Remimazolam besilate, a benzodiazepine, has been approved for general anesthesia!!

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Introduction: consideration of advantages

In January 2020, remimazolam besilate, a novel benzodiazepine, was approved as a general anesthetic in Japan firstly in the world. A novel anesthetic, remimazolam, would be desired to have advantages beyond existing anesthetics such as inhalation anesthetics, propofol, and midazolam. Inhalation anesthetics might trigger malignant hyperthermia, and is a risk for postoperative nausea and vomiting (PONV), while a benzodiazepine, midazolam, is not a trigger for malignant hyperthermia and has an advantage to reduce PONV [1]. Remimazolam induced mild and transient nausea after bolus but not seems to have high risk of PONV [2]. An inhalation anesthetic but not an intravenous anesthetic including remimazolam pollutes environmental air including in the operation room [3]. Large dose and longer infusion of propofol is a risk of propofol infusion syndrome in both children and adults [4]. Injection pain of propofol is also a clear disadvantage although the use of lidocaine or opioid may reduce the injection pain [5, 6]. Remimazolam had no notable injection pain in a phase I clinical trial [2]. Midazolam is sometimes used for general anesthesia but not often, maybe due to long-acting property than propofol and inhalation anesthetics and large interindividual variability [7]. Prolonged effect of an active metabolite of midazolam may cause a difficulty to use midazolam [8], while remimazolam is metabolized by tissue esterases to an inactive metabolite [9]. Context-sensitive half-time (CSHT) estimated from a pharmacokinetic/pharmacodynamic analysis has revealed that the off-set of the remimazolam after the

stop of its infusion is faster than that of the midazolam. For instance, when comparing half-time after 3 h constant rate infusion, the half-time of remimazolam is approximately one-fifth shorter than that of midazolam [10]. Note that the researchers calculated CSHT in untypical way (the detail is discussed below). On the above-mentioned beneficial properties, remimazolam has a potential to be a principal intravenous anesthetic for general anesthesia.

How rapid of the offset?

Remimazolam may be recognized to be rapid offset or ultra-short acting drug, but how rapid? When seeing CSHT in an article again, the half-time of arterial remimazolam concentration for 3 h constant rate infusion is approximately 7.5 min [10]. In the original article, CSHT is calculated using target-controlled infusion [11]. The half-time for 3 h TCI is longer than the half-time for 3 h constant rate infusion [12]. When seeing propofol CSHT, the half-time for 3 h TCI using Marsh model is 8.6 min, while the half-time for 3 h constant rate infusion is 7.5 min. Both half-times after 3 h constant rate infusion are 7.5 min, suggesting that remimazolam and propofol may have similar concentration decay curve after stop of continuous infusion. In other words, remimazolam may have rapid offset profile similar to propofol. However, in the study showing remimazolam CSHT [10], remimazolam was infused over just 1 min. Another pharmacokinetic model of remimazolam developed using dataset obtained during general anesthesia might result in another CSHT profile.

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Electroencephalographic index

Assessment of the effect of remimazolam during anesthesia would be practical issue especially for the next years after the start of the distribution. Nowadays, we often use electroencephalographic (EEG) monitor to assess the effect of anesthetics, especially for intravenous anesthetic due to larger interindividual variability than inhalation anesthetic. Appropriate ranges of EEG indices for remimazolam anesthesia are unclear, the ranges may be higher, e.g., 60–70 of BIS index or 50–60 of patient state index [2]. The databases to develop the EEG indices do not include EEG data from patients under remimazolam anesthesia, currently. These EEG indices or alternative EEG derived values such as spectral edge frequency 95 would be expected to determine appropriate level of remimazolam for general anesthesia.

Pharmacokinetic/pharmacodynamic model for predicted concentration

To have remimazolam concentration to control anesthesia level, pharmacokinetic and pharmacodynamic models are useful. Although a pharmacokinetic model with a pharmacodynamic model has been published [10], the final pharmacokinetic model is not a compartment model but a recirculatory model. A compartment model of remimazolam for general anesthesia is desired with following reasons: (1) clinically available medical devices showing the predicted drug concentration use compartment models, (2) the external validity of the published pharmacokinetic model is unknown [13] for general anesthesia patients, because the pharmacokinetic model was developed using the dataset derived from patients who received only 1 min infusion of remimazolam. Population pharmacokinetic and pharmacodynamic models will help to make and assess dose regimens in clinical practice [14, 15].

Body weight for dose regimen

Body weight is generally considered to determine bolus dose or infusion rate of a drug. For remimazolam, a previous study concluded that “dosing by body weight may offer no advantage over fixed doses in terms of consistency of exposure to remimazolam within the weight range studied (65–90 kg).” [10] Here is issues whether body weight has no impact on pharmacokinetic profile on remimazolam. Rapid infusion of remimazolam like bolus may cause large variability of remimazolam concentration time course [16]. Large concentration variability may conceal the influence of

a covariate such as body weight on pharmacokinetic profile and pharmacokinetic parameters. On the other hand, there is a study suggesting little impact of body weight on plasma concentration of a drug, where a pharmacokinetic model excluding body weight as a covariate predicts plasma concentration better than other pharmacokinetic models which incorporate body weight as a covariate [17]. In thin and obese patients, body weight may have an impact on remimazolam concentration [18, 19]. The influence of body weight should be examined using the dataset derived from patients who receive continuous infusion of remimazolam for general anesthesia.

Hypotension: side effect of induction agent

Hypotension is frequently observed as a side effect during induction of anesthesia using propofol [20–22]. A phase I clinical trial for remimazolam revealed that a 1-min bolus infusion of remimazolam 0.01–0.30 mg/kg did not cause hypotension, which was defined as systolic blood pressure lower than 80 mmHg, except one occurrence of hypotension 8 h after the dose of remimazolam [2]. Although this clinical trial for remimazolam was performed in healthy subject, a current induction agent, propofol can cause hypotension at concentrations during induction in healthy subjects [23]. There may be less occurrence of hypotension by remimazolam than propofol in healthy patients. There is no published data for hypotension in poor risk patients for remimazolam.

Influence of hepatic and renal impairment

How is the pharmacokinetic alteration of remimazolam in patients with hepatic or renal impairment? Remimazolam is expected to have organ-independent elimination as the following pharmacokinetic profile [24]: (1) incorporation of carboxylic ester, which is metabolized by tissue esterase, (2) 300-times lower affinity of metabolized compound (CNS 7054, which is carboxylic acid) than remimazolam (CNS 7056) [2], and (3) full agonist. This is the translated concept from remifentanyl [24]. Accumulation is related issue for a large total dose or a long high-dose infusion of remimazolam. As the terminal phase half-life of the main metabolite, CNS 7054, is 3–5 times longer than that of remimazolam [2], CNS 7054 can accumulate. Although this metabolites 300-times lower affinity than remimazolam, large accumulation might cause sedation especially in patients with hepatic or renal impairment. Clinical studies are necessary in these specific situations.

Pediatric anesthesia

For total intravenous anesthesia in pediatric patients [25], remimazolam might be preferable because of less injection pain and no risk of propofol infusion syndrome. Propofol has an advantage to reduce laryngospasm and airway reactivity [26] but midazolam rarely cause laryngospasm [27]. The risk of emergence laryngospasm by remimazolam might be low due to rapid elimination profile. Survey of remimazolam anesthesia in pediatric patients to clarify the safety and efficacy is desired in the near future.

Procedural sedation

For procedural sedation in emergency department in Japan, thiopental and midazolam are frequently used [28]. As these drugs have large pharmacodynamic variability and long CSHT after a long infusion [11], remimazolam, which has shorter CSHT, would be preferable. In some countries, clinical trials for approval have been implemented [2, 10, 23]. Currently, procedural sedation with remimazolam is off-label in Japan, but the approval for that is expected.

Publications

Several animals studies [29–32] and clinical trials for the phase I to III studies [2, 10, 23, 33, 34] have been published so that we can access useful information for remimazolam. As published human studies are limited in volunteers and procedural sedated patients, clinical studies for remimazolam anesthesia are necessary.

Conclusion

A novel benzodiazepine, remimazolam, has been approved as a general anesthetic. Remimazolam was developed as a soft drug, which is designed to be active, easily transformed to inactive metabolites. Future clinical experiences and experiments will clarify the utility and profile.

Compliance with ethical standards

Conflict of interest Kenichi Masui, MD, PhD. wrote and approved the final manuscript. He is a consultant/advisor for, and has a research grant from Mundipharma K.K. He has had no involvement with the human studies of remimazolam.

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