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THE ROLE OF PAIN AS A RESPIRATORY STIMULANT: A CASE REPORT OF SUDDEN RESPIRATORY DEPRESSION FOLLOWING REGIONAL ANESTHESIA IN A PATIENT ON HIGH-DOSE OXYCODONE

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ABSTRACT

This study provides a detailed case report of a 65-year-old patient with disseminated cancer who was receiving extremely high doses of oxycodone (2 g/day) for severe, uncontrolled pain. A suprascapular nerve block with bupivacaine provided almost immediate relief; however, after 25 minutes, it led to sudden respiratory arrest. This event necessitated urgent emergency medical intervention and ICU hospitalization. Clinical analysis ruled out local anesthetic systemic toxicity (LAST), identifying the physiological antagonism between nociception and the respiratory depressive effects of opioids as the cause. Pain, acting as a natural respiratory stimulant, masked the effects of severe oxycodone overdose. The block's analgesic effect abruptly removed this stimulus, resulting in apnea. The article discusses the underlying mechanisms and provides a differential diagnosis between tolerance and opioid-induced hyperalgesia (OIH). It emphasizes the importance of multimodal treatment, including ultra-low-dose naloxone, to prevent dose escalation. The findings indicate a critical need for hospitalizing patients requiring high analgesic doses for safe titration and the necessity of intensive monitoring during regional anesthesia in opioid-dependent individuals.

Introduction: The aim of this paper is to present and analyze a rare but life-threatening complication: respiratory arrest following local anesthesia in an oncology patient receiving extremely high doses of opioids. The work highlights the physiological role of pain as an antagonist of opioid-induced respiratory depression.

Methodology: A case of a 65-year-old male with disseminated cancer, treated with an extremely high dose of oxycodone (2 g/day), is described. Due to severe shoulder pain, a suprascapular nerve block was performed using 5 ml of 0.5% bupivacaine and methylprednisolone. A literature review was conducted to differentiate the causes of apnea, including the exclusion of Local Anesthetic Systemic Toxicity (LAST).

Results: Pain subsided almost immediately following the procedure; however, after 25 minutes, the patient experienced sudden apnea requiring intubation and ICU hospitalization. Analysis excluded technical error and systemic toxicity (LAST) based on dosage and symptom dynamics. The most likely cause was the elimination of the painful stimulus, which previously stimulated the respiratory center and balanced the depressive effects of high-dose oxycodone.

KEYWORDS

Oxycodone, Bupivacaine, Respiratory Depression, Cancer Pain, Opioid-Induced Hyperalgesia (OIH), Regional Anesthesia

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Case Studies:

A 65-year-old patient with a disseminated neoplastic process, suffering from severe pain in the right shoulder and receiving an extremely high dose of oxycodone (2 grams per day) in the form of controlled-release tablets (OxyContin), consistently complained of intense, persistent pain. The patient consulted a physician, who diagnosed compression and irritation of the right suprascapular nerve. To alleviate the suffering, the physician decided to perform a local anesthetic block using bupivacaine and methylprednisolone. The pain subsided almost immediately; however, approximately 25 minutes later, the patient experienced a cessation of respiratory function, and apnea was observed. Since the incident occurred in an outpatient pain clinic located outside of a hospital setting, emergency medical services were summoned. The arriving emergency medical team intubated the patient and transported him to a hospital equipped with an Intensive Care Unit (ICU).

In this palliative care patient, managed according to oncological guidelines for high-intensity pain, oxycodone was utilized as the preferred first-line agent from Step III of the WHO analgesic ladder. [1] Oxycodone is a semi-synthetic agonist of the μ and κ opioid receptors, used in the treatment of postoperative, neuropathic, and cancer-related pain. Compared to morphine, it exhibits higher potency and an extended pharmacokinetic profile. The clinical efficacy of the drug is subject to inter-individual variability due to genetic polymorphism. [22] Generally, dose modification is not required for elderly patients. [2, 3] Notably,

oxycodone lacks a maximum dose, meaning there is no ceiling effect, which allows for dose titration without an arbitrary therapeutic limit. [4]

The ceiling effect is defined as reaching a maximum pharmacodynamic response, after which further dose escalation does not enhance therapeutic (analgesic or anti-inflammatory) effects but only increases the risk of adverse events and toxicity.

According to the summary of product characteristics, cancer pain patients may, in rare cases, require daily doses of up to 400 mg. However, in this case, we are dealing with a significant oxycodone overdose. Dose escalation in this patient clearly failed to improve the therapeutic effect and likely increased the risk of secondary adverse effects. [5].

These effects remained latent until the administration of local anesthesia containing an appropriate dose of 5 ml of 0.5% bupivacaine. Bupivacaine is a potent amide-type local anesthetic commonly used for regional anesthesia. It blocks action potential generation in nerve cells by increasing the electrical excitation threshold. It may cause initial central nervous system (CNS) excitability followed by depression. [8]

The risk of respiratory depression is a significant factor for patients with pulmonary diseases or those using other CNS depressants during opioid therapy. The respiratory safety profile varies by agent: buprenorphine is unique in demonstrating a ceiling effect for respiratory suppression in monotherapy. Individualized dosing and extreme clinical caution are essential for high-risk patients. [6]

We suspect this issue in the presented patient, who was already receiving slow-release oxycodone (an opioid) and subsequently suffered respiratory arrest following the bupivacaine injection. Conversely, the site of local anesthetic administration significantly influences the risk of toxicity [8]. In this case, Local Anesthetic Systemic Toxicity (LAST) could be considered. LAST is a syndrome caused by excessive serum concentrations of local anesthetics, which may occur via unintentional intravascular injection or absorption from peripheral tissues. [2] A key difference between the typical course of LAST and the symptoms observed here is the progression dynamics. Typical LAST involves sequential CNS and cardiovascular symptoms, starting with excitation followed by depression. Symptoms include a metallic taste, paresthesia, dizziness, and seizures, progressing to loss of consciousness, apnea, or cardiac arrest—none of which were observed in this patient. [2, 9] Furthermore, symptoms of intravascular injection typically manifest within 5 minutes. [9] This patient felt well initially with immediate pain relief; the adverse event occurred suddenly 25 minutes post-injection. Given that the bupivacaine dose was below the toxic threshold and characteristic LAST symptoms were absent, we conclude the anesthesia was technically sound.

Instead, we focus on respiratory disturbances resulting from the interaction between circulating oxycodone and administered bupivacaine, both of which exert depressive effects on the CNS. Bupivacaine treatment in patients taking oxycodone is standard medical practice, provided appropriate dosages are maintained. [10, 11, 12]

An example of the proper administration of oxycodone and bupivacaine is a study comparing oral paracetamol/oxycodone with epidural analgesia (EDA) following radical prostatectomy. The group receiving oxycodone (10 mg on the day of surgery, and then every 12 hours until the second or third postoperative day) also received on-demand bupivacaine, among other treatments. The EDA group was administered ropivacaine, paracetamol, and on-demand morphine. Both protocols achieved effective analgesia. Complications such as lower-limb paresthesia and hypotension occurred in only 5% of patients in the oxycodone group. [11]

A comparison of multimodal analgesic treatment involving oxycodone and bupivacaine versus hydromorphone was conducted in patients following total knee replacement. Under the protocol, the multimodal pain management group received a pre-wound closure injection consisting of 30 ml of 0.5% bupivacaine, 10 mg of morphine sulfate, and 15 mg of ketorolac. Postoperatively, these patients received oral oxycodone (10 mg every 12 hours), tramadol (50 mg every 6 hours), parenteral ketorolac (15 mg every 12 hours), and parenteral hydrocodone (5 mg) or hydromorphone (1 mg) as needed for supplemental analgesia. The results demonstrated that multimodal pain management using bupivacaine and oxycodone combined with other analgesics significantly enhanced postoperative pain control, led to lower pain scores, enabled lower total opioid consumption, and resulted in markedly higher patient satisfaction compared to the hydromorphone-treated group [12].

An example of the correct and effective use of bupivacaine along with an opioid is a comparative study of two postoperative pain control regimens following anterior cruciate ligament (ACL) reconstruction. The first protocol involved a continuous femoral nerve block using ropivacaine supplemented with as-needed oral hydrocodone (5 mg). The second regimen was based on an intra-operative intra-articular injection (bupivacaine with morphine) and as-needed oral oxycodone (5 mg). Within the first 24 hours after the procedure, no

significant differences were noted between the groups in terms of pain intensity or total opioid consumption. Patient satisfaction levels with pain control were comparable in both cohorts. The authors demonstrated that the use of a continuous femoral nerve block with ropivacaine provides no clinical advantage over an intra-articular injection of bupivacaine with morphine in the immediate postoperative period [23]

There have also been reports that the use of regional anesthesia in opioid-dependent patients may lead to respiratory depression, suggesting that general anesthesia should be used in this patient group. However, in the case of a 65-year-old male diagnosed with gastric cancer metastasis to the femur, orthopedic surgery was performed using local anesthesia. The patient had been chronically taking oral oxycodone at a dose of 20 mg/day for over 50 days. Prior to surgery, he took his morning dose of oxycodone, followed by lumbar anesthesia with 2.6 ml of 0.5% hyperbaric bupivacaine. Intraoperative monitoring showed no respiratory distress during the 1 hour and 33-minute procedure, and the patient slept without additional sedation. Based on this patient, who was on long-term oxycodone therapy, it can be concluded that regional anesthesia is a safe method for cancer pain management even when oxycodone and bupivacaine are used concurrently. It is likely that long-term opioid use led to the development of tolerance to the depressive effects on the respiratory system, which explains why respiratory depression was not observed. [10]

A significant observation in the presented case report is the almost immediate resolution of the patient's pain following the administration of local anesthesia. Pain serves as an effective antagonist to the respiratory depressant effects of opioids. Consequently, the abolition of pain in patients receiving opioid therapy may precipitate respiratory depression. [13, 14]

Substance P and NK-1 receptors mediate both nociception and respiration, demonstrating a close link between these two processes. Nociceptive and chemoreceptive functions converge at several sites within the brainstem, where opioid receptors are expressed. Pain can counteract opioid-induced respiratory depression, which may lead to potentially catastrophic outcomes when alternative pain relief methods are implemented. This highlights the delicate balance between pain and respiration in clinical settings. This is particularly relevant in situations where a spontaneously breathing patient, who is receiving opioids yet still experiencing pain, subsequently undergoes regional anesthesia; such a scenario may lead to severe respiratory depression. [15]

An illustrative example of this relationship is the case of a 72-year-old male with bladder cancer and bone metastases suffering from severe back and leg pain. The patient had been receiving intrathecal morphine for six months, with the dose gradually titrated to 10 mg twice daily. Due to a suspected local infection at the intrathecal catheter insertion site, this route of administration was suspended for four days. During this interval, the patient was treated with extended-release and subcutaneous morphine. Upon resumption of the intrathecal route and the administration of an identical dose of morphine combined with bupivacaine and epinephrine, fatal respiratory failure occurred within 10 minutes. By attenuating nociceptive stimulation, bupivacaine increased the patient’s susceptibility to opioid-induced respiratory depression. [16, 17]

Another case involves a 92-year-old Caucasian female hospitalized for revascularization of the left lower limb secondary to arteritis. Due to pain associated with sacral and heel pressure ulcers, the patient had been receiving an oral modified-release morphine preparation for eight days. Ten minutes after the induction of a subarachnoid block with bupivacaine, the patient developed stupor, miosis, and apnea. Following the intravenous administration of naloxone, full consciousness and adequate respiratory function were restored. [16]

The two clinical cases described above are reminiscent of our patient's presentation and support the hypothesis that the underlying cause of respiratory depression was the inhibition of the stimulant effect of pain on respiration. Pain acts as a physiological antagonist to the depressant effect of opioids on the respiratory center. By abolishing nociceptive stimulation, bupivacaine may potentiate the risk of opioid-induced respiratory depression. This necessitates precise titration of analgesic dosages and intensified clinical monitoring of the patient. [16]

The case presented here underscores the critical importance of comprehensive medical history taking and physical examination, as well as verifying the status of specialist care—specifically oncological care in this instance—and assessing patient adherence to both non-pharmacological recommendations (such as lifestyle modifications and dietary habits) and pharmacological regimens.

Based on this case analysis, several syndromes associated with chronic opioid use warrant consideration and differential diagnosis. Opioid-induced hyperalgesia (OIH) is distinct from opioid tolerance, opioid withdrawal syndrome, and opioid use disorder (OUD). OIH is characterized by sensitized nociception resulting from opioid exposure, whereas opioid tolerance necessitates progressively higher doses to achieve an

equivalent analgesic effect. Withdrawal syndrome manifests clinically upon the cessation of opioid intake. Conversely, OUD is defined by the compulsive use of opioids despite adverse consequences, potentially involving symptoms of tolerance and withdrawal. [21]

Opioid use disorder is a chronic, relapsing central nervous system disease characterized by a loss of control over substance intake and the occurrence of intense opioid cravings.

One proposed strategy for preventing opioid-induced hyperalgesia (OIH), which may have occurred in the described patient, is treatment modification. One approach may involve the adjunctive use of naloxone. Opioid receptor antagonists—specifically naloxone and naltrexone—administered at ultra-low doses have demonstrated efficacy in attenuating the adverse effects of chronic opioid therapy (including morphine and oxycodone). Their proven antinociceptive properties and ability to improve clinical outcomes suggest significant potential in the management of opioid-induced hyperalgesia (OIH). Furthermore, the administration of naloxone via continuous subcutaneous infusion facilitates dynamic dosage personalization based on the patient's clinical status. [18]

Naloxone is a pharmacological agent intended to reverse opioid-induced respiratory depression. [19] In several cases, naloxone administered in very low doses has been used to counteract the adverse effects associated with long-term opioid use. Clinical observations have shown that this approach can enhance analgesia and mitigate certain negative effects of opioids. The combined use of oxycodone and naloxone has allowed for better dose management of both drugs and a reduced risk of OIH. For example, a 40-year-old patient diagnosed with B-cell acute lymphoblastic leukemia (B-ALL) undergoing chemotherapy reported severe spinal pain. Prior opioid therapy (fentanyl) had provided only transient analgesia. The introduction of low-dose naloxone resulted in a significant reduction in pain intensity and an improvement in mental status, which facilitated the patient's discharge. However, it must be emphasized that such treatment requires individualized dose titration and close patient monitoring to avoid serious adverse effects. [18]

Alternative therapeutic strategies may involve reducing the oxycodone dosage and adjunctive administration of ketamine and parecoxib. It is hypothesized that non-steroidal anti-inflammatory drugs (NSAIDs), such as parecoxib, help mitigate the impact of both inflammation and excitatory amino acid neurotransmitters that stimulate central pain pathways. [20] Another approach for the prevention and management of OIH is the combined use of ketamine and methadone, which may facilitate an opioid dose reduction of 40–50%. [21]

The case analysis of a 65-year-old patient with metastatic cancer and severe pain confirms that the combined use of oxycodone and bupivacaine is safe and effective, provided there is rigorous dose optimization and clinical monitoring. The safety profile of opioids exhibits significant heterogeneity depending on the specific substance used. Due to the increased risk of severe complications in the geriatric population, the selection of agents with optimal tolerability and a wide safety margin regarding respiratory depression is indicated. Gradual dose titration allows for the minimization of early, transient adverse effects. [6]

Consideration must be given to the physiological interaction between pain—a potent stimulant of the respiratory center—and opioids, which exert a depressant effect. During the course of therapy, the development of tolerance establishes a homeostasis between these opposing mechanisms. The sudden elimination of the painful stimulus during the concurrent administration of high-dose opioids poses a significant risk of clinical respiratory depression.

In my opinion, the patient should be admitted to a palliative care unit for appropriate opioid titration. Following several days of observation and clinical stabilization, the appropriateness of local anesthesia could be re-evaluated. Should the procedure be necessary, the patient's vital signs must be continuously monitored. Furthermore, local anesthesia should be performed under ultrasound guidance with meticulous precision and an aspiration test to minimize the risk of compromising vascular integrity during the injection.

Such procedures necessitate heightened clinical vigilance, particularly in this case, given the patient's age and comorbid burden. Bupivacaine administration must be performed under continuous monitoring of the ECG, SpO2, and arterial blood pressure. To facilitate the early identification of potential toxicity, it is essential to monitor the patient's subjective sensations and to immediately discontinue administration should any concerning symptoms arise.

In the pharmacological management of cancer pain, the selection of an extended-release opioid preparation is determined by the balance between the analgesic effect and the risk of adverse effects. Among the complications typical of this class of drugs, particular attention must be paid to respiratory depression due to its associated mortality risk. Despite a common target within the mu-opioid receptor system, individual substances exhibit heterogeneity in their modulation of the respiratory drive. In the case of buprenorphine, due

to its unique receptor-binding kinetics, the effective reversal of respiratory suppression requires a continuous naloxone infusion rather than bolus administration. [24]

It should be noted that if an opioid etiology of respiratory failure is established, the administration of naloxone—a specific opioid receptor antagonist—is indicated to reverse the depression of the respiratory center.

Discussion

The analysis of the described case sheds new light on the safety of multimodal pain management in patients with extremely high opioid tolerance. The patient's daily dose of 2 grams of oxycodone strongly suggests the presence of OIH. This physiological mechanism relies on a delicate balance: intense pain serves as a stimulant for the respiratory drive. The sudden analgesic effect of bupivacaine eliminated this protective stimulus, abruptly unmasking the suppressive effect of the circulating oxycodone. The clinical implication is the critical necessity of maintaining continuous vigilance and monitoring during regional anesthesia in opioid-dependent patients, even when standard anesthetic doses are used.

Conclusions

The primary finding is that pain plays a protective role in maintaining respiratory center stability in patients treated with high doses of opioids. Abruptly eliminating the nociceptive drive can lead to catastrophic respiratory failure. Future research should focus on developing standardized safety protocols for regional anesthesia in palliative care and investigating the role of ultra-low dose naloxone and ketamine in mitigating OIH.

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