CASE STUDY

Acute opioid withdrawal precipitated by ingestion of crushed Embeda (morphine extended release with sequestered naltrexone): Case report and the focused review of the literature

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ABSTRACT

Background: *The introduction of newly formulated extended release (ER) morphine with sequestered naltrexone (Embeda) has provided another treatment option for moderate to severe persistent pain. Embeda was designed to be an abuse-deterrent opioid formulation. Naltrexone is a centrally acting opioid receptor antagonist that blocks the action of opioid. When taken as directed, insignificant amount of sequestered naltrexone would reach systemic circulation, but upon tampering, the released naltrexone may blunt the euphoria of opioids, and possibly precipitate opioid withdrawal in opioid-dependent patient.*

Objective: *To describe a case report of a 50-year-old opioid-dependent male who developed acute opioid withdrawal after taking crushed Embeda.*

Case report: *A 50-year-old male with severe, chronic low back pain due to degenerative disc disease was referred to our clinic for pain management. He was taking ER oxycodone 80 mg tid and Roxicodone 30 mg qid prn, with inadequate pain relief. A trial of ER oxymorphone was decided, at 40 mg 1-2 doses bid. The patient returned to the clinic 1 week early, out of his ER oxymorphone. At this time, the decision to switch him to Embeda was made, at 80 mg/3.2 mg, 1-2 doses bid. The patient and his family members were counseled about risk involved with tampering with Embeda. A few hours later, our clinic was informed that the patient was brought to emergency room by ambulance, in severe opioid withdrawal. He was treated with IV fluid, antiemetics, clonidine, and IV hydromorphone. His condition improved and he was discharged home the next morning. Later on, the patient admitted that he took two prescribed Embeda within half an hour, the 1st one whole and the 2nd one crushed. He further admitted that he did so against our medical advice.*

Conclusion: *Taking tampered Embeda may precipitate opioid withdrawal in opioid-tolerant patient. To the best of our knowledge, this is the first report of induced opioid withdrawal following consumption of crushed Embeda.*

INTRODUCTION

Embeda has recently been available for the treatment of moderate to severe persistent pain. Designed as an abuse-deterrent opioid analgesic, Embeda consists of ER morphine with sequestered naltrexone. Naltrexone, a competitive opioid receptor antagonist, blocks the effects of opioid. Embeda was shown to provide satisfactory analgesia taken as a whole, but with less euphoria when tampered in comparison with morphine alone.[1-3] When taken as directed, insignificant amount of sequestered naltrexone reached systemic circulation.[1-3] If tampered, the released naltrexone may precipitate opioid withdrawal in opioid-dependent patient.[1-3] We present a case that a 50-year-old opioid experienced male went into immediate, florid opioid withdrawal after taking crushed Embeda.

CASE REPORT

A 50-year-old male with severe, chronic low back pain and hip pain due to degenerative lumbar disc disease, lumbar spondylosis, was referred to our clinic for pain management. He had been on ER oxycodone (Oxycontin) 80 mg tid and Roxicodone 30 mg qid prn with inadequate pain relief. His previous medical history was significant for hepatitis C. There was no previous psychiatric illness as per patient or records. He previously tried methadone 40 mg tid, Fentanyl patch 150 μg/hr Q72 hours, and ER morphine 100 mg tid, with variable responses. He previously tried physical therapy and some interventional spine procedures without long-term benefit. The patient took his last Oxycontin 80 mg on the day of initial consultation. Following the initial evaluation, after passing a random urine testing and obtaining the signed "Opioid Agreement," the decision to rotate his opioid to extended release oxymorphone (Opana ER) was made, based on its proven efficacy and minimal cytochrome P450 drug–drug interactions.[4,5] The patient was prescribed ER oxymorphone 40 mg 1-2 doses bid, with 120 doses written.

No opioid risk assessment was done at the initial evaluation. Our chief concern at the time was that the patient would need a long-acting opioid equivalent to his Oxycontin and Roxicodone for pain relief and preventing his opioid withdrawal.

However, 3 weeks later, the patient walked into the clinic stating the he used up all his Opana ER. He took the last Opana ER 40 mg in the morning before walking in. This was done without the prior acknowledgment of our clinical staff. A stat urine toxic screen was done in the clinic which did show "positive" for "Oxy" and negative for other illicit drugs. Since his insurance company would not allow Opana ER be filled before the due date and concerning the risk of opioid withdrawal if he was left alone without any opioid intake, we decided to try Embeda 80/3.2, 1-2 doses bid, with 60 doses written. Both the patient and his wife were educated how to take Embeda correctly and were counseled about the risk of Embeda when taking it tampered. The patient acknowledged understanding of the discussion and agreed to the treatment decision.

About 4 hours later, the on-call physician was paged by ER physician of a local hospital as our case patient was brought to hospital ER by paramedic for presumed severe opioid withdrawal. The patient's wife described to the ER physician that, about 1 hour after her husband took his newly prescribed medication he became agitated with progressive sweating, yet complaining of feeling "chills." She covered him with seven blankets with minimal help. She described that her husband looked "like he just came out of a shower." She called 911 and the paramedic arrived shortly. "The paramedics could not even stabilize his IV line or get an EKG because the tapes would not stick due to too much sweat," his wife stated. On arriving at ER, the patient was noted to have heart rate of 106, blood pressure of 192/108, respiration rate of 20, temperature of 98.5, with enlarged pupils at 8 mm, agitated with intermittent jerky movement of his arms, and complaining of "hurting all over." A working diagnosis of opioid withdrawal was made and the patient received supportive treatment with IV fluid, IV hydromorphone boluses (2 mg × 3 within 6 hours), antiemetics and clonidine, his symptoms improved subsequently, and he was discharged home the next morning without any complications.

On questioning at the clinic following his discharge, the patient admitted that on the day of the event, he took the 1st dose of Embeda 80/3.2 whole and waited for about 30 minutes "did not feel nothing"; then he took the 2nd dose of Embeda 80/3.2 crushed. He started to feel sick within 30 minutes and quickly his symptoms became full-blown in less than half an hour. He further acknowledged that he frequently took crushed pain killers, previously prescribed to him by others, to obtain quick relief, including Opana ER 40 mg prescribed by our clinic, yet without experiencing any problems. He states that although he was advised not to crush, dissolve this drug, he did not realize it would cause any problems based on his previous experience with other long acting opioids. He admitted that he knew he was doing it against our medical advice.

After explaining to the patient that he had breached his opioid agreement with our clinic, he was placed on clonidine 0.1mg tid prn and Phenergan 25 mg tid prn, and referred to a local addiction clinic. He agreed to our decision and was discharged from our clinic.

DISCUSSION

Americans constitute 4.6 percent of the world's population, but consume about 80 percent of the global supply of opioids.[6,7] Opioid usage for chronic

noncancer pain have increased substantially over the last two decades,[8,9] especially since the release of joint consensus statement by the American Pain Society and American Academy of Pain Medicine in 1997,[10] justifying the use of opioid for severe noncancer pain.

Prescription drug misuse or abuse, however, has been increasingly observed.[11,12] Abuse-deterrent opioid formulations are designed to resist extraction of the active opioid via physical barriers or to deter the reinforcing effect of opioid via incorporation of opioid atagonist.[13] Abuse-deterrent opioid formations are considered one aspect of comprehensive approach to prescription drug risk management.[14] Embeda, the ER morphine with embedded naltrexone, was an example of abuse-deterrent opioid formulation.

Naltrexone, a competitive opioid receptor antagonist frequently utilized in drug rehabilitation programs, acts at mu and kappa receptor to block the euphoria of exogenous opioid.[15] A randomized, double-blind, triple-dummy, four-way cross over study was conducted in opioid experienced, but none-dependent recreational drug users who showed significant reduction in drug liking when crushed Embeda was taken in comparison with morphine alone.[1-3] Nonetheless, naltrexone-induced opioid withdrawal was increasingly encountered in clinical practice.[15,16] The nature, severity, and duration of naltrexone-precipitated acute opioid withdrawal varies greatly between patients and the clinical courses of events are unpredictable.[16,17]

Opioid administration including methadone, in the setting of acute opioid withdrawal reaction precipitated by opioid antagonist, is potentially dangerous.[15,18-20] This is believed that naltrexone, a competitive opioid receptor antagonist, although potent, yet surmountable.[19,20] Any attempt to reverse the blockade by administering large amount of exogenous opioids may lead to fatal overdose, when a large amount of plasma opioid become sufficient to overcome the competitive opioid receptor blockade. As a consequence, severe opioid intoxication (eg, respiratory arrest, circulatory collapse) may happen.[15,18-20] There is also a possibility that patient treated with naltrexone may respond to lower doses of opioids than previously used.[19,20]

Fishman[21] reported a case of 17-year-old female, who was receiving ER naltrexone for opioid dependence, consumed ER oxycodone (presumably overcame the opioid receptor blockade) and experienced precipitated opioid withdrawal symptoms following administration of scheduled naltrexone maintenance injection. This published case report suggested that under certain circumstances, the opioid blockade may be overcome by exogenous opioid, especially when naltrexone level drops toward the end of the dosing interval, rendering vulnerability for subsequent natrexone-induced opioid withdrawal.

The concept of refrain from using exogenous opioid to overcome opioid receptor blockade, when the withdrawal is precipitated by an opioid antagonist, although not new, has not been widely recognized by many practitioners, which was the case in our patient, who was given IV hydromorphone at ER. Fortunately, our case patient only received relatively small does of hydromorphone (2 mg IV × 3 in 6 hours) comparing to his daily opioid equivalent of Opana ER 40mg, 2 doses bid, therefore not enough to overcome the receptor blockade. However, most clinicians naturally think of administering opioids to patients who are withdrawing from opioid; yet, there is an important distinction to be made, that is, whether or not the withdrawal is precipitated by an opioid antagonist, such as naltrexone. If so, opioid administration should be discouraged.

In conclusion, in opioid-dependent individuals, when taken tampered, Embeda may precipitate acute opioid withdrawal symptoms. To the best of our knowledge, this is the first report describing such an incident.

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