Total intravenous anesthesia with remimazolam in a patient with epilepsy who underwent deep brain stimulation: a case report

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Drugs administered for anesthesia can trigger seizure attacks in patients with epilepsy. Benzodiazepines have been consistently reported to be anticonvulsants, and a novel benzodiazepine, remimazolam, was recently introduced. We report a case of total intravenous anesthesia maintained with remimazolam in a patient with epilepsy who underwent deep brain stimulation of both anterior thalamic nuclei. Despite the administration of multiple anti-epileptic drugs, no tolerance to remimazolam was observed. Perioperative seizures were also not observed. Remimazolam can be considered the anesthetic of choice in patients with epilepsy.

KEY WORDS: Remimazolam, Intravenous anesthesia, Deep brain stimulation, Epilepsy, Case reports

INTRODUCTION

Epilepsy affects people regardless of race, age, or socioeconomic status, with a prevalence varying from 5 to 8 in 1,000 people depending on the country [1]. There is a possibility for every anesthesiologist to encounter patients with epilepsy; and thus, anesthesiologists need to be well informed about anesthetic considerations when managing them.

Benzodiazepines are commonly prescribed for the treatment of seizures. Remimazolam, a novel benzodiazepine, can be used to induce and maintain anesthesia. It is a potential alternative to propofol, and relevant studies have recently been actively reported [2]. However, there is limited literature regarding remimazolam administration in patients with epilepsy. We report a case of total intravenous anesthesia maintained with remimazolam in a patient with deep brain stimulation (DBS) of the bilateral anterior thalamic nuclei.

CASE REPORT

A 61-year-old Asian male (height, 161 cm; weight, 73.7 kg; body mass index, 28.4 kg/m²) was referred to the hepatobiliary surgical department of a tertiary ac-
academic hospital due to chronic cholecystitis. The patient complained of abdominal distension and pain. He was treated with oral medication for the symptoms and was observed for 7 months at the Department of Gastroenterology of the same hospital. Following computed tomography and ultrasonography of the abdominal cavity, surgical treatment was determined to be the best course of action.

The patient had a history of epilepsy for approximately 20 years, and the outpatient department documented that he had undergone surgery for DBS at another tertiary medical center where the patient had been followed-up for epilepsy in 2017. The patient also had hypertension and diabetes mellitus type 2. He previously underwent exploratory laparotomy for hemoperitoneum caused by a traumatic mesocolon injury in 2016. Chest radiography revealed an implanted generator below the left clavicle (Fig. 1). The preoperative HbA1c was 7.7%. Other preoperative findings were unremarkable.

The patient was taking the following anti-epileptic drugs (AED); valproic acid, lamotrigine, and oxcarbazepine. Clonazepam 0.5 mg, equivalent to diazepam 7.5 mg, was also administered. Other oral medications included angiotensin receptor blockers, beta-blockers, and a combination of diabetic pills. There was no history of hypersensitivity to the medical drugs and no relevant family medical history.

Laparoscopic cholecystectomy was planned, and conventional open cholecystectomy was considered in cases of intraperitoneal adhesions due to prior surgery. The patient’s anesthetic record in 2016 was reviewed, and no remarkable anesthesia-related events were noted.

No sedative premedication was prescribed on the day of surgery, except AEDs, which were continued on the day of surgery with 25 mL of water. Standard monitoring of anesthesia was performed following admission to the operating room. The electroencephalogram was monitored using SedLine (Masimo Corporation, Irvine, CA, USA). There was no significant interference in the intraoperative electrocardiographic monitoring by DBS.

Remimazolam infusion was initiated at a rate of 6 mg·kg⁻¹·hr⁻¹. Remifentanil was administered via target control infusion and titrated to the effect-site concentration using Minto model. Anesthesia induction was uneventful, and no hypotension developed. The implantable pulse generator was turned off after the confirmation of endotracheal tube placement.

A hepatobiliary surgical specialist initiated the laparoscopic surgery. Severe intra-abdominal adhesions were observed, and an open surgical approach was adopted. Bipolar electrocautery was used for hemostasis to prevent malfunction of the DBS device and thermal injury to the brain [3]. Radiofrequency or high-power ultrasound energy devices should be avoided in patients with an implanted pulse generator [4].

The operation lasted for 120 minutes, and no epileptic waves were observed in the electroencephalogram during anesthesia by the attending physician. Remimazolam infusion was stopped 8 minutes and 25 seconds before the conclusion of surgery, followed by reoperation of the implanted pulse generator. Flumazenil 0.2 mg was administered intravenously because there was no evidence of consciousness 20 minutes after cessation of remimazolam. One minute later, the patient recovered spontaneous ventilation and obeyed commands. Following this, the patient was extubated; the total anesthesia time was 160 minutes. The administered doses of remimazolam and remifentanil were 235 mg and 990 µg, respectively.

The patient reported mild dizziness in the postoperative care unit. Dizziness was alleviated after infusion of 100 mL of crystalloid. Drowsiness of modified observer’s assessment of alertness/sedation scale (MOAA/S) 3 was observed, and additional flumazenil 0.2 mg was administered intravenously. Alertness of MOAA/S 5 was achieved 2 minutes later.

Complications were limited to mild postoperative pain during hospitalization. After 7 days of planned observation, the patient was discharged and interviewed regarding the anesthetic experience on the day of discharge. Overall, the patient was satisfied with the anesthetic experience.

![Fig. 1. Plain chest posteroanterior (PA) film of the patient. A generator is seen below the left (Lt) clavicle.](https://doi.org/10.52662/jksfn.2022.00241)
The patient visited the emergency department on postoperative day (POD) 21 complaining of pain at the surgical site. Abdominal computed tomography revealed an intra-abdominal abscess. A percutaneous catheter was inserted for drainage. The patient was re-hospitalized for 7 days and discharged with the percutaneous catheter. The catheter was removed at the outpatient department on the POD 33. There were no further complications, including seizures.

In summary, patient with epilepsy controlled with DBS underwent cholecystectomy. Remimazolam was adopted as the main anesthetic drug because of its anti-convulsant properties. The patient had no tolerance to remimazolam, and the drug provided appropriate intraoperative hypnosis. There were no seizures during hospitalization or follow-up.

Ethical statements
Written informed consent was obtained from the patient for the publication this case report. A copy of the written consent is available for review on request.

DISCUSSION
Perioperative seizures are rare, and the reported incidence is 3.1 per 10,000 [5]. Seizure-like phenomena mostly occur during the induction and emergence periods of anesthesia [6]. In epilepsy patients requiring anesthesia, a low level of intravenous anesthetic drug can trigger seizure attacks [7]. Etomidate and ketamine are often avoided in patients with epilepsy owing to their proconvulsant properties. Propofol is commonly used in epileptic patients but there are multiple reports that it is related to perioperative seizure attacks, and in more severe cases, status epilepticus [6,8]. Benzodiazepines have consistently been reported to be potent anticonvulsants [9].

The anticonvulsant feature of benzodiazepines could be beneficial for patients with epilepsy, but these drugs are usually administered as an anesthetic adjuvant rather than as the primary agent [10]. This is because of the extended context-sensitive half time of these drugs. For example, context-sensitive half time is 4 hours after an hour infusion of midazolam, the most rapidly eliminated drug can trigger seizure attacks [11].

Propofol is the most widely used intravenous anesthetic drug; however, it also has proconvulsant properties. Perioperative seizure events identified through electroencephalogram monitoring have been reported in patients undergoing anesthesia with propofol [12,13]. A board-certified neurologist, one of the authors, reviewed the intraoperative 4-channel electroencephalogram acquired with SedLine postoperatively, and there was no evidence of a seizure attack. Remimazolam provided stable anesthesia for this patient and could be superior to propofol in terms of the prevention of seizure attacks.

The time to the loss of consciousness following the administration of remimazolam was similar to that of conventional hypnotic agents. The time to emergence of consciousness after cessation of remimazolam administration is usually 10 to 20 minutes [14]. Flumazenil can readily reverse the effect of benzodiazepine when emergence is prolonged or intraoperative awakening of a patient is required.

Benzodiazepines are often included in anti-epileptic prescriptions, and patients with epilepsy receiving AEDs can require a greater dose of anesthetic drugs [15]. Yoshikawa et al. [16] reported that remimazolam could be inappropriate in long-term benzodiazepine user. The patient was also administered benzodiazepines along with other AEDs. However, the loss of consciousness was followed by the administration of a standard dose of remimazolam for induction. Considering the infusion rate of 6 mg·kg⁻¹·hr⁻¹ and the time to loss of consciousness, 0.13 mg·kg⁻¹ of remimazolam was administered as an induction dose. During the maintenance of general anesthesia, a mean infusion rate of 1.36 mg·kg⁻¹·hr⁻¹ of remimazolam was adequate to maintain the desired anesthetic depth.

Postoperative nausea and vomiting can be minimized by maintaining anesthesia with remimazolam [14]. The patient did not complain of nausea and vomiting during hospitalization. Further administration of drugs that can potentially trigger seizures can be minimized in this setting [17,18]. In addition, remimazolam provides minimal hemodynamic perturbation and requires less support from vasopressors than propofol [19].

This case report describes for the first time the successful maintenance of anesthesia with remimazolam in a patient with epilepsy controlled by DBS. The drug is also expected to be beneficial in the sedation of patients with epilepsy or status epilepticus. However, generalization is limited by the study setting of the case report. Therefore, further randomized controlled studies are required.

CONCLUSION
To our knowledge, this is the first case of successful maintenance of anesthesia with the novel benzodiazepine, remimazolam, in a patient with epilepsy controlled by DBS of the bilateral anterior thalamic nuclei. Remimazolam could be a reasonable alternative to propofol as the main anesthetic agent in patients with epilepsy.
CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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