Delirium During Intravenous Sedation With Midazolam Alone and With Propofol in Dental Treatment

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A 62-year-old man visited our clinic for dental implantation under intravenous sedation. He demonstrated increased psychomotor activity and incomprehensible verbal contact during intravenous sedation. Although delirium caused by midazolam or propofol in different patients has been reported, the present case represents a delirium that developed from both drugs in the same patient, possibly because of the patient's smaller tolerance to midazolam and propofol.

Key Words: Delirium; Midazolam; Propofol; Dental treatment.

Midazolam has been frequently used for intravenous sedation in dental treatment because of reliable sedation and profound amnesia. Propofol has been applied not only for general anesthesia but also for intravenous sedation by using the bolus or continuous injection technique. It has been reported that the paradox phenomenon, represented by instances of hostility, rage, and physical violence, can be caused by midazolam¹⁻⁷ and that delirium is induced by propofol.^{8,9} We report 2 episodes of delirium caused by midazolam alone and by propofol in the same patient.

CASE REPORT

A 62-year-old man weighing 66 kg visited our clinic for dental implantation under intravenous sedation. At 46 years of age he had been diagnosed as having hypertension and had been prescribed an antihypertensive drug (amlodipine besilate) and an antiplatelet drug (ticlopidine hydrochloride). At the age of 56 he had been

diagnosed as having diabetes mellitus and had subsequently been taking an antiglycemic drug (glibenclamide). His blood pressure (BP) and blood sugar were well controlled at 133/89 mm Hg and 113 mg/dL. No neurologic or mental deficits were found. Clinical blood examination showed normal values except for aspartate aminotransferase (57 IU/l), alanine aminotransferase (68 IU/l), γ -GTP (90 IU/l), and triglyceride (306 mg/dL). There was nothing in the patient's history of possible relevance in relation to the raised liver enzymes such as high alcohol intake. Up until the implant procedure, the patient had experienced no abnormal episodes during his dental treatment.

FIRST EPISODE

A bone graft was scheduled under intravenous sedation before insertion of the dental implant. Ticlopidine hydrochloride was discontinued 1 week before the operation. After the last food and drink intake in the early morning, the patient took an antiglycemic drug. His BP, heart rate (HR), and body temperature (BT) were 141/90 mm Hg, 73 beats/min, and 36.1°C before intravenous sedation. After 2 mg of midazolam was injected intravenously for sedation, 7.2 mL of a 2% solution of lidocaine containing 1:160,000 epinephrine was injected around the molar mucosa of the right lower jaw.

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Five minutes later, immediately after the administration of an additional 2 mg midazolam to deepen the sedation level, the patient demonstrated uncontrolled agitation, a state of excitement, and moaning. The symptoms continued for about 10 minutes. Blood pressure, HR, and oxygen saturation as measured by pulse oximetry (SpO_2) were stable at 130/80 mm Hg, 70 beats/min, and 97% during the episode. Because his symptoms faded spontaneously 15 minutes after their occurrence, the operation was restarted. Ninety minutes after intravenous sedation, an additional 1 mg of midazolam was administered to keep the same sedation level. Agitation and the state of excitement reappeared during the surgical procedure. However, the patient did not complain of any pain, and the symptoms lasted for a maximum of 5 minutes. Because the patient's BP had risen to 170/105 mm Hg 7 minutes after the intravenous sedation, 0.5 mg of nicardipine hydrochloride was injected to lower the BP. The anesthesia time was 130 minutes and the operation time was 83 minutes. The patient was kept in the recovery room for 225 minutes. During recovery, his vital signs including BP, HR, SpO_2 , and level of consciousness were within normal levels.

SECOND EPISODE

The dental implant procedure was scheduled 4 months after the first episode. After the last food and drink intake in the early morning, the patient took an antiglycemic drug. His vital signs, BP, HR, and BT were stable at 111/85 mm Hg, 82 beats/min, and 36.4°C before intravenous sedation. After sedation was induced intravenously with 20 mg of propofol, continuous intravenous infusion of propofol was started at a rate of 2–3 mg/kg/h. Afterward, 10.8 mL of a 2% solution of lidocaine containing 1 : 160,000 epinephrine was injected around the molar mucosa of the right lower jaw. Ten minutes later, the patient demonstrated talkativeness, restlessness, and agitation for about 10 minutes. Because the anesthesiologist evaluated the level of sedation as poor, an increment dose of 10 mg ketamine was intravenously injected to control the symptoms, which disappeared. Blood pressure, HR, SpO_2 , and respiratory rate were within normal ranges during and after the ketamine injection. Afterward, BP, HR, and SpO_2 were stable and within normal ranges. The sedation was good. Propofol infusion was continued at a rate of 3 mg/kg/h until the end of the operation. The sedation time was 175 minutes and the operation time was 150 minutes. Immediately after the operation, the patient was able to have a verbal contact but was drowsy. He was kept in the recovery room for about 3 hours.

PROCEDURE AFTER THE 2 EPISODES

The second stage of the implant procedure was scheduled 4 months after the second episode. The patient refused intravenous sedation because he had experienced unpleasantness during the previous intravenous sedation. Therefore, the operation was carried out under BP, electrocardiogram, and SpO_2 monitoring without intravenous sedation. Preoperative vital signs including BP, HR, and SpO_2 were stable at 135/85 mm Hg, 80 beats/min, and 100%. The surgical site was anesthetized with 5.4 mL of a 2% solution of lidocaine containing 1 : 160,000 epinephrine. During local anesthesia and operation, no states of excitement, agitation, or restlessness were observed. Blood pressure, HR, and SpO_2 were stable during the operation. One year after the third operation, an apicoectomy procedure was performed under local anesthesia with BP, electrocardiogram, and SpO_2 monitoring without intravenous sedation. The intraoperative vital signs were stable and within normal ranges during the operation. There were no episodes of agitation, excitement, or restlessness during the operation.

DISCUSSION

Delirium, or acute confusional state, which is a form of dementia, is defined as a "transient organic mental syndrome of acute onset, characterized by global impairment of cognitive functions, a reduced level of consciousness, attentional abnormalities, increased or decreased psychomotor activity, and disordered sleep-wake cycle."¹⁰ Symptoms include restlessness, shouting, illusions, a feeling of disorientation, talkativeness, and agitation. The patient in our case demonstrated increased psychomotor activity and incomprehensible verbal contact during intravenous sedation. The symptoms included agitation, excitement, restlessness, talkativeness, and moaning. The midazolam-induced paradoxical phenomenon has been reported previously.^{1,7} According to the report by Weinbroum et al,³ the incidence of paradoxical events was less than 10.2%, and they occurred 45–210 minutes after sedation started. Under normal circumstances, delirium tends to occur when patients emerge from general anesthesia. Although delirium with intravenous sedation has been reported, it is infrequent for it to occur twice in the same patient under midazolam and propofol. There are various factors associated with delirium, including hypoxia, hypercapnia, increased intracranial pressure, pain, stress, anxiety, fear, surgical procedures, psychotic or neurotic disorders, and sedative or anesthetic agents.¹¹ In the present patient, hypoxia, hypercapnia, hypertension, and in-

creased intracranial pressure could be excluded as causes of delirium because his BP, HR, SpO₂, and BT were constantly stable and within normal levels. Hypoglycemia was ruled out because he ate breakfast and received fluid transfusion, including 5% glucose. Because the patient had no history of psychotic or neurotic disorders, psychiatric factors can also be ruled out as causes of delirium. Local anesthesia was successful in the first and second episodes; therefore, surgical pain cannot be considered as having caused delirium. However, unpleasantness, lack of communication, or frightening activities could have occurred intraoperatively.

Midazolam, propofol, and ketamine, which were administered to the patient in our case, are all capable of producing delirium. However, with all 3 of these agents, drug-induced delirium typically follows larger doses or more prolonged exposures.¹¹ The doses of midazolam or propofol and ketamine that were administered for sedation in the present case were small, but they could still be associated with delirium because delirium was not caused in the third or fourth operations in which midazolam and propofol were not used. In addition, the patient remembered the discomfort of his experiences during the previous intravenous sedations under midazolam and propofol. An additional dose of 2 mg midazolam was administered, leading to delirium in the first episode. In recent studies, it has been widely reported that flumazenil reverses paradoxical reactions with midazolam.^{3,7} Thurston et al⁷ reported that paradoxical reactions to midazolam can be treated with small doses of flumazenil without reversing the amnesic and sedative effects of the benzodiazepine. Therefore, flumazenil could have been an effective way of reversing delirium in this episode as well.

In the second episode, after an initial bolus injection of 20 mg propofol, 10-minute continuous infusion of propofol at the rate of 2–3 mg/kg/h deepened the sedation but resulted in delirium. On that occasion, a small dose of ketamine was administered to control the delirium. Ketamine, however, should not be used to control

agitation, restlessness, or a state of excitement because of the possibility of exacerbating these symptoms. There have been some reports of delirium caused by propofol. Whereas Gadalla⁸ noted prolonged delirium in patients emerging from anesthesia, Robinson⁹ reported delirium at the very beginning of anesthesia. Although delirium caused by midazolam or propofol in different patients has been reported, the present case represents a delirium that developed in the same patient with both drugs. The delirium in the present case might be due to unstable sedation caused by the patient's smaller tolerance to midazolam and propofol.

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