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LETTER TO THE EDITOR

Remimazolam and low-dose flumazenil for awake craniotomy

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To the Editor:

Remimazolam, a novel short-acting benzodiazepine, is reportedly a safe option for the anesthetic management of asleep–awake–asleep craniotomy [1–3]. In some cases, flumazenil may be required to achieve a fully awake condition during the awake phase. However, an appropriate dose of flumazenil to antagonize the sedative effect of remimazolam in this situation has not been determined yet. Re-induction of anesthesia after the awake phase may be performed using remimazolam. In such cases, an excessive dose of flumazenil during the awake phase can increase the dose of remimazolam required to achieve re-induction. Herein, we describe a case of asleep–awake–asleep craniotomy in which the patient was anesthetized with remimazolam. A low dose of flumazenil was effective in antagonizing the sedative effect of remimazolam during the awake phase. Moreover, it did not increase the dose of remimazolam for the re-induction of anesthesia after the awake phase.

Written informed consent for the publication of this case was provided by the patient. This report was approved by the Institutional Review Board of Nagasaki University Hospital, Nagasaki, Japan (Approval number: 22062030). A 45-year-old woman (height: 154 cm; weight: 39 kg) was scheduled to undergo awake craniotomy for the resection of a metastatic brain tumor located close to the eloquent cortical areas. Considering that propofol was in short supply due to the coronavirus disease pandemic, we decided to use remimazolam. Anesthesia was induced through manual infusion of remimazolam 4 mg for approximately 1 min and administration of remifentanil at 1 μg/kg/min. Following the administration of rocuronium 20 mg to facilitate its insertion, a size-3 laryngeal mask airway (LMA)® Supreme™ (Teleflex, Westmeath, Ireland) was placed to secure the airway [4]. A 14-Fr gastric tube was inserted through the drain tube of the LMA. We performed scalp blocks to the bilateral supraorbital and supratrochlear nerves, left greater and lesser occipital nerves, left auriculotemporal nerve, and left zygomaticotemporal branch of the zygomatic nerve. After the induction of anesthesia, remimazolam was infused at 1.0 mg/kg/h for 96 min, followed by infusion at 1.2 mg/kg/h for 140 min. Likewise, remifentanil was infused at 0.3 μg/kg/min for 6 min, followed by infusions at 0.1 μg/kg/min for 39 min and 0.3 μg/kg/min for 187 min. For the last 5 min before discontinuation, the infusion rate of remifentanil was decreased to 0.1 μg/kg/min. Acetaminophen 600 mg and flurbiprofen 50 mg were administered to prevent the occurrence of headache during the awake phase.

Treatment with remimazolam was discontinued following the preparation of language mapping; remifentanil was also discontinued 1 min later. Spontaneous breathing was restored 2 min after discontinuation of remimazolam. Although the patient opened her eyes 4 min after discontinuation of remimazolam, she was slightly drowsy with a bispectral index value of 71. We decided to administer flumazenil 5 min after the discontinuation of remimazolam. Accordingly, we removed the LMA 2 min after the administration of a bolus of flumazenil 0.05 mg, when the patient became fully awake with a bispectral index value of 90. Language mapping was successfully performed without causing re-sedation during the 75-min awake phase. There was no occurrence of nausea, vomiting, or seizures.

After completion of the language mapping, anesthesia was re-induced through the manual infusion of remimazolam 4 mg for approximately 1 min and administration of remifentanil at 1 μg/kg/min. As in the first induction, a size-3 LMA® Supreme™ and a 14-Fr gastric tube were placed. The supply of remimazolam was also insufficient at that time. Therefore, treatment with remimazolam was discontinued after an 11-min infusion at 1.0 mg/kg/h, and inhalation of sevoflurane was initiated to minimize the use of remimazolam. The surgery was successfully completed approximately 180 min after the re-induction of anesthesia. The patient regained consciousness, and the LMA was

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removed 7 min after discontinuation of sevoflurane without requiring additional administration of flumazenil. The postoperative course was uneventful, and the patient did not develop neurological deficits, including language ability.

The patient recovered spontaneous breathing and regained consciousness within a few minutes after discontinuation of remimazolam without the need for flumazenil. Therefore, infusion of remimazolam at a dose of 1.0–1.2 mg/kg/h during the initial asleep phase was appropriate. However, we decided to administer flumazenil to achieve clear communication with the patient during the awake phase. According to a retrospective study conducted by Sato et al., eight of 15 patients who were unable to communicate or open their eyes received treatment with flumazenil 0.2 mg after the initial asleep phase maintained with infusion of remimazolam at a dose of 1.0 mg/kg/h [1]. In these patients, approximately 15 min were required for the recovery of spontaneous breathing. Infusion of remimazolam at a dose of 1.0 mg/kg/h may be relatively excessive for these patients. According to the information provided in the package insert of flumazenil, approximately 0.2 mg of flumazenil may be administered as an initial dose to antagonize the sedative effect of remimazolam. In fact, some patients received flumazenil 0.2 mg [1] or 0.3 mg [3] before the awake phase during the anesthesia management of asleep–awake–asleep craniotomy using remimazolam. Both initial and second asleep phases can be induced and maintained with remimazolam [1, 2]. Because the appropriate dose of flumazenil may vary between cases, the administration of a large dose of flumazenil for the awake phase may increase the induction and maintenance doses of remimazolam during the second asleep phase, especially early in the process. Therefore, we planned to titrate the dose of flumazenil by initiating administration at a dose of 0.05 mg.

In our patient, administration of flumazenil 0.05 mg at the beginning of the awake phase was sufficient to antagonize the residual effect of remimazolam without increasing the induction dose of remimazolam for the second asleep phase. In addition, it did not cause re-sedation throughout the awake phase. In a case of re-sedation after reversal of remimazolam by flumazenil, no less than 0.5 mg of flumazenil was administered simultaneously with the discontinuation of remimazolam [5, 6]. In other words, flumazenil was administered when the residual effect of remimazolam could not be estimated. Therefore, flumazenil should be administered after confirming the spontaneous disappearance of the sedative effect of remimazolam by titrating the minimum required dose in patients undergoing asleep–awake–asleep craniotomy using remimazolam. Further studies are required to determine the appropriate dose of flumazenil during asleep–awake–asleep craniotomy managed with remimazolam.

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