Original Article

Up-down determination of the 90% effective dose (ED_{90}) of remimazolam besylate for anesthesia induction

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Background: Remimazolam besylate for injection is a novel benzodiazepine. Reasonable selection and proper application of anesthetics is critical for patients. This study aims to determine the 90% effective dose (ED_{90}) of remimazolam besylate for anesthesia induction in patients undergoing painless colonoscopy.

Methods: A dose-response study was carried out in 112 patients undergoing painless colonoscopy between December 2020 and January 2021. The initial dose of remimazolam was 7.5 mg. The anesthesiologist assessed whether the depth of sedation was satisfactory according to the Modified Observer's Assessment of Alertness and Sedation (MOAA/S) scale. If the MOAA/S score of one patient was >1 point, the loading dose for the next patient was increased by 2.5 mg. If the MOAA/S score was ≤1 point, the current dose was maintained or reduced by 2.5 mg for the next patient according to a 9:1 biased coin design. The ED_{90} of remimazolam besylate for anesthesia induction for painless colonoscopy was calculated. The adverse events and complications of remimazolam besylate were recorded.

Results: When the drug concentration was 1 mg/mL and the infusion rate was 1,000 mL/h, the ED_{90} of remimazolam besylate for painless colonoscopy was 11.43 mg [95% confidence interval (CI): 9.85–13.02 mg].

Conclusions: A loading dose of 12 mg remimazolam besylate for healthy adult patients undergoing painless colonoscopy can safely, effectively, and quickly induce patients to fall asleep and shorten the anesthesia induction time.

Keywords: Remimazolam; 90% effective dose (ED_{90}); painless colonoscopy; sedation; hypoxemia

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Introduction

Digestive tract endoscopy is the most commonly used and most reliable method for the diagnosis and treatment of digestive tract diseases, but it also brings varying degrees of pain and discomfort to patients. In clinical practice, general anesthetics such as propofol, midazolam, and opioids are often injected intravenously to relieve pain and discomfort, but this may lead to respiratory and circulatory depression (1-3). Remimazolam besylate for injection has a fast onset, short half-life, and rapid patient recovery, so it is an appropriate option for sedation during endoscopy (4). Additionally, remimazolam besylate for injection can largely avoid adverse reactions such as wide hemodynamic fluctuations, excessive sedation and injection pain caused by propofol (5). Although remimazolam has broad clinical application prospects, it still causes adverse reactions such as respiratory depression and circulation depression after

high-dose administration. Titrated administration is most often used, and the drug needs to be repeatedly added to make the patient fall asleep (6-8). As a result, it takes a long time for the patients to fall asleep, and the efficiency of painless colonoscopy is poor. The many patients in China who must wait before starting their colonoscopies and the physicians performing them are dissatisfied with this situation. It is necessary to determine the 90% effective dose (ED_{90}) for the anesthetic onset of the patient and provide the anesthesiologist with an accurate and optimal dosing plan in order to improve the efficiency of colonoscopies.

We present the following article in accordance with the MDAR reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-89/rc).

Methods

Patient data and inclusion criteria

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Hebei Hospital of Traditional Chinese Medicine (approval No. HBZY2020-KY-088-02). Patients signed an informed consent form. A total of 112 patients with American Society of Anesthesiologists physical status grade I–II, a body mass index (BMI) of 19–24 kg/m^2, and an age range of 18–65 years who planned to undergo painless colonoscopy in our hospital between December 2020 and January 2021 and underwent routine colonoscopy diagnosis and treatment were selected for this study.

Exclusion criteria: (I) patients with obvious respiratory or circulatory dysfunction, abnormal blood routine, or blood biochemical indicators. (II) Patients with severe neuropsychiatric disease. (III) Patients intermittently using benzodiazepines shortly before the examination. (IV) Patients who were allergic to or contraindicated for the drugs or their components used in this study. (V) Patients with suspected difficult airways.

Scoring criteria

Modified Observer's Assessment of Alertness and Sedation (MOAA/S) score: a score of 5 points was assigned when the patient was completely awake and responded readily to their name spoken; a score of 4 points was assigned when the patient showed a lethargic response to their name spoken; a score of 3 points was assigned when the patient responded after their name was called loudly and/or repeatedly; a score of 2 points was assigned when the patient only responded to mild pushing or shaking; a score of 1 point was assigned when the patient only responded to pain stimulation (trapezius squeeze); and a score of 0 points was assigned when the patient did not respond to pain stimulation (trapezius squeeze).

Study methods

All patients routinely abstained from drinking, fasted, and underwent intestinal preparation. Venous access was opened in the preparation room. Heart rate, blood pressure, and blood oxygen saturation (SpO_2) were monitored continuously. Oxygen was inhaled through the nasal cannula at a flow rate of 6 L/min. Remimazolam besylate (Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) was prepared as a 1 mg/mL solution using 0.9% sodium chloride for injection (Shijiazhuang No. 4 Pharmaceutical, Shijiazhuang, China) and was infused using an infusion pump (Shenzhen Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China) at a bolus rate of 1,000 mL/h. The initial anesthesia induction dose of intravenous remimazolam besylate for injection (Yichang Humanwell Pharmaceutical Co., Ltd.) was 7.5 mg (5). If the MOAA/S score of a patient after receiving the induction dose of remimazolam besylate was >1 point, the induction dose for the next patient was increased by 2.5 mg. If the MOAA/S score was ≤1 point, the current dose was maintained with a probability of 90% and reduced by 2.5 mg with a probability of 10% for the next patient. During the operation, the investigators added remimazolam besylate (2.5 mg each time) to maintain sedation if needed given the condition of the subject. If the intraoperative heart rate was <50/min, the patient was treated with 0.3 mg atropine. If the systolic blood pressure decreased by more than 30% from the baseline value or the investigators believed that medical intervention was needed, the patient was given 4 μg norepinephrine and the drug was administered repeatedly when necessary. If SpO_2 dropped below 90%, the patient was subjected to jaw support or face-masked pressure respiration. If the subject failed to recover to an MOAA/S score of 5 points 10 minutes after the end of the operation, the patient was treated with benzodiazepine antagonist flumazenil for antagonism.

Table 1 Demographic data

General information	Value
Case number	112
Sex, n (%)	
Male	57 (50.9)
Female	55 (49.1)
Age (years), mean ± SD	48.5±11.6
Height (cm), mean ± SD	163.6±12.9
Weight (kg), mean ± SD	67.6±12.5

SD, standard deviation.

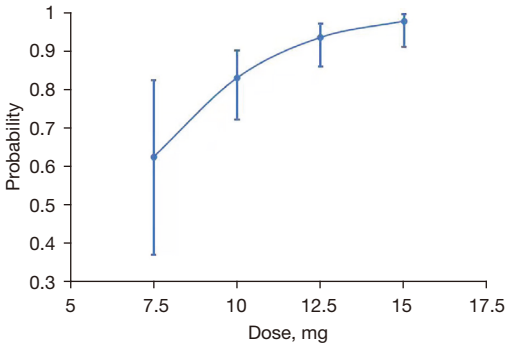

Figure 1 Anesthetic onset probabilities and 95% CIs at different doses. CI, confidence interval.

Table 2 Anesthetic onset raw numbers and probabilities at different doses

Dose (mg)	Onset (cases)	Not effective (cases)	Total	Onset probability (%)	95% CI lower bound (%)	95% CI upper bound (%)
7.5	9	3	12	62.50	37.26	82.38
10	15	6	21	82.95	72.12	90.15
12.5	60	3	63	93.42	85.92	97.06
15	16	0	16	97.64	90.95	99.42
Total	100	12	112	–	–	–

CI, confidence interval.

Observation indicators

The primary observation indicator was the dose of remimazolam besylate for injection from the beginning of drug administration through pump infusion to when the patient fell asleep (with an MOAA/S of ≤1 point). Secondary observation indicators included (I) the number of jaw support and the amount of vasoactive drugs and (II) adverse events during the procedure, including bucking, diaphragm spasm, nausea, vomiting, and injection pain.

Statistical analysis

Quantitative data are expressed as mean ± standard deviation (SD). Categorical data are expressed as the incidence rate for statistical description. The ED_{90} and 95% confidence interval (CI) of the dose of remimazolam besylate for anesthesia onset were calculated through Firth's logistic regression method. Data were statistically analyzed using the SAS 9.4 software.

Results

General characteristics

The general information of the patients, including age, sex, and body weight, is shown in *Table 1*.

Cases and probability of anesthesia onset

Out of the 112 patients, 12 patients did not achieve satisfactory sedation, so more drug was needed. The initial dose range for remimazolam besylate was between 7.5 and 15 mg (*Table 2*).

ED_{90}

Firth's penalized maximum likelihood estimator for logistic regression method showed that the ED_{90} of remimazolam besylate for injection for anesthesia induction was 11.43 mg (95% CI: 9.85–13.02 mg) (*Figure 1*).

Table 3 Adverse events during anesthesia

Adverse event	Cases
Cases of jaw support	0
Norepinephrine (μg)	0
Atropine (mg)	0
Bucking	0
Nausea	0
Vomiting	0
Diaphragm spasm	3
Injection pain	0

Adverse events

During the procedure, the vital signs of all the patients were stable, and vasoactive drugs were not used. None of the patients had jaw support, bucking, nausea, vomiting, or injection pain. Three patients had diaphragm spasm (*Table 3*).

Discussion

Colonoscopy is widely used in the diagnosis and treatment of colon diseases (1). With the continuous improvement of the economic level, the patient's demand for comfortable medical treatment continues to increase, and painless endoscopy has become a trend. Currently, propofol or benzodiazepines (which can be combined with opioids) are commonly used for sedation in endoscopy (9). Propofol not only has a fast onset, short action time, and quick recovery but can also prevent postoperative nausea and vomiting. However, propofol has a significant impact on the hemodynamics of patients and has the disadvantages of injection pain and obvious respiratory and circulatory depression (10,11). Furthermore, the elimination half-life of most benzodiazepines is long, which prevents patients from recovering their normal cognitive level within a short time after the end of a colonoscopy. Remimazolam besylate is safe, effective and controllable. Now more and more attention has been paid to the application of remimazolam besylate in the induction and maintenance of general anesthesia. Remimazolam is a novel type of benzodiazepine that has a fast onset of sedation, has a short maintenance and recovery time, and can be quickly hydrolyzed by tissue esterase into a metabolite with minimal activity. Remimazolam does not accumulate and does not rely on liver or kidney function for its metabolism. Therefore, remimazolam besylate for injection can be used safely and effectively in colonoscopies for diagnosis and treatment (12).

The pharmacokinetics of remimazolam is linear. Within the body weight range of 60–100 kg, there is no clear relationship between body weight and systemic remimazolam clearance, and the difference between drug administration according to body weight and fixed-dose administration is not statistically significant (13). To simplify our protocol, we administered remimazolam at a fixed dose. ED_{50} refers to the effective dose covering 50% of the patients. Anesthesiologists generally infer the more clinically valuable effective dose ED_{90} and the effective dose covering 90% of the patients based on ED_{50}. Therefore, ED_{90} has more guiding significance for clinicians to use drugs. The ED_{90} can accurately reflect the dose-effect relationship of the drug. The sequential method is a classic method for calculating ED_{90} in clinical practice, and this method is simple and effective and requires a small sample size (14).

When 2 points ≤ MOAA/S score ≤3 points, the patient often moves or frowns when the colonoscope is inserted. Therefore, our study used an MOAA/S score ≤1 point as the effective sedation score. The initial dose of remimazolam besylate was set to 7.5 mg. We calculated that the ED_{90} of remimazolam besylate for anesthesia induction for painless colonoscopy was 11.43 mg (95% CI: 9.85–13.02 mg). The current recommended loading dose of remimazolam besylate is 7 mg. When the loading dose has all been added, 2.5 mg remimazolam besylate can be added every 2 minutes as needed. However, our calculated ED_{90} of remimazolam besylate was 63% higher than this loading dose. It can also be seen from *Table 2* that the anesthesia onset probability of 7.5 mg was only 62.5%. Therefore, approximately 1/3 of the patients would have difficulty falling asleep according to the current recommended dose, so it would be necessary to add more drug every 2 minutes. As a result, it would take a long time for the patient to fall asleep, lowering the efficiency of colonoscopy and reducing the satisfaction of patients and physicians.

In this study, we did not observe any severe adverse events, including respiratory depression, hypotension, nausea, and vomiting, though 3 of the 112 patients had diaphragm spasm after drug administration. Although the diaphragm spasm was transient and did not require additional treatment, it had some negative impact on colonoscopy, and sometimes the operation needed to be paused, which affected the efficiency. Further clinical

investigation is needed to reduce such problems. This study showed that patients recovered quickly after flumazenil antagonism, significantly reducing the risk.

This study only included healthy adult patients but not elderly patients. Future studies should determine the drug dose needed for elderly patients.

In summary, our study showed that the ED_{90} of remimazolam besylate was 11.43 mg (95% CI: 9.85–13.02 mg) for painless colonoscopy when the drug concentration was 1 mg/mL and the infusion rate was 1,000 mL/h. The best dose of remimazolam besylate to fall asleep was 12 mg. It is a safe and reliable method to maintain additional drugs according to sedation score during operation. We recommend that the anesthesiologist use 12 mg as the loading dose for adult patients for painless colonoscopy to safely, effectively, and rapidly induce sedation in patients undergoing colonoscopy, shortening the anesthesia induction.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-89/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-22-89/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-89/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Hebei Hospital of Traditional Chinese Medicine (approval No. HBZY2020-KY-088-02). Patients signed an informed consent form.

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