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Case Report

Internal Medicine Section

Naloxone in Buprenorphine Overdose: A Life Saving Intervention

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ABSTRACT

Buprenorphine acts as a partial agonist at μ-opioid and ORL-1 (nociceptin) receptors, an antagonist at κ-opioid receptors, and an agonist at σ-opioid receptors. It is available in a range of formulations, including intravenous, sublingual, buccal and transdermal delivery systems. A serious drawback of buprenorphine is its potential for abuse and overdose. For the treatment of opioid dependence, the Food and Drug Administration (FDA) authorised buprenorphine and naloxone in 2002. Naloxone, when administered subcutaneously, blocks the effects of opioid agonists by competitively binding to mu, kappa and delta opioid receptors, thereby eliminating the euphoria and reinforcing properties typically associated with abuse. A 53-year-old obese female presented to the emergency department with increased drowsiness following a road traffic accident that occurred two days prior. The patient sustained multiple rib fractures along with pulmonary contusions, as well as abrasions over the chest and elbow, for which she was prescribed buprenorphine transdermal patches at the primary healthcare facility. Non Contrast Computed Tomography (NCCT) of the brain and cervical spine revealed no acute abnormalities. There was no tenderness upon palpation of the long bones and the pelvic compression test was negative. The Focused Assessment with Sonography for Trauma (e-FAST) was also negative. Upon examination, three drug-eluting patches of undetermined composition were identified affixed to the patient's anterior thorax and were subsequently removed. Through differential diagnosis, buprenorphine overdose was concluded, supported by significant observed clinical parameters. Naloxone was administered intravenously, followed by an infusion, resulting in a marked improvement in the patient's condition. Within 20 minutes of receiving naloxone, the patient's Glasgow Coma Scale (GCS) score demonstrated significant improvement, highlighting the efficacy of naloxone in reversing the effects of a buprenorphine overdose.

Keywords: Drug eluting patches, Emergency service, Opioid overdose, Pain management, Trauma

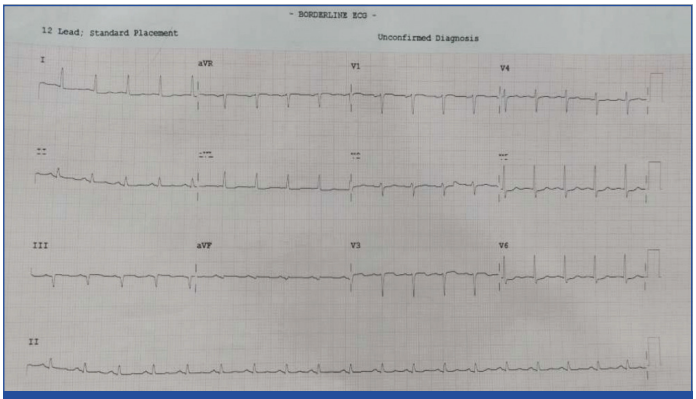
CASE REPORT

A 53-year-old obese female presented to the emergency department of a tertiary care centre in Pune, Maharashtra, exhibiting increased drowsiness over the past two days. Upon arrival, the patient exhibited signs of a compromised airway, which was subsequently secured through endotracheal intubation. Her respiratory rate was 12 breaths per minute, marked by shallow breathing, with oxygen saturation of 70% on room air. Her pulse rate was 140 beats per minute, with unrecordable blood pressure, a capillary refill time of more than three seconds, and no external bleeding sites.

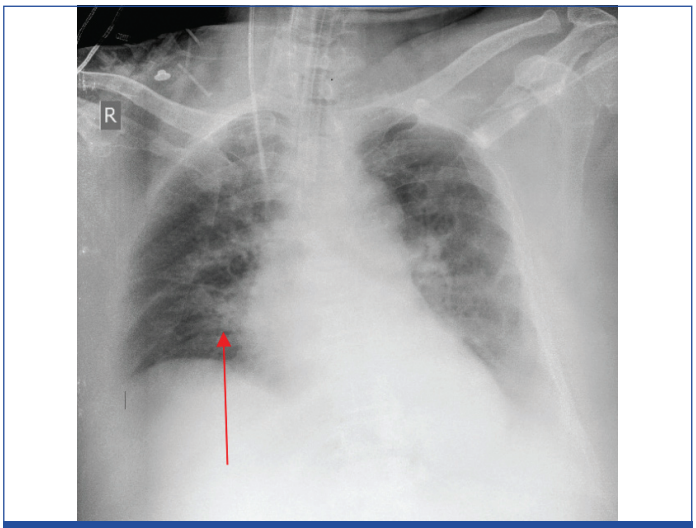
After securing two large-bore IV cannulas, a fluid bolus was initiated; however, there was no improvement in blood pressure, prompting the initiation of vasopressors. A random blood sugar level was measured at 167 mg/dL, and the patient exhibited a GCS score of E1V1M1 (3/15). The pupils were pinpoint and unresponsive to light. Upon exposure, three drug-eluting patches of unknown composition were observed on the patient's chest, which were removed immediately.

The ECG indicated that sinus tachycardia was within normal limits (360 ms) and therefore corresponded to a low risk of torsades de pointes as per the QT nomogram [Table/Fig-1]. Arterial blood gas analysis revealed respiratory acidosis with type 2 respiratory failure. The chest X-ray showed patchy consolidation in both lung fields [Table/Fig-2]. Point-Of-Care Ultrasound (POCUS) demonstrated B-lines in bilateral lung fields, while the focused 2D echocardiogram was within normal limits. The patient's relatives reported a fall from a two-wheeled vehicle two days prior to presentation. This incident resulted in multiple rib fractures, pulmonary contusions and abrasions to the chest and elbow, for which she received initial medical treatment and analgesic patches for pain management.

Physical examination revealed no tenderness to palpation of the long bones and the pelvic compression test was negative. Notably,

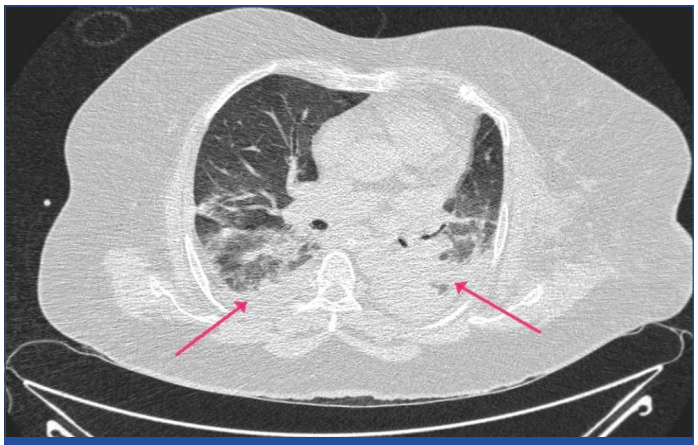


[Table/Fig-1]: Sinus tachycardia with normal Qtc interval.



[Table/Fig-2]: Chest X-ray shows Patchy, scattered, alveolar opacities noted in bilateral lung fields suggestive of Pulmonary contusion with bilateral pleural effusion.

there was no reported history of head or spine trauma associated with the fall. NCCT of the brain and cervical spine revealed no acute abnormalities. High-Resolution Computed Tomography (HRCT) of the chest showed mild bilateral pleural effusion with loss of lung volume on the left side and mediastinal shift to the left [Table/Fig-3]. Consultation with the primary physician revealed that she had been prescribed buprenorphine patches (Buvalor) with a strength of 20 µg/h. Although the prescription indicated one patch for a duration of seven days, the patient had applied three patches in response to significant pain.



[Table/Fig-3]: High-Resolution Computed Tomography (HRCT) chest shows mild bilateral pleural effusion with loss of lung volume on the left-side with mediastinal shift.

At this point, a diagnosis of buprenorphine overdose was made by exclusion, based on significant clinical findings. Naloxone 400 µg/h was administered intravenously, followed by an infusion. The patient became responsive, demonstrating an improvement in the GCS from E1V1M1 to E2V5 within 20 minutes of naloxone administration. There was a significant improvement in the cardiovascular system, with blood pressure recorded at 100/60 mm Hg, which was successfully titrated down on vasopressors. Additionally, there were notable positive changes in the arterial blood gas results, which were within normal limits. After a five-hour stay in the emergency department, the patient was transferred to the surgical intensive care unit for further management.

DISCUSSION

Buprenorphine is a unique partial agonist of the µ-opioid receptor with robust receptor affinity, reduced highs, and a ceiling effect, which eliminates the risk of excessive sedation and respiratory depression. In 1985, buprenorphine was introduced into the market as an opioid analgesic. It was sold at low dosages as a controlled substance (Schedule V) in the United States [1]. It was marketed as Buprenex® in injectable form at 0.3 mg/mL. Two more buprenorphine medications were approved by the FDA and released onto the market in the early 2000s [2].

For the treatment of opioid dependence, the FDA authorised buprenorphine and buprenorphine/naloxone in 2002 [3]. In the event of a buprenorphine overdose, individuals may present with symptoms such as confusion, dizziness, constricted (pinpoint) pupils, hallucinations, hypotension, respiratory depression, seizures, or even coma. The risk of respiratory depression is significantly heightened when buprenorphine is combined with other Central Nervous System (CNS) depressants, particularly benzodiazepines [4]. The primary prevention of opioid use disorder starts with reducing a patient's exposure to prescription opioids at the first visit. Opioid medications should be prescribed for pain only if alternative interventions, including non opioid analgesics and physical therapy, have failed. The use of prescription opioids should not be initiated with a patient unless they have been assessed by a prescription monitoring program for risks. Opioid use should be strictly confined to the dosages and for as short an interval as possible on the original prescription because the risk of prolonged opioid use increases directly with the duration of the original prescription. Buprenorphine patches come in different doses: 5, 10, and 20 µg/h. An opioid-naïve patient administered a patch for short-term management of acute pain should be started at the lowest effective dose, likely 5 µg/h, and patients should be monitored during the first 24 hours [5]. In present case, patient might be a good candidate for the use of a transdermal opioid patch, which provides effective analgesia, enhances compliance and has other inherent advantages over other opioid analgesics. In addition, if the opioids are appropriate, there should be a general treatment plan that is discussed clearly with the patient. Although buprenorphine seldom causes cardiovascular side-effects, it has been shown to cause dose-dependent lengthening of the QT interval. The therapeutic dose of buprenorphine transdermal patches (10 µg/h) did not cause clinically significant QT interval prolongation during 13 days of use in two randomised, placebo-controlled, and positive-controlled parallel-group clinical investigations with dose escalation. Conversely, QT interval prolongation was seen at supratherapeutic dosages of 40 and 80 µg/h, to a comparable degree to that caused by 400 µg of moxifloxacin [6].

In some situations, ongoing pain management may be necessary after initial acute pain treatment. The healthcare provider may choose to transition to a different pain medication or continue with the transdermal buprenorphine patch, depending on the patient's needs. While a 1:75 buprenorphine-to-morphine equianalgesic ratio has been proposed, it has not been clinically confirmed. A recent study has indicated that buprenorphine is 75 to 100 times more potent than morphine [7].

Naloxone is a potent, competitive opioid antagonist that exhibits the highest affinity for the µ-opioid receptor, facilitating the reversal of opioid-induced effects. Research demonstrates that naloxone mitigates opioid effects by competitively binding to the µ, κ, and σ-opioid receptors within the CNS, with the greatest binding affinity observed for the µ receptors [8]. It can be administered intravenously, intramuscularly, or subcutaneously. In most cases, relatively low doses of naloxone (e.g., 0.4-2 mg) will not effectively reverse buprenorphine-induced respiratory depression. Higher doses of naloxone (2.5-10 mg) may provide only partial reversal of buprenorphine's respiratory effects. Patients who have been exposed to buprenorphine may require several doses of naloxone because naloxone's effects wear off faster. The half-life of naloxone is about 33 minutes in healthy adults, which is much shorter than the longer-lasting effects of buprenorphine. This means that naloxone may need to be repeated to maintain its effectiveness [9]. For buprenorphine exposures of 0.2 mg and 0.4 mg, the most effective naloxone dose ranges from 2 to 4 mg per 70 kg of body weight [10]. When administered in single-dose increments, high doses of naloxone (up to 10 mg) may be required to counteract the clinical effects of buprenorphine. If naloxone fails to reverse the clinical symptoms, it is crucial to maintain ongoing supportive ventilatory care.

A few similar situations have been reported in the literature that involve medication errors. The first case involved a grandmother who mistakenly placed a fentanyl patch on her grandchild's wound instead of a bandage. The patch has an innocent appearance with a flesh-coloured tone, which can lead children to mistake it for a basic adhesive bandage or dressing [11]. In a second similar incident reported in the literature, a 12-year-old girl awoke with symptoms of dizziness, visual disturbances, weakness and potential fainting, accompanied by difficulty urinating, although no signs of infection were present. Upon further investigation, a buprenorphine patch was discovered on her thigh, which she had unknowingly applied during a role-playing game. Once the patch was removed, her symptoms began to resolve within 24 hours. The diagnosis of unintentional buprenorphine exposure was made, and she was discharged with

comprehensive guidance on the risks associated with medications and the critical importance of preventing such accidental exposures in children [12].

In cases of fentanyl overdose, the extended-release buprenorphine injection alone does not provide sufficient protection, particularly in the early stages. It should be used in conjunction with sublingual buprenorphine and naloxone until the patient achieves stability and the levels of buprenorphine and norbuprenorphine reach their peak. This approach benefits not only stable patients who are pretreated with buprenorphine to prevent cravings and withdrawal but is especially crucial for unstable patients who require additional protection against the risk of a fatal overdose [13].

In contrast to the cases mentioned above, present case underscores the critical importance of thorough history-taking, with particular emphasis on exposure, which plays a pivotal role in patient examination and differential diagnosis. Ideally, the area of exposure should range from the nipples to the knees; however, this is not always feasible. In most clinical examinations, the exposure typically extends from the nipples to the lower abdomen [14]. Additionally, it highlights the vital role of naloxone in managing buprenorphine toxicity, as well as the necessity for vigilant monitoring. Furthermore, it stresses the importance of educating both patients and their families about the risks of opioid overdose prior to prescription.

CONCLUSION(S)

A high index of suspicion for opioid toxicity should be maintained if a patient presents with a sudden onset of loss of consciousness in the Emergency Department (ED). History-taking plays a crucial and foundational role in the assessment of buprenorphine toxicity. The patient became responsive, demonstrating an improvement in the GCS within 20 minutes of naloxone administration and was transferred to the surgical intensive care unit for further management. A comprehensive, multidisciplinary approach involving emergency physicians, surgeons, pulmonologists and other specialists is vital in managing the complex interplay of risk factors and developing personalised treatment plans for each patient. In the future, continued research and advancements in the field of toxicology are expected to result in enhanced diagnostic methods, more precise therapies and improved outcomes for patients.

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