

# Interactions Between Remimazolam and Propofol in Combination With Sufentanil for Anesthesia During Gastroscopy

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## Research Article

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# Abstract

## Background

This study was conducted to determine how remimazolam and propofol interact when given with sufentanil.

## Methods

In this single-arm study, patients were assigned to one of five groups. The sample size was not determined in advance. When the median effective dose ( $ED_{50}$ ) and 95% confidence intervals were calculated, participants were stopped. The study included 159 patients who were scheduled for a gastrointestinal endoscopic examination and had an American Society of Anesthesiologists physical status of I/II. Patients were intravenously administered sufentanil (0.1  $\mu\text{g}/\text{kg}$ ), along with different doses of remimazolam and propofol depending on the group to which they were assigned. The endpoint for an effective response was the disappearance of the bilateral eyelash reflex. The up-and-down method was used to determine the  $ED_{50}$  within each treatment group. The  $ED_{50}$  deviations from the additive line were analyzed using isoradiometric analysis. The interaction coefficients were calculated by algebraic analysis. Interval estimation is used in statistical inference.

## Results

In combination with sufentanil, the  $ED_{50}$  of remimazolam and propofol was determined to be 0.065 (0.057-0.074) mg/kg and 0.657 (0.590-0.724) mg/kg, respectively. After sufentanil administered, when 0.25, 0.5, and 0.75  $ED_{50}$  remimazolam were given in combination with propofol, the interaction coefficients were 1.03, 1.2 and 1.08, respectively.

## Conclusions

The dose of propofol with remimazolam may need to be reduced regardless of the additive or synergistic effect. There was a strong synergistic effect when the dose ratio of the two drugs was about 6:1 in mg/kg.

## Trial registration:

The project was retrospectively registered on October 26, 2021 in Chinese clinical trial center with the registration number of ChiCTR2100052425.

## Background

Remimazolam, a novel short-term sedative and anesthetic benzodiazepine, is effective and safe; however, it is metabolized faster than midazolam [1]. Midazolam acts synergistically with propofol in inducing anesthesia [2, 3]. Synergistic effects have been reported when midazolam and propofol were used in combination with alfentanil [4]. Sufentanil is a commonly used analgesic in gastroscopy [5]. The duration of gastrointestinal endoscopy is short, which is convenient to observe drug effects and potential adverse reactions.

Rememazolam, currently used as painless gastroenteroscopy anesthetic, can be possibly used in combination with propofol and potent opioids for anesthesia induction in other clinical conditions. To use drugs accurately, we need to see if there is any synergy between remimazolam and propofol, and if so, what the synergy coefficient is.

## Methods

We intend to evaluate the interaction between remimazolam and propofol when combined with sufentanil by isoradiometric analysis. To minimize the discomfort of patients, we believe that the disappearance of eyelash reflex is the endpoint of anesthesia induction [6]. Before inserting the endoscope, propofol was given immediately to deepen the anesthesia according to the ongoing examination or operation.

## Patients

The study was approved by the Clinical Investigation Committee of Hainan Medical University's Second Affiliated Hospital. The up-and-down method can significantly reduce the number of subjects required for the study [7, 8]. The sample size was not determined in advance because this was an adaptive clinical study, and it was adjusted based on certain criteria. [9] When the  $ED_{50}$  and 95% confidence intervals were calculated, participants were stopped.

Patients were excluded from the study if they had: 1. anemia (hemoglobin < 90 g/L), 2. albumin levels < 30 g/L, 3. platelet count <  $50 \times 10^9$  /L, 4. anticipated difficult airway, 5. obvious respiratory or circulatory dysfunction before the procedure, 6. severe neuropsychiatric disease, 7. allergies or contraindications for the use of benzodiazepines, opioids, propofol, flumazenil, naloxone or other drugs and their components, and 8. taken similar drugs recently.

Patients who had an American Society of Anesthesiologists physical status of I/II and were scheduled for gastrointestinal endoscopy were included in the study, and they all gave their informed consent.

## Intervention and Measurements

Patients were assigned to group A (administered remimazolam in combination with 0.1  $\mu\text{g}/\text{kg}$  sufentanil), B (administered propofol in combination with 0.1  $\mu\text{g}/\text{kg}$  sufentanil), C (administered propofol in combination with 0.1  $\mu\text{g}/\text{kg}$  sufentanil and 0.25 median effective dose ( $ED_{50}$ ) remimazolam), D

(administered propofol in combination with 0.1 µg/kg sufentanil and 0.5 ED<sub>50</sub> remimazolam), or E (administered propofol in combination with 0.1 µg/kg sufentanil and 0.75 ED<sub>50</sub> remimazolam).

An intravenous line was secured in the waiting area. The patient's blood pressure, electrocardiogram, and oxygen saturation were monitored after entering the endoscopy suite. The administration time was determined based on the results of a pretest.

The patients were intravenously administered 0.1 µg/kg sufentanil (01A10011, Sichuan Renfu, China) over 10 s, and the cannula was flushed with saline (5 mL). After 90 seconds, the drug was administered according to the dose required by the grouping.

Remimazolam (201114AK, Jiang Su Heng Rui, China) was diluted to 0.5 mg/mL with normal saline. A dose-proportional to the patient's body weight was administered intravenously over 10 s, and the cannula was flushed with 5 mL normal saline.

Propofol (2011171, Si Chuan Guor Rui, China) was diluted to 1, 2, and 10 mg/mL with normal saline and was administered 20 s after the administration of remimazolam. The observation time was 1 min after the administration of propofol.

To minimize any discomfort to patients, the disappearance of the eyelash reflex was considered the endpoint for anesthesia induction. Propofol was given shortly before endoscopy to deepen the anesthesia based on the procedure.

For the up-and-down method [10], the first patient in a group was administered a dose of the drug that was close to the ED<sub>50</sub>. If the first patient lost consciousness, the second patient was administered a smaller dose; if the first patient did not lose consciousness, the second was given a higher dose. As the procedure was repeated with more patients, the mean of the doses administered tended towards the ED<sub>50</sub> value. According to references [11] and pre-experimental results, the increment/decrement ratio was determined to be 1:0.8.

## Statistical analysis

Age and weight are presented as medians and interquartile ranges. Using SPSS version 22 (IBM Corporation, USA), the ED<sub>50</sub> and 95% confidence intervals were calculated by probit regression analysis [10]. Interval estimation is used in statistical inference.

The statistical significance of ED<sub>50</sub> deviation from the additive line was analyzed using isoradiometric analysis. The equation of the additive line was obtained using the ED<sub>50</sub> values of remimazolam (0.065 mg/kg) and propofol (0.657 mg/kg) (Fig. 1). This was calculated as:  $Y = -10.108x + 0.657$ .

The lower limits of the 95 % CIs of the ED<sub>50</sub>s of remimazolam (0.057 mg/kg) and propofol (0.59 mg/kg) were used to calculate the lower limit of the additive line's 95% CI. The equation for this was found to be:  $Y = -10.351x + 0.59$ .

The upper limits of the 95% CIs of the ED<sub>50</sub>s of remimazolam (0.074 mg/kg) and propofol (0.724 mg/kg) were used to calculate the upper limit of the 95% CI additive line. The equation for this was found to be:  $Y = -9.7838x + 0.724$ .

The interaction coefficients were calculated by algebraic analysis.

## Results

A total of 159 patients were included in the study based on the inclusion and exclusion criteria. The number of patients in group A-E was 27, 34, 29, 39, and 28 respectively. There were no significant differences in the age and weight of patients in the five groups (Table I).

**Table I.** Dose gradients of remimazolam and propofol and patients' baseline characteristics.

Group	Remimazolam (mg/kg)	Propofol (mg/kg)	n	No eye opening	Age [y, Q2(IQR)]	Weight [kg, Q2(IQR)]
A	0.1	0	2	2	54(17)	57(14)
	0.08	0	6	5		
	0.064	0	12	7		
	0.051	0	7	0		
B	0	0.9	5	5	51(17.5)	61(21)
	0	0.72	14	10		
	0	0.58	12	3		
	0	0.46	3	0		
C	0.016	0.62	7	7	53.5(13.8)	55.5(17.5)
	0.016	0.49	13	6		
	0.016	0.39	7	2		
	0.016	0.32	2	0		
D	0.033	0.31	2	2	50.5(20.8)	57.3(14)
	0.033	0.25	9	8		
	0.033	0.20	15	9		
	0.033	0.16	11	2		
	0.033	0.13	2	0		
E	0.049	0.15	6	6	51.5(16.8)	60(15.5)
	0.049	0.12	12	6		
	0.049	0.10	8	3		
	0.049	0.08	2	0		

Patients in group A were administered remimazolam in combination with 0.1 µg/kg sufentanil to determine the ED<sub>50</sub> of remimazolam in this combination. Intra-group remimazolam efficacy measurements were carried out with a 1:0.8 increments/decrement ratio. In the pretest, the ED<sub>50</sub> of remimazolam was estimated to be 0.08 mg/kg; hence, this was taken as the intermediate dose. Doses of

0.125, 0.1, 0.08, 0.064, and 0.051 mg/kg were chosen for evaluation (Table 1). The ED<sub>50</sub> of remimazolam was found to be 0.065 mg/kg (CI: 0.057–0.074 mg/kg) in combination with 0.1 µg/kg sufentanil.

Patients in group B were administered propofol in combination with 0.1 µg/kg sufentanil for the determination of propofol ED<sub>50</sub> in this combination. Naguib and coworkers reported that propofol has an ED<sub>50</sub> value of 0.9 mg/kg in this combination [12]. Based on these data and using the 1:0.8 increment/decrement ratio, the selected doses of propofol were 1.41, 1.13, 0.9, 0.72, 0.58, and 0.46 mg/kg (Table 1). The ED<sub>50</sub> of propofol was found to be 0.657 mg/kg (CI: 0.59–0.724 mg/kg) when used in combination with 0.1 µg/kg sufentanil (Fig. 1).

The ED<sub>50</sub> of propofol was determined in groups C-E using the same method as group B. Thus, the ED<sub>50</sub> of propofol in combination with 0.1 µg/kg sufentanil and doses of 0.25, 0.5, and 0.75 ED<sub>50</sub>s of remimazolam were evaluated.

Group C patients were administered 0.1 µg/kg sufentanil, 0.25 ED<sub>50</sub> (0.016 mg/kg) remimazolam, and varying propofol doses. The propofol 0.75 ED<sub>50</sub> (0.49 mg/kg) was chosen as the central point. The propofol ED<sub>50</sub> value was 0.476 mg/kg (CI: 0.411–0.545 mg/kg)

Group D patients were administered 0.1 µg/kg sufentanil, 0.5 ED<sub>50</sub> (0.033 mg/kg) remimazolam, and varying propofol doses. The 0.5 The ED<sub>50</sub> of propofol (0.25 mg/kg) was used as the central point. The propofol ED<sub>50</sub> value was 0.194 mg/kg (CI: 0.171–0.217 mg/kg).

Group E patients were administered 0.1 µg/kg sufentanil, 0.75 ED<sub>50</sub> (0.049 mg/kg) remimazolam, and varying propofol doses. The 0.25 The ED<sub>50</sub> of propofol (0.15 mg/kg) was used as the central. The propofol ED<sub>50</sub> value was 0.114 mg/kg (CI: 0.095–0.132 mg/kg).

An isoradiometric diagram (Fig. 2) and algebraic analysis (Table X) showed that the synergistic coefficients of remimazolam and propofol were 1.03, 1.26, and 1.08 with doses of remimazolam equivalent to 0.25, 0.5, and 0.75 ED<sub>50</sub>s, respectively, in combination with sufentanil (0.1 µg/kg). The synergy coefficient of group E was 1.08, but the 95% CI of the propofol dose was within the 95% CI of additive action (Fig. 2).

**Table II.** Interactions of remimazolam and propofol, in combination with 0.1 µg/kg sufentanil, evaluated through observation of eyelash reflex inhibition.

Group	Remimazolam		Propofol		Coefficient sum	Expected value of additive action	Interaction coefficient
	ED50 coefficient	ED50 (mg/kg)	ED50 coefficient	ED50 (mg/kg)			
A	1	0.065 (0.057-0.074)	0	0	1	1	1
B	0	0	1	0.657 (0.590-0.724)	1	1	1
C	0.25	0.016	0.725	0.476 (0.411-0.545)	0.975	1	1.03 (p=0.154)
D	0.5	0.033	0.295	0.194 (0.171-0.217)	0.795	1	1.20 (p=0.000)
E	0.75	0.049	0.174	0.114 (0.095-0.132)	0.924	1	1.08 (p=0.000)

The table shows median effective dose (ED50) equivalent doses of remimazolam and propofol in combination with 0.1 µg/kg sufentanil.

## Discussion

Drug synergism is attributed to pharmacodynamic or pharmacokinetic interactions [13]. When 0.5ED<sub>50</sub> remimazolam was combined with propofol, it produced a synergistic effect in group D. As the metabolic pathways of remimazolam and propofol are different, there is no metabolic interference, suggesting that this synergy occurs after the two drugs bind to the receptor.

Remimazolam and propofol showed an additive effect only in groups C and E. At 0.25ED<sub>50</sub>, the plasma drug concentration of remimazolam or propofol was near the threshold concentration. Since both the drugs metabolize rapidly, the effects were short-lived. Before the synergistic effect can be observed, the drug will be eliminated. The occupied receptor is less and the efficacy is weakened, so it only shows additive effect.

The interaction coefficient of the combination was the highest at a dose equivalent to 0.5 ED<sub>50</sub> of remimazolam. As shown in Table 2, the dose of remimazolam divided by the dose of propofol in group D is about 1:6. This implies that there is a synergistic effect when the dose ratio of remimazolam and propofol is about 1:6 mg/kg.

Table 2

Interactions of remimazolam and propofol, in combination with 0.1 g/kg sufentanil, evaluated through observation of eyelash reflex inhibition.

<b>Table 1. Dose gradients of remimazolam and propofol and patients' baseline characteristics.</b>						
Group	Remimazolam (mg/kg)	Propofol (mg/kg)	n	No eye opening	Age [y, Q2(IQR)]	Weight [kg, Q2(IQR)]
A	0.1	0	2	2	54(17)	57(14)
	0.08	0	6	5		
	0.064	0	12	7		
	0.051	0	7	0		
B	0	0.9	5	5	51(17.5)	61(21)
	0	0.72	14	10		
	0	0.58	12	3		
	0	0.46	3	0		
C	0.016	0.62	7	7	53.5(13.8)	55.5(17.5)
	0.016	0.49	13	6		
	0.016	0.39	7	2		
	0.016	0.32	2	0		
D	0.033	0.31	2	2	50.5(20.8)	57.3(14)
	0.033	0.25	9	8		
	0.033	0.20	15	9		
	0.033	0.16	11	2		
	0.033	0.13	2	0		
E	0.049	0.15	6	6	51.5(16.8)	60(15.5)
	0.049	0.12	12	6		
	0.049	0.10	8	3		
	0.049	0.08	2	0		

According to group D data in Table 2, the synergy coefficient is 1.25. It can be understood that if a patient changes from the original propofol requirement of 1 mg/kg to combined medication, the same effect can

be achieved with only 0.3 mg/kg propofol with 0.05 mg/kg remimazolam.

As there were other adjacent dose ratios, this may lead to a stronger synergy. Therefore, further experiments are required to probe the effects of adjacent dose ratios. The disappearance of the eyelash reflex is only one of the common endpoints in clinical anesthesia. The interaction of other clinical endpoints needs to be further studied and determined. The occurrence of side effects also need be observed simultaneously.

## **Conclusions**

The dose of propofol with remimazolam may need to be reduced regardless of the additive or synergistic effect. There was a strong synergistic effect when the dose ratio of the two drugs was about 6:1 in mg/kg.

## **Declarations**

### **Ethics approval and consent to participate**

The study was approved by the Clinical Investigation Committee of Hainan Medical University's Second Affiliated Hospital (number/ID was LW2021001). All participants signed informed consent. All methods were performed in accordance with the relevant guidelines and regulations.

### **Consent for publication**

“Not applicable”

### **Availability of data and materials**

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### **Competing interests**

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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### **Authors' contributions**

Song Lyu and Qingchun Deng contributed equally to the preparation of this manuscript. They have given substantial contributions to the conception or the design of the manuscript, analysis and interpretation of the data. All authors have participated to drafting the manuscript. All authors read and approved the final version of the manuscript.

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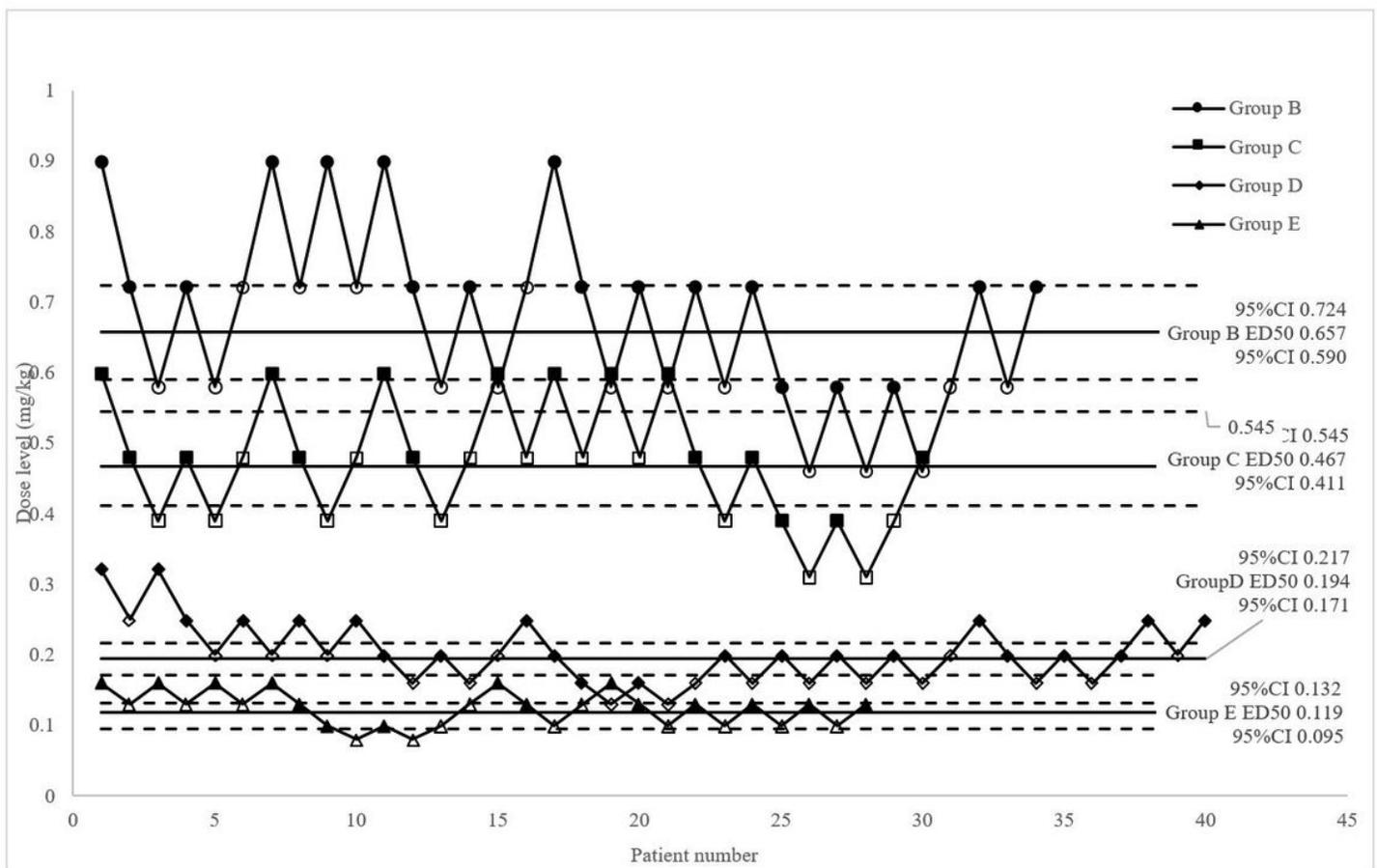
Participating Investigator: The authors acknowledge Hu Sun who served as scientific advisor.

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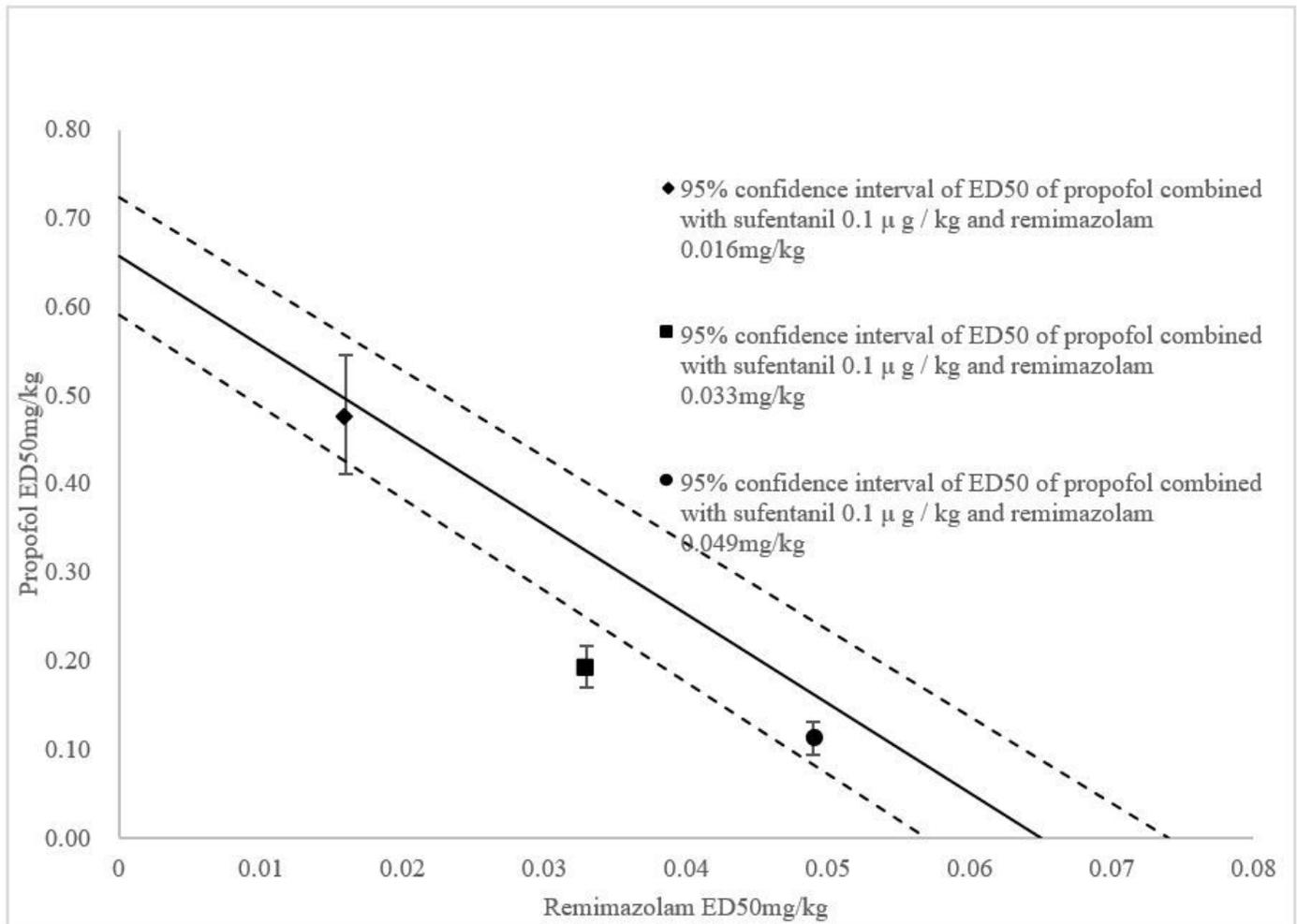
## Figures



**Figure 1**

Determination of the median effective dose (ED<sub>50</sub>) of propofol in combination with 0.1 µg/kg sufentanil and varying doses (0, 0.049, 0.033, 0.016 mg/kg) of remimazolam. The patient sequence number (x-axis) is the order in which patients were administered the dose as per the up-and-down design. ● Group B assigned doses (y-axis) were 0.62, 0.49, 0.39, and 0.32 mg/kg propofol. ■ Group C assigned doses (y-axis) were 0.9, 0.72, 0.58, and 0.46 mg/kg propofol. ◆ Group D assigned doses (y-axis) were 0.62, 0.49,

0.39, and 0.32 mg/kg propofol. ▲ Group E assigned doses (y-axis) were 0.31, 0.25, 0.20, 0.16, and 0.13 mg/kg propofol. ●■◆▲ Effective dose (disappearance of bilateral eyelash reflex observed); ●□◇△ ineffective dose; — ED50; - - 95% confidence interval of ED50.



**Figure 2**

Isotherms of the interactions between remimazolam and propofol when administered in combination with 0.1 µg/kg sufentanil. Remimazolam 0.065 mg/kg (0.057-0.074 mg/kg) and propofol 0.657 mg/kg (0.59-0.724 mg/kg) were used to calculate the equation of the additional line and the 95% confidence interval lines. The x-axis represents the remimazolam dose with 0.1 g/kg sufentanil, while the y-axis shows the propofol ED50 at this remimazolam dose.