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Morphine for Intravenous Patient-Controlled Analgesia May Inhibit Delirium Tremens

A Case Report and Literature Review

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Abstract: Alcoholism is common among trauma patients and often lacks the appropriate monitoring. Alcohol withdrawal syndrome (AWS), including delirium tremens (DT), can be associated with significant postoperative morbidity and mortality. However, appropriate acute pain management may protect against delirium; the administration of intravenous patient-controlled analgesia (IV-PCA) may not only alleviate pain, but also reduce the incidence of postoperative delirium. IV-PCA is widely used today; however, little attention has been paid to its influence on the development of AWS or DT postsurgery. Here we present a case in which the administration of IV-PCA may have delayed the onset of DT that interfered with postoperative care and the initiation of psychiatric consultation. The literature was reviewed to determine the potential mechanisms behind the effects of IV-PCA on the onset of AWS or DT.

IV-PCA may delay the onset of DT. It is imperative to take into consideration trauma patients' psychiatric history including answers to questions on alcoholism, so that when an IV-PCA is administered and then discontinued, adequate interventions to prevent further morbidity associated with AWS and DT can be initiated in sufficient time.

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Abbreviations: AWS = alcohol withdrawal syndrome, CNS = central nervous system, CT = computed tomography, DT = delirium tremens, ED = emergency department, EEG = electroencephalogram, GABAA = gamma-aminobutyric acid type A, IV-PCA = intravenous patient-controlled analgesia, NMDA = N-methyl-D-aspartate.

INTRODUCTION

The prevalence of chronic alcoholism is estimated to range between 50% and 60% in trauma patients,[1] and alcohol withdrawal syndrome (AWS) occurs in 31% of these patients.[2] AWS usually develops within 6 to 72 h after the cessation of drinking alcohol. Delirium tremens (DT) typically appears later in the withdrawal process, occurring on average 48 to 72 h after the last drink.[3,4] Although DT occurs in approximately 5% to 20% of patients treated for AWS,[2] the mortality rate of patients with DT has been previously reported to be as high as 15%. [5] Due to early detection and effective treatments, the mortality rate of DT has decreased to 1% to 5% in recent years.[2,6,7]

Although pain and opioid use have both been reported as risk factors for postoperative delirium,[8] clinicians sometimes hesitate to administer opioids for acute pain management due to their potential adverse effects. Meperidine and fentanyl had been known to increase the likelihood of postoperative delirium, whereas intravenous pain control with morphine appears less likely to cause delirious symptoms.[8–10] A recent study provided further evidence that improved pain control with intravenous patient-controlled analgesia (IV-PCA) is associated with a lower rate of postoperative delirium.[11] Patients with chronic alcoholism are more sensitive to painful stimuli due to lowered pain thresholds; therefore, the adoption of a multimodal approach and administration of IV-PCA to effectively manage acute pain has been recommended for these patients.[12–14] However, to the best of our knowledge, there have been no studies reported in the literature investigating the effects of IV-PCA on the development of AWS. Using a framework provided by the CARE Statement,[15] we present a case report documenting the occurrence of DT after discontinuation of a 4-day treatment with an IV-PCA. In this case, DT manifested >5 days after the patient's last drink of alcohol, far exceeding the typical 48- to 72-hour time interval. The delayed onset of DT led to delayed diagnosis and incorrect treatment recommendations made by the consulting psychiatrist during the patient's initial evaluation.

CASE REPORT

First Hospitalization

A 41-year-old married man, who was a taxi driver by profession at the time of admission, was admitted to the plastic surgery unit because of a right ankle abscess. On admission, he reported drinking between 200 and 300 mL of whisky daily, beginning each evening ''only with dinner after work,'' for the preceding 20 years. He was treated 2 months previously for an alcohol withdrawal seizure at the neurology unit. At that time, Valproate 500 mg every 12 h effectively suppressed the signs and symptoms of the seizure. His last drink had been several hours before this admission. He had no history or evidence of any other substance use. The abscess was debrided 3 times and then a split-thickness skin graft reconstruction with a gracilis muscle flap was performed. He received an IV-PCA for 4 days after the reconstruction surgery for acute pain control set to

self-administered 2-mL boluses without a continuous background infusion (morphine 1 mg/mL and ketorolac 1.2 mg/mL). The lockout interval was 10 min with a 4-h morphine limitation of 20 mg. The total amount administered to the patient was 142 mL and he used 12 mL in the last 24 h before it was discontinued. The patient received continuous valproate 500 mg every 12 h and no AWS or delirium was observed throughout the 37-day hospitalization. He was discharged on valproate 1000 mg daily and was able to continue working as a taxi driver.

Second Hospitalization

Two years later, the patient presented to the emergency department (ED) with a 2-day history of intermittent epigastric pain. A medical work up revealed his lipase level was within the normal range. Abdominal computed tomography (CT) revealed a linear foreign body in the second portion of the duodenum penetrating the right mesentery with surrounding inflammation. The patient's mother recalled that he ''accidentally swallowed a toothpick after being drunk 2 days ago.'' A preliminary diagnosis of intra-abdominal foreign body with peritonitis was made and an emergent laparotomy was performed under general anesthesia. He was induced with fentanyl 2.5 μg/kg, thiamylal sodium 5 mg/kg, and cisatracurium 1.5 mg/kg intravenously, and general anesthesia was maintained using desflurane-cisatracurium. The toothpick was removed, and the perforated duodenum was repaired. After the 3-hour operation, the patient had a smooth recovery with minimal blood loss and stable vital signs. In the postanesthesia care unit, after a 3-mg intravenous bolus of morphine, an IV-PCA was initiated and set at self-administered 2-mg boluses without a continuous background infusion (morphine 1 mg/mL and ketorolac 1.2 mg/mL). The lockout interval was 10 min with a 4-hour morphine limitation of 20 mg. The patient was transferred to the general surgical unit with a modified Aldrete recovery score of 10.

Since the patient could not take anything by mouth following duodenal repair, valproate 500 mg every 12 hours was discontinued. His condition remained stable for the next 4 days and the IV-PCA was administered for 96 hours (the total amount used was 146 mL, and 12 mL were used in the last 24 hours). No benzodiazepines, Z-class hypnotics, or additional analgesics were administered.

Twelve hours after discontinuing the IV-PCA, the patient became tachycardic (his heart rate increased from 66 beats/min in the morning to >100 beats/min in the afternoon) and diaphoretic (his mother changed his hospital clothes four times that afternoon) with tremulous extremities. There was no aggravation of wound pain and no additional analgesics were given. Central nervous system (CNS) symptoms, such as disorganized speech with intermittent curse words, disorientation to time, place, and people, visual hallucination (eg, he saw some ''Transformers'' fighting near the ceiling), and disruptive behaviors (eg, pulling out his nasogastric and IV tubes) were observed 2 hours later. He lacked fever or chills. Since it had been >5 days since his arrival to the ED, he had not any alcohol for at least 120 hours.

An injection of 2 mg of lorazepam was immediately administered by slow-push and an additional 2 mg was prescribed 2 hours later. Intravenous thiamine was administrated to prevent Wernicke encephalopathy. Intramuscular haloperidol 5 mg was injected and was repeated 2 hours later; however, the patient's agitation continued throughout the entire night. The patient received IV cefmetazole 1 g every 8 hours following the operation, and the follow-up laboratory tests revealed leukocytosis (19,900 cells/μL) and mildly elevated C-reactive protein (5.4 mg/dL). The wound was clean, and there was no fever or abdominal pain. Renal and liver functions as well as serum electrolyte, ammonia, hemoglobin, blood glucose, and albumin levels were all within normal limits.

Psychiatric consultation was initiated the next day because despite the administration of IV lorazepam every 8 h, the patient had become increasingly delirious. Since >5 days had passed since the patient's last alcoholic drink at the time delirium developed, DT was not considered by the consulting psychiatrist who diagnosed delirium due to multiple causes (chronic alcoholism, recent major surgery, and residual focal infection). Ongoing monitoring for underlying medical and surgical conditions was recommended along with the administration of oral quetiapine 25 mg bid and 50 mg at bedtime. An electroencephalogram (EEG) and brain CT were performed. The EEG showed a moderate degree of nonspecific diffuse cortical dysfunction; however, no seizure waves were found. The brain CT did not reveal edema, acute ischemia, intracranial hemorrhage, mass lesion, or mass effect.

Two days later, because the patient remained tachycardic and diaphoretic with tremulous extremities, visual hallucination, and disorientation during the second evaluation, a diagnosis of DT was considered by the psychiatrist. Further treatment and management were based on that diagnosis. The dose of lorazepam was increased to 2 mg every 4 hours, quetiapine was reduced to 50 mg at bedtime, and valproate 500 mg every 12 hours was reinitiated. Within 8 hours, the patient's agitation, disorientation, hallucinations, delusions, and tachycardia began to diminish. No further signs or symptoms of delirium were observed thereafter.

DISCUSSION

To date, there has been only a single case report addressing the issue of delayed-onset DT. The authors reported the case of a young man with onset of DT activity on day 15 of his hospitalization for alcohol abstinence and, theoretically, the DT were attributed to the delayed effects of Indian liquor that contains a high percentage of alcohol.[16] In the present case, while receiving continuous treatment with valproate, DT did not appear during the patient's first hospitalization for skin grafting and reconstruction, including during the administration of an IV-PCA and after its discontinuation. During the second hospitalization, valproate was discontinued due to the patient's inability to take anything by mouth postsurgery and the DT appeared 14 hours after discontinuation of an IV-PCA that had been administered for 96 hours. Although a few studies have found anticonvulsants, with the potential exception of carbamazepine, have a limited effect on DT,[17,18] a recent retrospective cohort study revealed that valproate may have better efficacy and tolerability as an adjunct treatment for AWS.[19] Therefore, if valproate had been continued by IV, as the patient could not take anything by mouth during the second hospitalization, the occurrence of DT could potentially have been prevented.

There were no generalized tonic-clonic movements or epileptic waves on the EEG during the patient's delirium; therefore, his agitation could not be explained by seizures, interictal, or postictal confusion. Laboratory findings, including blood ammonia level, were not suggestive of a clinically significant metabolic derangement. The patient received only a limited amount of morphine as an analgesic for a brief period; therefore, neither the limited exposure to morphine nor the

patient's signs and symptoms supported a diagnosis of opioid withdrawal.[20] Furthermore, the elimination half-life of valproate is 14 hours[21] and it had been approximately 5 days (120 hours) since the last valproate dose. Therefore, as >8 half-lives had passed by the time the DT began, the delirium could not be related to the discontinuation of valproate. A total of 146 mg of morphine was administrated over the 96-hour IV-PCA was administered. Since the elimination half-life of IV morphine is approximately 2 hours in healthy volunteers,[21] the appearance of the DT correlated with the clearance of the morphine.

There were 3 observations that supported the clinical diagnosis of DT. First, the patient received general anesthesia with the CNS-suppressive agents, fentanyl, thiamylal sodium, and desflurane. There was no postanesthetic emergence delirium following the 3 hours of general anesthesia. A recent study showed that postanesthetic emergence delirium usually develops in the immediate postoperative period, with the primary manifestation comprising hypoactivity.[22] However, delirium in this patient was noticed 5 days after the general anesthesia and manifested itself as extreme agitation. Second, the patient's delirium indicated signs of alcohol withdrawal including autonomic hyperactivity (tachycardia and sweating) and limb tremors. The presence of these autonomic hyperarousal signs occurred 12 hours after the discontinuation of 96 hours of IV-PCA and DT appeared 2 hours later. The signs and symptoms of alcohol withdrawal and agitated delirium persisted concurrently throughout the 2-day course of the delirium, matching the diagnostic criteria of alcohol withdrawal.[20] Autonomic hyperactivity is the core feature of DT, but not of postoperative delirium. Third, the autonomic hyperactivity and agitated delirium did not subside despite the continued administration of an atypical antipsychotic agent and low-dose lorazepam; however, it did remit 8 hours after the lorazepam dose was titrated up, the antipsychotics were titrated down, and valproate was added. In postoperative delirium, the administration of benzodiazepines could be a precipitating or maintaining factor; only patients withdrawing from alcohol or sedatives-hypnotic-anxiolytic benefit from the timely and adequate use of benzodiazepines.[8,23]

The signs and symptoms of DT in this patient subsided within 2 to 3 days, consistent with previous studies.[24,25] Foy et al[24] noted that the median time of onset of DT was 46 hours after arriving at the hospital and the median time for resolution was 23 hours. Monte et al[25] reported that the minimum time of onset of DT was 4 hours, the first quartile was 22 hours, the median time was 24 hours, the third quartile was 48 hours, and the maximum time of onset was 87 hours; the median time to resolution was found to be 72 hours. However, the time of onset of DT in present case was >120 hours after the patient's last drink, a time interval far exceeding the documented range. It is worth noting that DT appeared sequentially after cessation of the 4-day IV-PCA morphine administration, occurring approximately 14 hours after discontinuation of the IV-PCA. We therefore hypothesize that administration of IV-PCA morphine could delay the onset of DT.

Benzodiazepines are the first-line treatment for AWS and DT.[26,27] Alcohol is concurrently a gamma-aminobutyric acid type A (GABA$_A$) receptor agonist and a glutamate N-methyl-D-aspartate (NMDA) receptor antagonist. The chronic consumption of alcohol can downregulate the GABA$_A$ receptors and upregulate the NMDA receptors. When a chronic alcoholic suddenly stops or significantly reduces alcohol intake, the excessive downhill GABA effect and uphill glutamate effect induce

AWS.[3,4] AWS initially manifests as a hyperactive autonomic nervous system and may progress to seizures and even DT in patients with multiple risk factors.[28] Benzodiazepines treat AWS and DT by acting as GABA$_A$ receptor agonists. Carbamazepine and propofol are effective treatments via their dual actions as GABA$_A$ agonists and NMDA antagonists. Other drugs, including clomethiazole, valproate, baclofen, and barbiturates, may also be effective due to their ability to boost the GABA system.[28] Opioids are known to evoke an analgesic effect via mu receptors; however, only a few studies have discussed their effect on AWS. Blum et al[29] reported a suppressive effect of morphine on alcohol withdrawal seizures in mice; the authors proposed that the increase of dopamine in the CNS after the administration of morphine played a significant role.[29] Tsueda et al[30] reported the use of opioids to suppress DT in 3 patients and postulated that opioid deficiency in the CNS may be related to AWS. This viewpoint has been supported by some human and animal studies.[31,32]

Other potential mechanisms explaining the suppressive effect of opioids on AWS and DT include an inhibitory effect on the locus coeruleus. Increased firing rates of the norepinephrine neurons in the locus coeruleus can be found in alcohol withdrawal or opioid withdrawal and account for most of the withdrawal signs and symptoms, such as anxiety, tremors, tachycardia, hypertension, sweating, nausea, and insomnia.[33,34] Furthermore, alpha-2 receptors, GABA receptors, and opioid receptors can be found on the neurites of the locus coeruleus neurons and comprise the sites that exert inhibitory effects.[35] Therefore, alpha-2 agonists help to relieve not only AWS[36] but also opioid withdrawal[37,38]; however, benzodiazepines are also known to relieve the symptoms of opioid withdrawal.[39]

In conclusion, the case described here illustrates that, although IV-PCA is one of the most common and effective methods of providing postoperative analgesia in patients with chronic alcoholism, its administration may delay the onset of DT. This highlights the importance of taking into consideration trauma patients' psychiatric history including answers to questions on alcoholism, so that when an IV-PCA is administered and then discontinued, adequate interventions to prevent further morbidity associated with AWS and DT can be initiated in sufficient time.

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