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LETTER TO THE EDITOR

Precipitation of remimazolam in coadministration with Plasma-Lyte 148: two case reports

Dear Editor,

Remimazolam besylate is a novel ultrashort-acting benzodiazepine drug that is a recent innovation in the field of anesthesia.[1] A carboxylic ester-incorporated benzodiazepine, remimazolam undergoes organ-independent metabolism by tissue esterases into an inactive metabolite. Therefore, it has fast onset, quick recovery time, and prolonged infusions, or higher doses of remimazolam are unlikely to result in accumulation and extended effect, making it favorable for use as an intravenous anesthetic.[2] When applying newly approved drugs, we should consider the appropriate administration method and infusion dose. We describe two cases of the precipitation phenomenon noted in the intravenous line of patients after coadministration of intravenous remimazolam and Plasma-Lyte 148 solution. Written authorizations from both patients were provided for publication of case reports and any accompanying images. A 26-year-old man (weight: 80 kg; height: 175 cm) underwent open reduction and internal fixation surgery of the right patella bone under general anesthesia. The patient had no underlying disease and no relevant medical history. All results from preoperative laboratory tests including chest X-Ray, electrocardiogram, as well as blood tests were in the normal range. A clinical diagnosis of fracture of the right patella bone was made and the patient was taken to the operating room. Noninvasive blood pressure, electrocardiogram, oxygen saturation, and Bispectral Index (BIS) were used for patient monitoring. The patient had a peripheral intravenous line in the right cephalic vein and the infusion solution was Plasma-Lyte 148. We administered Plasma-Lyte 148 solution at a rate of approximately 180 mL.h^{-1}. General anesthesia was planned to be induced via intravenous infusion of remimazolam besylate. We mixed 50 mg of remimazolam and 10 mL of 0.9% normal saline to create a remimazolam mixture of 5 mg.mL^{-1}. For general anesthesia, an induction dosage of 0.2 mg.kg^{-1}.min^{-1} was administered with BIS monitoring and Modified Observers Assessment of Alertness and Sedation score assessment. About 30 seconds after the infusion of remimazolam, the patient was not sedated at all. The clinician noticed a decrease in the fluid administration rate and a precipitate inside the intravenous line (Fig. 1A). An obstruction occurred, and the intravenous line did not function properly after this event. The clinician decided to remove the intravenous line and placed another peripheral intravenous line. General anesthesia was induced with the injection of 120 mg of propofol. No further crystallization events were observed (Fig. 1B). Laryngeal airway mask insertion was safely performed after injection of 50 mg of rocuronium. The operation was completed without any complications. In another case, a 39-year-old woman (weight: 68 kg; height: 172 cm) with no underlying medical problems was scheduled for debridement and suture of a peroneus brevis of the left ankle under general anesthesia. The patient was taken to the operating room without any premedication. The patient received Plasma Lyte 148 solution at rate of approximately 180 mL.h^{-1}. Intravenous 5 mg.mL^{-1} of remimazolam infusion was maintained at 0.2 mg.kg^{-1}.min^{-1} for induction of general anesthesia. After

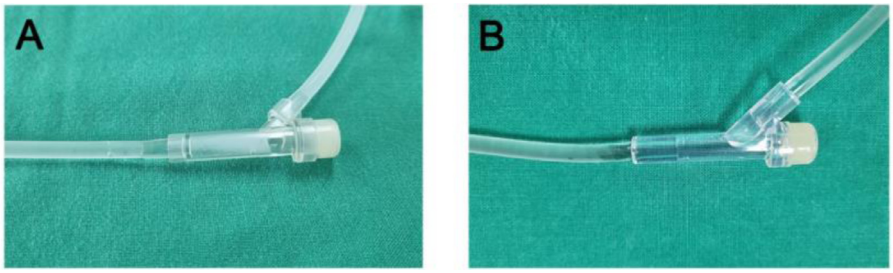

Figure 1 (A) Precipitation of remimazolam when administered with Plasma Lyte 148; 5 mg.mL^{-1} of remimazolam was infused at a rate of 0.2 mg.kg^{-1}.min^{-1}. (B) Normal intravenous line with Plasma Lyte 148.

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the continuous infusion of remimazolam, precipitation inside the intravenous line was found. Given an obstruction occurred and the intravenous line did not function properly, the intravenous line was removed and replaced with another peripheral intravenous line. General anesthesia was induced with the injection of 100 mg propofol, and the operation was completed without further incidents.

Remimazolam is desirable as it has advantages beyond existing inhalation anesthetics, propofol and midazolam. Inhalation anesthetics might trigger malignant hyperthermia and are a risk for Postoperative Nausea and Vomiting (PONV), while a benzodiazepine is not a trigger for malignant hyperthermia and has reduced PONV risk.[3] Propofol has several drawbacks, such as pain upon intravenous injection and cardiorespiratory depression, while remimazolam had no notable injection pain or cardiovascular depression in a phase I clinical trial.[2] Midazolam has the risk of excessive sedation and can accumulate in situations such as renal impairment and prolonged infusion. On the other hand, the carboxylic ester linkage of remimazolam allows for fast onset and quick recovery time despite prolonged infusions or higher doses.[1,2] In addition, it can be used relatively safely in patients with hepatic or renal failure.[4] For general anesthesia, an induction dosage of 0.2 $mg.kg^{-1}.min^{-1}$ of remimazolam and a maintenance dose of 1 $mg.kg^{-1}.h^{-1}$ can achieve a satisfactory effect.[5]

According to the FDA approval of remimazolam, it has been shown to be compatible with the following fluids: 0.9% sodium chloride injection, 5% dextrose injection, 20% dextrose injection, 5% dextrose and 0.45% sodium chloride injection, and Ringer's solution.[6] However, there are two similar case reports of precipitation phenomena observed during administration of intravenous remimazolam. Sasaki et al. reported precipitation after intravenous administration of remimazolam in a concentration of 5 mg.mL-1, with rate at 0.2 $mg.kg^{-1}$, when using Ringer's acetate solution as an infusion solution.[7] Yoshida et al. also reported intravenous line occlusion when using remimazolam in a concentration of 2 $mg.mL^{-1}$, with Ringer's acetate solution.[8] They also conducted tests on whether remimazolam concentration, infusion rate of Ringer's acetate solution, or both contribute to precipitates. They concluded that when 5 $mg.mL^{-1}$ of remimazolam was used, crystals were formed even at slow infusion rates (100 and 150 $mL.h^{-1}$) of Ringer's lactate solution. This is because the solubility of remimazolam decreases at pH > 4.0, and hence, it did not dissolve in alkaline solution.[1] One liter of Plasma Lyte 148 solution contains 140 mmoL of sodium, 5 mmoL of potassium, 1.5 mmoL of magnesium, and, 27 mmoL of acetate, and the average pH varies from 7.35 −7.45.[9] Considering the solubility of remimazolam decreases at pH >4.0 and the higher pH of Plasma Lyte 148 solution, we conclude that this could have led to precipitate formation. Also, the concentration of remimazolam used in both cases was 5 $mg.mL^{-1}$, which could have accelerated the precipitation. We suggest the pharmaceutical company to emphasize the possibility of precipitate when using Plasma Lyte 148.

In conclusion, precipitation can occur after coadministration of remimazolam and Plasma-Lyte 148 solution due to decreased solubility of remimazolam at pH > 4.0. Since unexpected clinical events may occur, the administration method should be carefully considered when applying new drugs clinically.

Conflicts of interest

The authors declare no conflicts of interest.

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