as 2*5 mg until the last day of his treatment. Naltrexone implant treatment was planned for the first time for the patient who received psycho-training and whose motivational interviews were completed. Urine screening test (opiates/cocaine/amphetamine/methamphetamine/buprenorphine/benzodiazepine/tetrahydrocannabinol) was negative except for benzodiazepine on the 9th day of treatment with IV cefazole 1 g and 40 mg Methylprednisolone pre-application. Naltrexone implant 765 mg was placed by a general surgeon and the patient was discharged with stable vital signs half an hour after the implantation. It was learned from the patient and his relatives that complaints of dizziness, balance disorder, generalized weakness, and loss of consciousness all over the body developed approximately one hour after the implant was applied. In the evaluation of the patient, who did not have a prior chronic disease other than hypertension and was taken to the emergency room by his relatives after the development of blurred consciousness, fever was 37.3°C, pulse was 134/min, blood pressure was 120-70 mmHg and O2 saturation was measured as 92%. In the examination, ethanol level in blood was 0 (zero), white blood cell in hemogram was 15.3 (4.5-11.0 10^9/L), hemoglobin was 12.8 (13.5-17.5 g/dl), Hematocrit was 39.8 (41-53 %), neutrophils were 12.62 (2-8 10^3/uL) and other values were within the normal range. In biochemistry tests, glucose was 156 (74/106 mg/dl), urea was 13.33 (15-50 mg/dl), LDH was 360 (120-246 IU/L), phosphorus was 2.28 (2.4-5.1 mg/dl), and other values were within the normal range. The thoracic CT scan examination of the patient whose COVID-19 PCR test was negative reported that "Ground glass areas and interlobular septal thickenings were observed in both upper lobe apical segments of both lungs, COVID-19 was low-moderate level suspicious for pneumonia. Further examination with PCR was recommended". The brain CT scan examination performed during the sleep period was reported as normal, and the diffusion MRI examination was interpreted as not appropriate for the evaluation of the images, and re-examination was recommended. It was reported in the neurology consultation held at this time that acute neurological pathology was not considered in the foreground and that the patient should be evaluated in terms of intoxication.

Since the general confusion continued in the follow-up of the patient, there was no neurological or internal reason to explain this condition, the patient's complaints started half an hour after the naltrexone implant application, and there was no history of substance intake during this period, this was considered to be a side effect of naltrexone and the removal of the implant from the patient was suggested by me. The general surgery department was consulted about the patient and the naltrexone implant was removed 9 hours after the implant. The patient was followed up in the intensive care unit. The second neurology consultation the next day revealed that "The patients is conscious, cooperative, oriented, has a mild tendency to sleep, and there are no other pathological neurological findings. Brain tomography, diffusion MRI was normal. The electroencephalography (EEG) was found to be within the normal range". No cultures were taken from the patient during the emergency observation for any infectious agent.

The patient was transferred to the psychiatry ward after regaining consciousness during the follow-up in the intensive care unit and his general condition improved. In the mental state examination 36 hours after the implant was removed, the patient's conscious and cooperative space-time orientation was fully evaluated and the associations were regular and in line with purpose. Thought content was normal, delusions and hallucinations were not detected. Anterograde amnesia period was identified in the patient, which started approximately 1 hour after the implant application and ended 10-12 hours later in the intensive care unit, and due to which the patient could not recall the events during this time period. Other than this, memory was normal. In the follow-ups, the general condition continued to be stable and no psychiatric pathology was detected except for ongoing anterograde amnesia. The patient was discharged with full recovery on the 15th day of his hospitalization.

DISCUSSION

Oral naltrexone is an approved agent for the treatment of alcohol and opioid dependence; however, patient compliance is generally problematic in oral naltrexone use and causes reverting to opioid use (Hulse, Basso, 2000). For this reason, extended-release naltrexone preparations were developed as an alternative to oral naltrexone treatment to facilitate patient compliance (Comer et al. 2007).

Among the side effects of naltrexone, headaches, sleep disorders, weakness, irritability, abdominal pain and cramps-nausea, vomiting, joint and muscle pain, weakness, rash were reported as the most common ones. Treatment retention and compliance rates with oral naltrexone are low. The implant used in the Alcohol and Drug Addiction Treatment and Research Center *(Alkol ve Uyuşturucu Madde Bağımlıları Tedavi ve Araştırma Merkezi (AMATEM))* Clinic of Mersin Toros State Hospital is a preparation containing 765 mg of naltrexone hydrochloride and is stated to provide therapeutic blood levels of naltrexone over 2 ng/ml for 2-3 months. (Krupitsky et al. 2010). Naltrexone implant form has been widely used in the treatment of alcohol and opioid use disorder for about 4 years in our clinic and 1560 naltrexone implants were applied in four years. The most common side effects in these applications are infection and allergic reactions at the implant site, nausea, vomiting, muscle-joint pain and spasms. Some of these infections were severe and necrotic, leading to tissue loss. There were no findings (age, gender, type of substance used, purification time, implant type, etc.) to predict these side effects in our clinic. In addition, information regarding the side effects of surgically applied naltrexone is limited (Akan et al. 2020). In a study conducted in Australia, 12 patients, who had implants inserted and applied to the hospital when side effects developed, were examined. Six of them developed severe dehydration because of rapid opioid detoxification and naltrexone implant treatment. Opioid withdrawal symptoms such as severe vomiting, diarrhea, abdominal cramps, agitation, lethargy and general aches that began immediately after the procedure. In 5 cases, the reasons for admission varied, such as abscess, suicidal thoughts, and pain. The half-life of naltrexone is 3.9-10.3 hours (Crabtree 1984). This patient developed unconsciousness and anterograde amnesia, which started immediately after the implant application and resolved approximately 10 hours after the removal of the implant, which could not be explained by neurological or internal causes. From these complaints, the blurring of consciousness completely resolved and the patient returned to his social and occupational functionality, but the anterograde amnesia did not improve. This, which scores 4-5 points according to the Naranjo drug side effect scale, falls into the "probable" drug side effect class (Naranjo et al. 1981). It was concluded that the clinical picture of the patient whose neurological examination was completely normal and whose EEG, Brain CT scan and Brain Diffusion MRI results were found to be normal is related to the naltrexone implant.

There are many studies in the literature on the efficacy of naltrexone molecule in alcohol, opioid and amphetamine addiction and it was reported that it can be an effective pharmacological agent for the treatment of multiple substance addiction (Tihonen et al. 2012). The side effects of this molecule, which is a promising method in addiction treatment, are debatable and the literature should be developed in this respect. Sometimes, it can be difficult to eliminate the side effects of extended-release drugs. In such drugs, it is a preferred way to observe patient tolerance with daily dose. The treatment options for alcohol and opioid use disorders are limited and patient compliance is problematic. For this reason, extended-release naltrexone will be important in these two disorders in the future, perhaps as a good treatment option in pathological gambling and other models of addiction. Clinicians should be careful in terms of the confusion and anterograde amnesia, which are the unexpected and serious side effects that were experienced by this patient, and it should be kept in mind that the removal of the naltrexone implant is the most important treatment option.

REFERENCES

Ak S, Can Gürel Ş (2020) Letter To The Editor Drug Eruption After Sustained Release Naltrexone Pellet Implantation. Turk Psikiyatri Derg Summer; 31:146-7.

Akan M, Toplu SA et al (2020) Naltrekson İmplanta Bağlı Gelişmiş Lokal Komplikasyonlara Multidisipliner Yaklaşım: Olgu Sunumu Current Addiction Research 4: 28-34.

Comer SD, Sullivan MA et al (2007) Sustained-release naltrexone: novel treatment for opioid dependence. Expert opinion on investigational drugs. 16:1285-94.

Crabtree BL (1984) Review of naltrexone, long acting opiate antagonist Review Clin Pha May-Jun 3:273-80.

JR Alterman A, Hayashida M et al (1992) Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry Nov 49:876-80.

K Hulse, MR Basso G (2000) The association between naltrexone compliance and daily supervision. Drug and Alcohol Review. 19:41-8.

Kjome KL, Moeller FG (2011) Long-Acting Injectable Naltrekson for the Management of Patients with Opioid Dependence Subst Abuse. 5:1–9. Published online 2011 Feb 6.

Krupitsky E, Blokhina E et al (2019) Slow-release naltrexone implant versus oral naltrexone for improving treatment outcomes in people with HIV who are addicted to opioids: a double-blind, placebo-controlled, randomised trial. The Lancet HIV. 6:e221-e9.

Lintzeris N, Lee S et al (2008) Unplanned admissions to two Sydney public hospitals after naltrexone implants. Medical journal of Australia 188: 441-4.

Naranjo CA, Busto U et al (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:239-45.

Sudakin D (2016) Naltrexone: Not Just for Opioids Anymore J Med Toxicol 12:71–5.

Tiihonen J, Krupitsky E et al (2012) Naltrexone implant for the treatment of polydrug dependence: A randomized controlled trial. Am J Psychiatry 2012;169:531–6. Volpicell