



Comment on “Psychogenic coma after general anesthesia with remimazolam and remifentanyl -a case report-”

The case report published in October 2022 with the title ‘Psychogenic coma after general anesthesia with remimazolam and remifentanyl’ [1] would be very interesting to readers as remimazolam was launched as a new general anesthesia drug in South Korea. Since I previously used midazolam to reduce the anxiety of preoperative patients, I read the paper with full attention. In this report, it took 36 h for the patient to recover consciousness from a coma with no neurological deficits. The first step in finding the cause of the coma began with reversing the perioperative opioid and sedative drug with naloxone and flumazenil. The next step was to consult a neurologist to exclude any organic brain problems and obtain a magnetic resonance imaging scan. Finally, a diagnosis of psychogenic coma was reached [1]. Little is known about the pathophysiology of psychogenic coma, and the diagnosis is made by excluding known organic causes or functional ones of the coma only after the patient recovers consciousness with no neurological damage. Thus, the diagnosis of psychogenic coma is made retrospectively in coma patients with unknown causes.

Although aphonia is an on-label adverse drug effect of midazolam, the anesthesiologist who administered the drug would panic if the patient could not speak. Oh et al. [2] reported that the incidence of aphonia caused by midazolam was 0.19%. However, the clinical features accompanying aphonia vary from the inability to open the eyes to quadriplegia-like weakness in the four extremities. Midazolam, in the benzodiazepine class, also has anxiolytic effects with centrally acting muscle relaxation. It would be natural for the physician to consider aphonia at the extreme end of the dysarthria spectrum as a side effect of midazolam. Oh et al. [2] reported that the clinical symptoms and signs caused by midazolam were very similar to Broca’s aphasia (expressive aphasia). Aphonia by midazolam and Broca’s aphasia exhibits common symptoms as being unable to speak. However, aphonia by midazolam resolved spontaneously with no neurological deficits. Patients with aphonia caused by midazolam recalled that they tried to say something but failed. Of them, 45% remembered that they were unable to speak. In the recovery room, they had panicked because they were afraid that they would be unable to speak forever. Additionally, some patients could not open their eyes and others were unable to freely move their four extremities, almost mimicking a coma-like state. Of the patients with aphonia caused by midazolam, 75% recovered their speaking ability after flumazenil treatment and

25% of them had to wait up to 2.5 h until they were able to speak again [2].

Several clinical manifestations are similar between psychogenic coma and aphonia caused by midazolam. First, there is transient functional derangement of the central nervous system without any positive findings in the neurological examination or brain imaging studies. Second, despite conservative treatment, patients recover normal brain function without any neurological damage. Third, there is no secondary gain in the clinical manifestations. Of course, there are several differences between psychogenic coma and aphonia caused by midazolam. Although the mechanism by which aphonia develops from midazolam administration is known, little is known about how psychogenic coma develops and disappears spontaneously. Thus, aphonia caused by midazolam could be reversed by the midazolam antagonist flumazenil. However, there is no way to reverse psychogenic coma with medical treatment. Additionally, there is a difference in patients’ recall of what happened to them during their coma-like state. However, there are no data on whether psychogenic coma patients can remember what happened to them during their comatose state.

Based on the above discussion, I would like to suggest some reasons why we should exclude the possibility of aphonia caused by remimazolam in the differential diagnosis of patients with psychogenic coma. 1) As remimazolam belongs to the benzodiazepine class, it would have the same adverse effects as midazolam, such as aphonia. 2) A patient with psychogenic coma caused by remimazolam remembered that she could not sleep because of the noisy atmosphere in the intensive care unit. Until that time, she was regarded to be in a comatose mental state. According to the report, she might have been in an alert mental state at the time she appeared to be in a comatose mental state [1]. From my viewpoint, she might have been alert and unable to speak at that time, such as patients with aphonia caused by midazolam. 3) According to the report, the patient did not recover consciousness following the administration of 0.6 mg of flumazenil [1]. The guidelines for flumazenil treatment for reversing remimazolam adverse effects recommend administering 1.0 mg of flumazenil [3]. If they had tried 1.0 mg of flumazenil instead of 0.6 mg to reverse her psychogenic coma, nobody could know what might have happened. Generally, up to 3.0 mg of flumazenil is recommended to reverse aphonia caused by midazolam [4].

Nevertheless, considering that the plasma concentration of remimazolam was continuously declining in her blood, it is not easy to explain why she lost consciousness after regaining her alert mental status in the recovery room. One possibility is that pain may have played an antagonist role to the sedative effect of remimazolam and made her alert. Her pain score was 8 when she was transferred to the recovery room. However, after taking 30 µg of fentanyl to control pain, she became unconscious. There is a possibility that she was alert due to

the severe pain, but she lost consciousness due to the administration of the painkiller, fentanyl. A close association between painful procedures and high bispectral index scores was reported [5].

In conclusion, it is an enormous stress not only for an anesthesiologist but also for the patient's family if a patient does not recover consciousness from general anesthesia. Medical costs to find the cause of a coma are also excessive. Therefore, I suggest trying the maximum recommended dose of flumazenil in patients who received benzodiazepine and show a coma-like mental state. None but the brave deserves the fair result.

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Anesthetic management with remimazolam for laryngectomy in a severely underweight patient with facioscapulohumeral muscular dystrophy

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common muscular dystrophy worldwide [1]. It is characterized by the slowly progressive wasting of facial, scapular, and humeral muscles in adolescence but eventually extends to the lower extremities [1]. As with other muscular dystrophies, total intravenous anesthesia (TIVA) is the preferred. Because volatile anesthetics can be associated with anesthesia-induced rhabdomyolysis, hyperkalemia, and cardiac arrest [2]. We report the successful administration of remimazolam TIVA in a severely underweight patient with FSHD. This study was approved by the Institutional Review Board of Yeouido St. Mary's Hospital (approval number: SC23ZESI0019). The patient authorized the publication of this letter with anonymized details.

A 27-year-old female patient (height: 165 cm, weight: 30 kg, body mass index [BMI]: 11.02 kg/m²) was scheduled for a total laryngectomy. She was diagnosed with FSHD 17 years earlier. The disease continued to progress, and she finally lost her ability to ambulate. She underwent a tracheotomy one year earlier and was using a home ventilator. She had frequent aspiration pneumonia, so a total laryngectomy was decided.

Her initial vital signs were within the normal range in the operating room. Neuromuscular blockade was monitored via train-of-four (TOF) acceleromyography on the right hand for the ulnar nerve and the left foot for the sural nerve simultaneously. After the tracheotomy tube was connected to the circuit of the anesthesia workstation, remimazolam was infused at a rate of 12 mg/kg/h with remifentanyl (0.3 µg/kg/min) under bispectral index (BIS) monitoring. After approximately 10 mg of remimazolam was infused, her BIS value decreased to below 70, and the eyelash reflex disappeared. Then, 20 mg of rocuronium was injected, and the remimazolam infusion rate was decreased to 2 mg/kg/h. The TOF ratio was initially 100% on both sites, and the TOF count became 0 on the sural nerve after about 80 s but remained at 1 even after about 90 s on the ulnar nerve, so an additional 10 mg of rocuronium was administered. After we confirmed the disappearance of the TOF count on the ulnar nerve after 60 s and BIS value less than 60, we changed the tracheotomy tube to an armored 6.5 mm endotracheal tube. The left dorsalis pedis artery was cannulated and connected to a FloTracTM/Vigileo system (Edwards Lifesciences, USA) to measure cardiac output.

For maintenance, we continued the infusion of remimazolam at a rate of 1.5–2 mg/kg/h and remifentanyl at a rate of 0.2–0.45 µg/kg/min to achieve a BIS of 40–60. Stable hemodynamic variables were maintained (Fig. 1), with a cardiac index value of 3.5–4.7 L/min/m² throughout the whole procedure. Additional rocuronium at 10 mg was administered 3 h after anesthesia induction because twitches raised to 4/4 in the TOF count on both sites. Total laryngectomy was finished after 3.5 h. We discontinued remimazolam and remifentanyl