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CLINICAL REPORT

Nystagmus caused by epidural fentanyl

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Abstract Anesthesiologists commonly use opioids for pain control in the operating room and postanesthesia care unit, and are constantly vigilant in looking for possible adverse outcomes. Therefore, common complications such as nausea, vomiting, and pruritus are well known. However, neurologic complications after opioid administration are relatively rare except for reduced consciousness, for example drowsiness or sedation. We recently experienced a case in which a 73-year-old woman presented predominantly vertical nystagmus as a neurological complication after epidural administration of fentanyl. A few previous reports on opioids as causative agents for nystagmus have all after use of epidural morphine, and there are yet no publications reporting epidural fentanyl as the cause of nystagmus. Physicians should keep in mind that epidural fentanyl could cause the nystagmus as a neurological complication even though it is used within conventional dosage ranges, although this is very rare. Also, when a patient develops nystagmus after epidural fentanyl, it could be a benign side effect caused by epidural fentanyl as we have experienced, but it could also be a sign of serious central nervous system lesions especially in patients with underlying risk factors such as old age, diabetes mellitus, hypertension, and cerebrovascular disease, and thus special attention should be paid to this.

Keywords Opioid · Nystagmus · Fentanyl · Epidural analgesia

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Introduction

Fentanyl is a drug commonly used for analgesia via various routes in the perioperative period. Because of its wide use, its common complications, for example pruritus, nausea, and vomiting (NV) are well known. Other than those complications, there are some complications related to fentanyl use that deserve particular attention because the symptoms mimic serious clinical situations that call for immediate medical intervention. The following is such a case—a 73-year-old woman presented predominantly vertical nystagmus as a neurological complication after epidural administration of fentanyl.

Case report

A 73-year-old woman (54 kg, 149 cm) was scheduled for left nephrectomy to treat renal tuberculosis. She had diabetes mellitus (DM) and hypertension, and was also receiving synthetic thyroid hormones because she had undergone total thyroidectomy because of thyroid cancer. The patient was prone to motion sickness and reported having experienced postoperative NV after the previous thyroidectomy. Her laboratory results were all within the normal range. Midazolam 2 mg IM and glycopyrrolate 0.2 mg IM were injected as premedication 30 min before surgery.

Before anesthesia induction, an epidural catheter was placed by midline approach via the T12/L1 intervertebral space, and the catheter was advanced 4 cm in the cephalic direction. Ten minutes after a negative test dose of 3 ml 2% lidocaine with epinephrine 1:200000, her blood pressure (BP) and heart rate (HR) were 130/80 mmHg and 78 beats/min. Anesthesia was induced with thiopental

sodium 250 mg IV and rocuronium 50 mg IV, and maintained with 4–6% desflurane, 50% oxygen, 50% nitrous oxide, and atracurium.

During the surgery, her vital signs were stable. Before the end of surgery, a loading dose of fentanyl 50 μg and 9 ml 0.2% ropivacaine was injected through the epidural catheter for analgesia in two divided aliquots, 5 min apart with frequent aspiration, and epidural infusion (infusion rate: 2 ml/h, total volume: 100 ml comprising 89 ml 0.2% ropivacaine plus fentanyl 550 μg) was started.

Ten minutes after arriving at the postanesthesia care unit (PACU), the patient was cooperative and her BP, HR, and respiratory rate were 145/85 mmHg, 94 beats/min, and 15 breaths/min. However, she complained of dizziness and nausea, and was unable to keep her eyes open. She reported that opening her eyes exacerbated the dizziness and nausea. Metoclopramide 10 mg IV was slowly administered, but her symptoms persisted. Ondansetron 8 mg IV was also injected but still no favorable change could be seen. After convincing her to open her eyes, we observed vertical, predominantly downbeat nystagmus. Other than that, her neurologic examinations ranging from cranial nerves to the legs were normal. Intrathecal administration of the epidural drugs could be ruled out because the patient displayed intact motor function, especially of both legs.

Because we were unable to determine the cause of the nystagmus, a neurologist was consulted and advised stopping all drug administration and recommended brain magnetic resonance imaging (MRI). An MRI scan was taken, the results were reviewed by a neurologist and a radiologist, and it was confirmed there was no evidence of any central nervous system (CNS) lesion. Still the nystagmus, nausea, and dizziness persisted, and the advice was to look for any changes, because further radiologic and neurologic examinations may be needed if any condition change should occur.

About 2 h had passed since initial discovery of the symptoms at the PACU, and the patient reported that the nausea and dizziness were much better, but now wound pain from the operation was unbearable. On evaluation, her neurological response was completely normal, and no nystagmus could be observed. For her pain control, previously discontinued epidural infusion was restarted, and a loading dose of fentanyl 50 μg and 9 ml 0.2% ropivacaine was given via the epidural catheter. About 15 min later, she again complained of nausea and dizziness, and the vertical nystagmus could be observed. Her BP, HR, and respiratory rate were 120/70 mmHg, 65 beats/min, and 12 breaths/min, respectively. This time, naloxone hydrochloride 0.1 mg IV was injected because the nystagmus was strongly suspected to be a complication of the epidural opioid, and the nystagmus disappeared within several minutes. During the 2-h PACU stay after the loss of the nystagmus, her vital signs were stable and only ropivacaine was administered for pain control. No more epidural opioid was administered to the patient and after nystagmus disappeared it did not recur. The patient was discharged 13 days later without any complications.

Discussion

Anesthesiologists commonly use opioids for analgesia in the operating room and PACU, and are constantly vigilant in looking for the possible adverse outcomes. Opioid-related neurologic complications are relatively rare, and if they occur it is as drowsiness or sedation.

In this case, the patient was discovered with newly developed vertical nystagmus postoperatively. Although other neurologic examinations were normal, we could not help suspecting a CNS lesion because of her old age, underlying DM, and hypertension, and the fact that acquired nystagmus is commonly regarded as a sign of midbrain, midline cerebellum, and lower brainstem lesion [1, 2]. Thus, a neurologic consultation and imaging studies were undertaken.

After a CNS lesion had been ruled out, we suspected a temporal association between epidural drug injection and the development/termination of nystagmus. Nystagmus disappeared 2 h after initial appearance and reappeared minutes after epidural drug injection. Therefore, considering the duration and onset of the symptom, of the two agents injected epidurally, fentanyl was thought to be the cause. Thus, when the nystagmus reappeared, naloxone, an opioid antagonist, was given and the nystagmus disappeared within minutes. These events correlate well with the fact that onset and duration of epidural fentanyl are 5–10 min and 1–3 h, respectively [3]. Also, onset and duration of IV naloxone are 1–2 and 30–60 min, respectively [4]. On the other hand, we confirmed a negative test dose of 3 ml 2% lidocaine with epinephrine 1:200000 before injecting an epidural bolus. Also, an epidural bolus was given in small incremental doses after frequent aspiration. Therefore, we consider unintended intravascular injection into epidural veins highly improbable. Moreover, no single case of nystagmus, evoked not by accidental intravascular injection but by normal epidural administration of ropivacaine has yet been reported, because it is a very unlikely event. Decisively, nystagmus did not recur when continuous infusion of ropivacaine, only, was resumed, which enabled us to exclude ropivacaine as the cause for nystagmus.

The site of action of epidural opioids depends mainly on their lipophilicity versus hydrophilicity, as do other properties, for example complications and duration of action [3]. The site of analgesic action for hydrophilic opioids is

overwhelmingly spinal, but this (i.e. spinal vs. systemic) is not as certain for lipophilic opioids [3, 5]. Morphine is a hydrophilic opioid which tends to remain within the CSF and produce a delayed but longer duration of analgesia, along with increased complications, for example pruritus and NV, because of its extensive cephalic spread, whereas fentanyl is a lipophilic opioid, with rapid onset of analgesia, but its rapid clearance from CSF may limit cephalic spread and the development of complications [3, 6]. Therefore, previous reports of opioids evoking nystagmus have been all of epidural morphine [7, 8], whereas the cause in this case is thought to be epidural fentanyl. To the best of our knowledge there is no report identifying epidural fentanyl as the cause of nystagmus.

Another point of note is that nystagmus was observed at a very low dose. Although the recommended infusion dose of epidural fentanyl is 20–100 μg/h [3], in this case it was 12.5 μg/h. The duration of infusion of the epidural drug until the nystagmus was first observed was approximately 50 min and thus the amount of fentanyl administered was approximately 60 μg. Several previous reports have concluded that epidural and intravenous fentanyl administration are equal in analgesic potency, and the action of fentanyl depends mainly on its systemic absorption, irrespective of its route of administration [9, 10]. However, these results were obtained after a loading dose of 1.5 μg/kg epidural fentanyl was given, and infusion at 0.75–1.5 μg/kg was continued for over 18–24 h. In contrast, when a single bolus of epidural fentanyl 1 μg/kg was given, there was minimal vascular uptake [11]. This implies that with the initial single bolus of fentanyl, there is redistribution to lipophilic tissues, which become saturated after continuous long-term administration. Ginosar et al. [12] suggested that the site of action of lipophilic opioids may primarily be determined by the mode of administration, that is, bolus administration of fentanyl has a segmental (spinal) analgesic effect whereas its epidural infusion has a nonsegmental (systemic) effect. Therefore, in this case, because a small, conventional dose of fentanyl was administered for a short time, its serum concentration was probably low. The fentanyl administered in the lower thoracic level with 9 ml 0.2% ropivacaine would have shown cephalic spread, and be rapidly absorbed across the dura mater. The fentanyl within the CSF would then undergo further cephalic migration because of passive CSF flow. Finally, it would have directly affected the CNS including the cerebellum, pontomedullary area, or vestibular nucleus, and evoked nystagmus. Therefore, the mechanism that epidural fentanyl evoked nystagmus in this case is thought to be more spinal, because of the cephalic spread of fentanyl within the CSF, rather than systemic.

In conclusion, physicians should keep in mind that epidural fentanyl could cause nystagmus as a neurological complication even when it is used within conventional dosage ranges, although this is very rare. Also, nystagmus could be just a benign side effect caused by epidural fentanyl, but physicians should pay special attention to the possibility of serious CNS lesions especially in patients with underlying risk factors.

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