Fentanyl-Induced Hypothermia in a Dog

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ABSTRACT

A 14-year-old spayed female Poodle developed hypothermia following intravenous and transdermal administration of fentanyl after total mastectomy. Hypothermia was reversed immediately after removal of the fentanyl patch and injection of naloxone. The fact that opioids such as methadone alter the set point of the thermoregulatory center in the hypothalamus is well known. However, the clinical significance of this has been ignored in small animal practice. If persistent hypothermia of unknown cause is encountered in patients sedated with fentanyl, the fentanyl should be considered as a possible cause. In such case, the hypothermia can be effectively treated by discontinuing the fentanyl and administering an opiate antagonist.

INTRODUCTION

Pain management during the perioperative period is critical for decreasing postoperative mortality and complications. Fentanyl is a synthetic full mu agonist with high potency (80 to 100 times that of morphine) and rapid onset (1–2 min after intravenous [IV] injection), which makes it widely used in veterinary medicine for perioperative pain management.[1,2] It can be administered through various routes such as IV, subcutaneous, intramuscular, transdermal, intranasal, or transmucosal.[2,3] Because the half-life of IV fentanyl is very short (0.75–6 h in dogs), it is generally administered intravenously at a constant rate infusion (CRI) or by means of a transdermal patch. The fentanyl patch system, designed by Alza Corporation in 1991, works by continuously delivering fentanyl through the skin and into the systemic circulation.[4,5] Prolonged and steady analgesia is achieved with the transdermal fentanyl patch, and it has a high transdermal bioavailability in dogs (63.8%).[6] In dogs, the therapeutic blood concentration of fentanyl is reached in about 24 h after patch application and is maintained for up to 72 h.[2] Despite the various advantages of fentanyl, side effects such as bradycardia, sedation, anorexia, and skin reactions at the site of patch application have been reported in dogs.[4] If clinical signs are suspected as adverse effects of fentanyl, removal of the fentanyl patch and administration of mu-

receptor antagonists, such as naloxone or naltrexone (a longer acting antagonist than naloxone), is indicated. Although a previous study reported decreased body temperature in dogs using opioids such as methadone,[7] the clinical significance of this has been ignored in small animal practice. In the present case study, we describe the case of a canine patient with fentanyl-induced hypothermia during the perioperative period.

CASE

A 14-year-old, 6.0-kg spayed female Poodle was presented to the Veterinary Medical Teaching Hospital of Seoul National University with an ulcerative mammary gland tumor. The mammary gland tumor was first detected by the owner 4 years before presentation, and inflammation and an ulcer began to develop around the tumor as its size increased one year before presentation. However, considering the patient's age and the extent of surgery, only ovariohysterectomy was performed by a veterinarian 10 months before presentation to our hospital. On physical examination, a 4.2 × 3.8 cm mass was palpated in the right 5th mammary gland with a 1 × 1.2 cm ulcerative lesion. In addition, several mammary tumors with a diameter of 1–3 cm were found throughout the mammary gland. No other peripheral lymph node enlargement suggesting metastasis was detected on palpation.

Radiographic and abdominal ultrasonography for the evaluation of metastasis did not reveal any abnormalities other than renal calculi. The results of a complete blood count were within the reference ranges, except for mild leukocytosis (17,460 cells/μL; reference range, 5,200–17,000 cells/μL). Serum biochemical analysis revealed mild hyperglycemia (122 g/dL; reference range, 74.5–120 g/dL), hypernatremia (155.0 mmol/L; reference range, 145.1–152.6 mmol/L), and hyperchloridemia (126.4 mmol/L; reference range, 113.2–122.9 mmol/L). The canine C-reactive protein level was elevated (38.1 mg/L; reference range, 0–20 mg/L).

Urinalysis indicated a urine specific gravity of 1.038, a pH of 6, and trace proteinuria. Cytologic examination of a fine-needle aspirate of two representative masses suggested a diagnosis of mammary gland adenoma with cyst. The diagnosis of benign mammary gland tumors was made, and the dog was scheduled for total mastectomy.

On a physical examination conducted before surgery, rectal body temperature was 39.0 °C and heart rate and respiratory rate were within the reference ranges. The patient was premedicated with cefazolin (22 mg/kg, IV), followed by acepromazine (1 μg/kg, IV). Analgesia was provided with a combination of fentanyl, lidocaine, and ketamine (FLK) by a CRI of 3–6 μg/kg/min, 1.5–3 mg/kg/h, 0.3–0.6 mg/kg/h, respectively), and transversus abdominis plane block was performed with lidocaine (0.5 mg/kg) and bupivacaine (0.25 mg/kg). Anesthesia was induced with propofol, titrated to effect (total dose, 5.5 mg/kg, IV) to achieve a sufficient depth of anesthesia for endotracheal intubation. General anesthesia was maintained with 2% isoflurane vaporized in 2 L of oxygen/min. The Hartmann solution (5–10 mL/kg/h) was administered IV during the procedure.

Core body temperature was monitored during the surgery using an esophageal temperature probe, and continuous hypothermia (33.5–35.0 °C) was noted throughout the procedure. A circulating warm water blanket (40.0 °C) was applied under the patient, and a fluid warming device was used during surgery to maintain body temperature. The rectal body temperature of the patient did not exceed 38.0 °C.

Total mastectomy was performed successfully, and the patient recovered from anesthesia without any notable complications. The analgesia was provided by the CRI of FLK immediately after surgery, and the fentanyl patch was applied simultaneously. The CRI of FLK was stopped after 24 h, when the therapeutic blood concentration of fentanyl was reached. After surgery, the patient warmed up to approximately 38.0 °C with continuous warming. However,

when the warm air blanket or hot pack was removed, the patient immediately became hypothermic, with a temperature of around 36.0 °C.

In the meantime, the patient was bright, alert, and responsive, and there was no shivering. This situation occurred repeatedly when the patient was admitted to the intensive care unit for a day. To determine the cause of hypothermia, the fentanyl patch was removed, and naloxone (0.01 mg/kg, IV) was administered 40 h after the operation. Immediately after that, the patient experienced shivering and panting, and body temperature continuously increased to 38.0 °C or higher, even after all the warming devices were removed. The patient was treated with meloxicam (0.1 mg/kg, PO, SID) instead of fentanyl for pain management, and hypothermia was not confirmed until the removal of sutures.

DISCUSSION

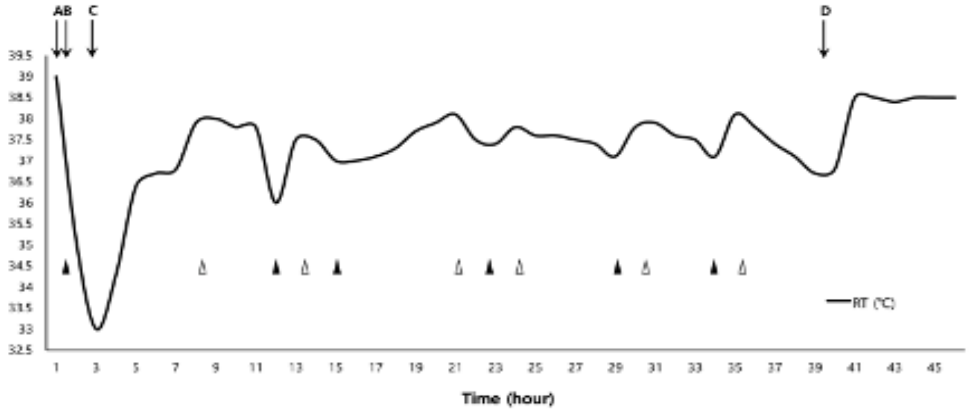
Hypothermia is one of the major complications that occur after anesthesia in small animal practice, despite the efforts to prevent it. Body temperature is sensed by temperature-responsive cells throughout the body, and this information is integrated in the hypothalamus. In healthy, unmedicated, conscious individuals, body temperature, especially core body temperature, is tightly regulated by maintaining a temperature gradient between the skin surface and the body core. During hypothermia, behavioral thermoregulation (huddling, heat seeking) and reflex physiological changes (piloerection, peripheral vasoconstriction, shivering, and arteriolar-venous anastomosis) are observed.[8]

However, in the anesthetic state, anesthetics or sedatives induce peripheral vasodilation, leading to a mixing of core and peripheral blood that causes a decrease in core body temperature and alters the thermoregulatory thresholds for a compensatory response.[9] Hypothermia can be a cause of delayed recovery from anesthesia,[10] wound infection,[11,12] prolonged hospitalization,[11] cardiac complications including bradycardia, decreased cardiac output, and hypotension,[13] coagulation abnormalities,[14] and consequent blood loss.[15] Although these heat balance changes resulting from anesthesia cannot be avoided, proper monitoring and rapid intervention in the perioperative period can minimize the degree and duration of postoperative hypothermia.

Opioids act directly on neurons in the preoptic anterior hypothalamus to alter the thermoregulatory set point, resulting from decreased heat production and increased heat loss in humans and dogs.[7,16,17] In addition, it has been experimentally confirmed that epidural fentanyl decreases the shivering threshold.[18] Therefore, in human medicine, agents with mu-agonist activity, such as tramadol, are used to limit inadvertent postoperative shivering without sedation.[19] In a retrospective study of human infants, the incidence of postoperative hypothermia was significantly higher in patients who received fentanyl during surgery than in those who received morphine or epidural bupivacaine.[20] Moreover, the decrease in body temperature was significantly greater in patients who received fentanyl than in the patients receiving the other drugs.[20] Furthermore, fentanyl also dulls the metabolic and hormonal response to surgical stress, which is mediated by beta-endorphin.[20,21] As fentanyl is a kappa receptor antagonist, while beta-endorphin is a strong agonist of the kappa-receptor, the metabolic response to stress mediated by beta-endorphin can be blocked by the administration of fentanyl.[21]

Several canine experiments have demonstrated that hypothermia is induced by fentanyl administration in a dose-dependent manner in experimental settings.[22, 23] Although these studies have suggested that fentanyl may cause hypothermia, they concluded that postoperative hypothermia following fentanyl administration in conscious dogs is mild (37.2 to 37.8 °C), and thus is not a primary concern in patient management.[23, 24] In addition, hypothermia decreases the systemic absorption of fentanyl patches. Nonetheless, it has been confirmed that the

Figure 1. *Graph of rectal temperature (RT, solid line; °C) versus time, from the time of induction for surgery to the postoperative management period (total 45 h) in a spayed female Poodle with a mammary gland tumor who presented perioperative hypothermia. A forced-air warming device and hot pack were used to treat the perioperative hypothermia in this patient. The specific time points for induction (A), start of surgery (B), end of surgery (C), and fentanyl discontinuation and administration of naloxone (D); and the application (filled arrowhead) and discontinuation (unfilled arrowhead) of the forced-air warming device and hot pack are indicated in the figure.*



fentanyl flux and the analgesic effects are maintained in the clinical environment.[25-27]

Interestingly, changes in body temperature caused by opioids are species-specific. For instance, opioids are known to cause hypothermia in dogs, rabbits, and birds, and hyperthermia in cats, horses, pigs, goats, and cattle.[28] Among the various opioids, this tendency is remarkable in pure mu-agonists,[29,30] which increase body temperature in a dose-dependent manner in cats.[29] As in cats, opioids affect the thermoregulatory center of the hypothalamus in dogs, but they alter the threshold point in the opposite direction in the latter species. In addition, Posner et al.[31] found that post-anesthetic hyperthermia was inversely associated with body temperature at extubation, indicating that overcompensation after temporal inhibition of thermoregulation is one of the mechanisms of post-anesthetic hyperthermia in cats.

In the present patient, acepromazine was injected before anesthesia as a tranquilizer, and inhalation anesthesia was maintained with isoflurane. These two drugs are known to typically cause profound peripheral vasodilation and, consequently, to rapidly decrease the body temperature of patients. Notably, the hypothermic effect of opioids is increased when combined with other drugs.28 In addition, total mastectomy, which was performed in the present case, is a surgery requiring large incisions with exposure of the subcutaneous surgical site and can cause a large amount of evaporation from the operating field, which is the main cause of heat loss in small animal surgery.

It is thought that these pre-anesthetic drugs and surgical procedures may have affected the hypothermia before and during surgery in this patient. However, mild hypothermia was continuously identified for 36 h after surgery despite active patient warming using a hot pack and a forced air warming device with a blanket, and moderate hypothermia (body temperature around 36 °C) was observed when the thermal support was discontinued. After removal of the transdermal fentanyl patch and injection of naloxone, the patient started shivering, and body temperature increased from 36.8 °C to 38.5 °C in an hour without any special warming treatment. Therefore, fentanyl was considered the main cause of continuous

hypothermia in this patient.

Above all, if clinicians use pre-anesthetic drugs that cause vasodilation combined with opioid drugs, body temperature should be closely monitored during and after surgery and prewarming should be performed before anesthesia due to the possibility of hypothermia. If hypothermia is confirmed, active warming treatment to increase the patient's body temperature is recommended first, considering the excellent analgesic effects of opioids. However, if hypothermia persists despite active warming treatment, as in this case, it is necessary to discontinue opioids and induce the reverse effect. The plasma concentration of fentanyl decreases below the analgesic range 4–6 h after removal of the transdermal fentanyl patch in dogs,2,32 while IV administration of fentanyl has a short duration of action (20–30 min in dogs). Therefore, when using a transdermal fentanyl patch, injection of naloxone is recommended for a rapid reversal effect. The onset of action of naloxone is reported to be 1–2 min, and the effect lasts for 30–60 min.2 Therefore, repeated administration of naloxone to reverse long-acting mu agonists, such as morphine, hydromorphone, and methadone, may be required.

CONCLUSION

Fentanyl can induce hypothermia in dogs, especially when administered with other preanesthetic and anesthetic agents. If persistent hypothermia during and after anesthesia is encountered despite active warming, and other contributing factors are ruled out, discontinuation of fentanyl administration and injection of the opioid antagonist naloxone are recommended.

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