Case Report
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Management protocol for the naltrexone ımplant in the patients with acute abstinence symptoms: Mexican case series

Abstract

Abuse and addiction to opioids, including prescription painkillers, heroin and synthetic opioids such as fentanyl, buprenorphine, constitute a serious crisis that affects public health and has economic repercussions.[1] Naltrexone implants are effective tools used in hospital environments and they can not only save patient´s lives but also maintain a prolonged effect, free of relapse and with better therapeutic adherence. The aim of this study is to describe that the management protocol of acute abstinence symptoms in patients with a history of opioid use prior to naltrexone implant placement.

Keywords: implant naltrexone, addiction, opioids, health care workers, naloxone, abuse drugs

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Introduction

Abuse and addiction to opioids, including prescription painkillers, heroin and synthetic opioids such as fentanyl, buprenorphine, oxycodone, constitute a serious crisis that affects public health and has economic repercussions. It is estimated that the number of opiate users and people with abuse of these substances in the last year is approximately 35.1 million people (range 28.3 million to 42.7 million).[1] The abuse of opioids remains a concern in many countries, particularly in the United States of America where shows an increase in the use of heroin and fentanyl, has resulted in an epidemic and an increase in related morbidity and mortality with opiates.[1]

Opioids continue to be a major concern in south-west and central Asia and in eastern and south-eastern Europe. In the south-eastern Europe, almost three out of five people who are on drug treatment are also under treatment for opioid use disorders. According to the "National Survey of Consumption of Drugs, Alcohol and Tobacco 2016-2017", in Mexico, there is an accumulated incidence of opioid use in the population aged 12 to 65 years.[2]

Naltrexone is a long-acting opiate antagonist and derived from thebaine with a structure very similar to oxymorphone.[3] Naltrexone has been used with a recommended daily oral dose of 50 mg in patients who have detoxified from heroin.[4] Opioid effects can be blocked by naltrexone because of the methyl group. Methylnaltrexone antagonizes the peripheral μ receptor and has a lower affinity for the κ and δ receptors. Moreover, Naltrexone has better oral bioavailability and a longer duration of action than naloxone. However, previous studies showed that oral naltrexone had the lack of clinical success.[5,6] Therefore researchers started to search for developing sustained release technologies that would decrease compliance problems by reducing the number of dropout opportunities. Naltrexone implants might increase the clinical feasibility. This article describes the management protocol of acute abstinence symptoms in patients with a history of opioid use prior to naltrexone implant placement, 6 pellets with microspheres 200 mg each.Implants were donated to the Pain Management and Palliative care service in Hospital General de Occidente by the company: Esterimex Soluciones S de RL de CV and each patient had thorough information on the current status of implants and informed consent was obtained from the patients.

Cases

Case 1:

A 37-year-old man with a history of consumption of 12 tramadol ampoules per day (1,200 mg), each with 100 mg part of the group of patients to whom 1200 mg total of naltrexone was implanted for 3 months (200 mg per pellet); Positive toxicological test for marijuana, opioids, benzodiazepines, and amphetamines. Verbally, the patient denied opioid consumption in the last 2 weeks prior to the date of implantation. The patient was tested with intravenous naloxone 0.80/mg/2 ml infusion with 250 ml saline for 45 minutes without presenting clinical data of abstinence. We proceeded to place the implant in the posterior -upper region of the right or left iliac crest indistinctly, which was performed without any complications, he was kept under observation for 30 minutes after the event, without clinical data of abstinence, and was discharged home.

While traveling home, he presented diaphoresis and anxiety and he was hospitalized in the emergency department with persisting diaphoresis, tachycardia, high blood pressures. Within minutes after his hospitalization, myoclonus and altered state of consciousness manifested with stupor were started. Noninvasive monitoring was performed, sedation with propofol 60 mg, dexmedetomidine 400 mcg, diazepam 20 mg, olanzapine 10 mg, haloperidol 10 mg total dose of each drug, which was administered according to his response until adequate sedation was achieved. Then spontaneous ventilation was supported only with a face mask at 5 liters per minute of supplemental oxygen. He was under observation for 24 hours, with a chest x-ray, urinary catheter, and continuous vital sign monitor.

Once the sedation was withdrawn, it was learned that 6 tramadol ampules (600 mg) were administered by himself at the night before the implant was placed. The blood samples were taken for liver and toxicological tests and a test dose of intravenous (IV) naloxone (0.80 mg) was performed three months later. Naltrexone implant was placed after the correction of the results was negative. The patient was discharged without clinical data of abstinence after application. The patient in the intermediate period after the first event, there was no any abstinence symptom of the tramadol.

Case 2:

A 31-year-old man anesthesiologist with a history of fentanyl and ketamine consumption, once or twice in a month for the last two years. He got a negative toxicology report and verbally denied opioid or ketamine consumption for more than 4 weeks. Therefore, he enrolled in the implant program. Naloxone 0.80 mg IV was administered in 45 minutes, with no clinical data of abstinence. He went to the operating room where the naltrexone implants were placed, without any complications. He was discharged home without any adverse reaction or abstinence event.

The patient remained without consumption of fentanyl or ketamine for more than 3 weeks, ensuring the absence of abstinence data. 3 months later, a new blood sample was taken for liver and toxicological tests, both without alteration. The patient remained without desire or anxiety for the consumption of opioids and ketamine. Once again, intravenous administration of intravenous naloxone 0.80 mg in 45 minutes, when the toxicology results are negative. The naltrexone implant was placed, he was kept under observation 30 minutes after the event, with no abstinence data. The patient remained without opioid consumption prior to the placement of naltrexone, which prevented the appearance of a withdrawal syndrome, it also contributed to the absence of craving, avoiding the consumption of fentanyl and ketamine. Currently, the patient has re-incorporated into his work life and has not presented craving or relapses. Implant placement is planned for the fourth time.

Case 3:

56 years old woman who is a nurse with a history of abuse of buprenorphine during the past 10 years, each ampoule contains 300 mcg and her average the consumption was 20 ampoules per day. The patient had a negative toxicology reports and verbally denied the consumption of buprenorphine 4 weeks before the implant. An Intravenous test dose of naloxone was administered in 45 minutes and the naltrexone implant was placed. She was kept under observation for 30 minutes, there was no clinical data of withdrawal. She presented anxiety, diaphoresis, sphincter relaxation, myoclonus and systemic hypertension 20 minutes later. Sedation was provided with total doses of 400 mg propofol, 200 mcg dexmedetomidine, and 30 mg of midazolam and 10 mg of haloperidol without loss of spontaneous breathing. She received ventilator support with mask facial at 6 liters per minute of supplemental oxygen, under non-invasive monitoring. Serum glucose, quantification, diuresis quantification and control chest x-ray were taken. She remained under surveillance for 24 hours in the emergency department and she reported that 6 ampoules of buprenorphine were administered by herself at the day prior to the placement of naltrexone.

Once again, we were faced with a case where the patient omitted information regarding the last consumption. The protocol was followed up, continuing at home with alprazolam and topiramate (0.50 mg and 25mg respectively every nigth); 3 months after the incident, she came in for a re-implantation, naloxone 0.80 mg i.v. was administered without clinical withdrawal data. The naltrexone implants were placed, and she remained under observation without withdrawal data. She was discharged home. The patient currently continued her work as a nurse and remains without consumption, with minimal craving. Waiting for new implant placement for the four time.

Case 4:

21 years old man who is a medical student currently in his internship program, with a history of daily consumption of 16 tramadol ampoules, each with 100 mg. He had a medical history of seizure. His toxicological report was negative and he verbally denied the use of tramadol 7 days previously. 0.80 mg test dose of naloxone was administered intravenously for 45 minutes, he just mentioned about anxiety. The naltrexone implants were placed and the patient presented diaphoresis, tachycardia, systemic hypertension, myoclonus and urethral sphincter relaxation within a period of 10 minutes. Sedation was provided with propofol 800 mg IV initially and followed by dexmedetomidine 600 mcg, diazepam 20 mg, haloperidol 10 mg and olanzapine 10 mg were administered. He received 8 liters per minute of supplemental oxygen. He was kept under non-invasive monitoring, with intravenous fluids, saline base, serum glucose, chest x-ray, and urinary catheter were placed 6 hours after the event, due to urinary retention. He remained under close monitoring for 24 hours in the emergency department. Sedation was gradually withdrawn. It was learned that he injected 8 tramadol ampoules on the day of implantation. The protocol was followed up, continuing at home with alprazolam and topiramate (0.5mg and 25mg respectively at nigth). The patient reported little desire for opioid use 30 days after the

implant, as additional information, he commented that his seizures had stopped during the period after naltrexone. He was scheduled for another implant placement 3 months later and blood samples were taken for liver function, and toxicology tests, which were shown without alteration. We administered 0.80 mg of intravenous naloxone in 30 minutes. During the procedure during he presented diaphoresis and anxiety and the patient reported having consumed tramadol 3 days prior to the appointment for implantation. Therefore, we decided to cancel the procedure.

He was scheduled one week later, however he consumed tramadol again 3 days prior to the appointment. This was it important risk factor for withdrawal syndrome when re-implanting naltrexone. Tramadol can have a redundant inhibitory effect on the inhibitory system, possibly mediated by GABA receptors, explaining involuntary muscle movements that can easily be confused with a convulsive condition. This patient had a history of consumption of tramadol doses above 800 mg, exceeding the maximum doses of this opioid, which is closely linked to the history of "seizures" that he presented before the placement of naltrexone.

Discussion

Abuse and addiction to opioids, including prescription painkillers, heroin and synthetic opioids such as fentanyl, buprenorphine, constitute a serious crisis that affects public health and has economic repercussions.[1] The opioid receptor antagonist oral naltrexone has been available since the 1980s and it was used for the treatment of opiate dependence. Naltrexone is available in Mexico in capsules of 50 mg as well, unfortunately the pill form of naltrexone was ineffective due to poor adherence daily. On the other hand, naltrexone in the form of implants for 3 months of a dose of 1,200 mg is one of the alternatives that keep these patients without relapse, accompanied by their psychiatric support and follow-up by the work team. Moreover, oral naltroxane has been associated with hepatoxicity. The naltrexone implant was generally well tolerated and not associated with increased levels of ALT or AST.[7] During this project, no data of hepatotoxicity by naltrexone were found in implants, and the adverse effects were somnolence and this has been already described severe abstinence.

The abuse of substances, particularly of opioids within the hospital environment and by health personnel, is very similar to what is known in the general population. One of the most vulnerable groups is the anesthesiology realm, however, the hospitals of assistance and support for this type of patients in the western region mentions that there is no significant difference between the medical specialties and the health groups, within a 2.5 % of 1000 cases.[8] In Finland, Georgia, and Mauritius, the vast majority of all opioid-dependent people now inject buprenorphine or buprenorphine-naloxone sold illegally instead of heroin, as in developing countries like Mexico.[9-12] The existence of detoxification protocols of physicians with an opioid abuse obtained in the black market or legally within hospitals, is a problem that seriously threatens health workgroups.[9,10] In our article, one of the patients had a history of abuse of buprenorphine during 10 years, and the patient was getting 20 ampoules of buprenorphine which is equivalent to 200 mg of morphine per day. The patient got successful result after the treatment of naltrexone implant every three months for a year without any relapse. He currently keeps his job as a nurse in our hospital. Based on the current available literature, we used naltrexone implant for buprenorphine dependence in Mexico for the first time. In countries where the buprenorphine/naloxone combination was introduced, it was observed that patients continue to abuse it. Therefore, it might be considered that the combination does not block all agonist effects when used intravenously. In our study, patients administered intravenous naloxone prior as part of the protocol to implant placement, they did not respond immediately with withdrawal. It may be considered that the potency of naloxone is less than Naltrexone or that the binding of buprenorphine to the receptors is so intense. So, the naltrexone implant offers an excellent option for patients with buprenorphine dependence. A Previous study showed that patients have a high level of satisfaction with a naltrexone implant of long duration.[13] The majority of drug-dependent patients use more than one drug.[14] Comer et al.[15] suggested that naltrexone depot formulations might have a beneficial effect on cocaine abuse and even on cannabis and benzodiazepine abuse. Therefore the opioidergic system may be the common pathway for the effects of all these drugs of abuse.

Conclusion

The illicit consumption of legal drugs in medical and non-medical environments is one of the great challenges that our country faces.[9-12] Naltrexone implants are effective tools used in hospital environments and they can not only save patient´s lives but also maintain a prolonged effect, free of relapse and with better therapeutic adherence. More randomized control studies are needed to determine the effects and possible side effects of Naltrexone implants in opioid addicts, polydrug dependence.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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