Interactions of propofol and remifentanil on bispectral index under 66% N₂O: analysis by dose-effect curve, isobologram, and combination index

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Background: Propofol and remifentanil are usually co-administered and have shown synergistic effect for anesthesia. However, the synergistic effect of the two drugs on hypnosis measured by bispectral index (BIS) was controversial in previous studies. The aim of this study was to identify the interaction of propofol and remifentanil on BIS and the optimal dose combinations for hypnosis under 66% N₂O during surgery.

Methods: Patients (age 55–75 and American Society of Anesthesiologists [ASA] 1–2) undergoing gastrectomy were enrolled in this study. Propofol and remifentanil were co-administered incrementally at 1 : 1 potent ratio (the P1R1 group), at 1 : 2 potent ratio (the P1R2 group), or at 2 : 1 potent ratio (the P2R1 group) using effect site target-controlled infusion and BIS was measured. 66% N₂O was concomitantly administered to all groups. The dose-effect curves, the 90% effective dose (EC₉₀) for adequate hypnosis (BIS 40), isobolograms and combination index were obtained by Calcusyn program (Biosoft) to reveal the interaction of propofol and remifentanil.

Results: The P2R1 group showed synergistic action on BIS. However, the other groups needed larger amount of each drug than the doses of additive action. The EC₉₀ of the P2R1 group was propofol, 3.34 µg/ml and remifentanil, 2.41 ng/ml under 66% of N₂O.

Conclusions: Propofol dominant co-administration is needed for dose reduction in BIS guided hypnosis. (Korean J Anesthesiol 2010; 59: 371-376)

Key Words: Bispectral index, Isobologram, Propofol, Remifentanil, Synergies.
Introduction

Propofol and remifentanil are commonly co-administered in intravenous anesthesia and have shown a synergistic effect [1,2]. However, reports on hypnotic interaction between propofol and remifentanil measured by bispectral index (BIS) have been a few and contradictory [3-7].

The combination index (CI), dose-effect curve and isobologram have been used in many biomedical studies to evaluate drug interactions and to determine the optimal doses of combined injection [8-10]. However, there have been few studies employing these parameters to analyze the interactions of propofol and remifentanil.

Therefore, in this study, we determined the interaction of the two drugs on BIS and the best hypnotic dose combinations using dose-effect curve, isobologram, and CI on patients undergoing a gastrectomy.

Materials and Methods

This study was approved by the hospital ethics committee and informed consent was obtained from the patients. Patients undergoing an open gastrectomy were randomly assigned by sealed envelope technique into the propofol : remifentanil 1 : 1 potent ratio (P1R1) group (n = 20), the propofol : remifentanil 1 : 2 potent ratio (P1R2) group (n = 20) and the propofol : remifentanil 2 : 1 potent ratio (P2R1) group (n = 20). The inclusion criteria were American Society of Anesthesiologists (ASA) 1 or 2 patients between the ages of 55 and 75. The exclusion criteria were patients with severe cardiovascular, renal, hepatic, or neuropsychiatric diseases, and a history of addiction or allergic reactions to opioids and sedatives. Patients and an anesthesiologist evaluating the BIS were blinded to the group assignment. Modulation of the infusion pump was unaffected by the dose of drug 1 and 2, fu = 1 - fa, m: an exponent signifying the sigmoidicity (shape) of the dose-effect curve.

CI = (D)1/(Dx)1 + (D)2/(Dx)2

Where (D)1, (D)2: the dose of drug 1 and 2, (EC50)1, (EC50)2: the median-effect dose of drug 1 and 2, (fa)1,2: the fraction affected by the dose of drug 1 and 2, (fu)1,2: the fraction unaffected by the dose of drug 1 and 2, fu = 1 - fa, m: an exponent signifying the sigmoidicity (shape) of the dose-effect curve.

The CI shows the type of interaction of the combined drugs. Usually, a CI in the range of 0.9 and 1.1 is considered to be an additive action. A CI < 0.9 and CI > 1.1 indicate synergism and antagonism, respectively.

The isobologram is a convenient graphical display, in which equipotent pairs of the doses of two drugs are connected by
a line, which represents the additive activity between the two drugs. Synergism or antagonism was considered to exist between the two drugs if the dose of the combined drugs was lower or higher than this line, respectively [8].

Data analysis

The primary outcome variable was the difference in the CI at EC90 between the three groups. The expected differences in means were set at 0.5 with an expected standard deviation of 0.5. A sample size of 20 in each group was required to achieve a power of 80% with an alpha error of 0.05. A z-test with Bonferroni’s correction was carried out to compare the CI in the three groups. The comparisons of the effect site concentrations between the co-administration groups were performed by One way analysis of variance or Kruskal-Willis one way analysis of variance according to the normality of the data. A P value < 0.05 was considered significant.

Results

No differences in demographic data were evident among the three groups (Table 1).

| Table 1. Demographic Data |
|---------------------------|
| Group       | P1R1 | P1R2 | P2R1 |
| Age (yr)    | 63.1 ± 6.0 | 65.9 ± 6.1 | 65.1 ± 5.4 |
| Weight (kg) | 63.9 ± 10.6 | 63.6 ± 9.3 | 62.4 ± 11.9 |
| Height (cm) | 163.7 ± 6.9 | 162.8 ± 7.4 | 162.0 ± 8.8 |
| Sex (M/F)   | 16/4 | 16/4 | 16/4 |
| Duration of anesthesia (min) | 169.5 ± 25.6 | 165.6 ± 32.2 | 192.2 ± 52.7 |
| Duration of operation (min)  | 144.1 ± 21.9 | 138.5 ± 26.3 | 164.5 ± 47.3 |

Values are mean SD or number of patients. There were no differences between the groups. P1R1: propofol : remifentanil 1 : 1 potency, P1R2: propofol : remifentanil 1 : 2 potency, P2R1: propofol : remifentanil 2 : 1 potency, M: male, F: female.

Mean blood pressure and heart rate were lower in the P1R2 group compared to the other groups (Fig. 1).

Each effect site concentration and the corresponding BIS in the three groups were shown in the Table 2.

In our study, synergism is defined better efficacy than a simple additive action shown in isobologram and CI < 0.9. In this regard, only the P2R1 group showed synergism. Higher effect site concentration of each drug than that in additive action was needed in other dose combinations (Table 3, Fig. 2–4).

The EC90 of the P2R1 group was propofol, effect site concentration 3.34 μg/ml and remifentanil, effect site concentration 2.41 ng/ml under 66% N2O (Table 3, Fig. 3).

Discussion

Most previous studies used arbitrary chosen dose combinations of propofol and remifentanil [3-7]. We used propofol and remifentanil 1 : 1, 1 : 2, and 2 : 1 ratio combinations based on

| Table 2. The Effect Site Concentration and BIS |
|-----------------------------------------------|
| Group       | P1R1 | P1R2 | P2R1 |
| Propofol EC | 0.3  | 0.7  | 1.3  | 2.0  | 2.6  |
| Remifentanil EC | 0.5 | 1.0  | 1.9  | 2.9  | 3.9  |
| BIS          | 71.3 | 68.9 | 61.3 | 54.1 | 46.6 |

Values are mean. BIS: bispectral index, P1R1: propofol : remifentanil 1 : 1 potency, P1R2: propofol : remifentanil 1 : 2 potency, P2R1: propofol : remifentanil 2 : 1 potency, EC: effect site concentration.
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To find out whether propofol or remifentanil is dominant co-administration or the same potent co-administration of each drug would be more synergistic. Most previous studies also did not include N₂O in their studies, however, N₂O is routinely administered in our institution and in many others during propofol and remifentanil anesthesia. To reflect clinical practice, we administered 66% N₂O simultaneously.

In this study, the P₂R₁ group was found to be the most effective combination for adequate hypnosis measured by BIS and the effect site concentration at EC₉₀ was propofol, 3.34 μg/ml and remifentanil, 2.41 ng/ml under 66% N₂O.

In general, most studies on the co-administration of propofol and remifentanil have reported synergism. They used the clinical responses, such as Observer Assessment of Alertness/Sedation, autonomic, hemodynamic, or somatic responses to various stimuli as a potency measurement of the combined drugs [1,2,14,15].

The studies regarding the interactions of propofol and remifentanil on the BIS showed controversial results. Strachan and Edwards [3], Koitabashi et al. [4], and Röpcke et al. [5] showed the dose-dependent decrease in the BIS or a decrease in the propofol requirements to maintain a certain BIS with increasing remifentanil concentrations and presented them as evidence of synergism. On the contrary to above reports, Lysakowski et al. [16] and Guignard et al. [7] found that the relationship between propofol effect-site concentration and BIS was preserved with or without opioids. Wang et al. [6] also found that an infusion of remifentanil did not reduce the propofol requirements.

In our study, the addition of remifentanil reduced the propofol

Table 3. EC₅₀, EC₉₀, CI, and DRI

|               | EC₅₀       | EC₉₀       | CI          | EC₅₀       | EC₉₀       |
|---------------|------------|------------|-------------|------------|------------|
| Single drug   |            |            |             |            |            |
| Propofol      | 1.34 (0.98–1.82) | 4.73 (3.75–6.03) |             |            |            |
| Remifentanil  | 1.93 (1.52–2.45)   | 12.93 (10.93–14.74) |             |            |            |
| Group P₁R₁    |            |            |             |            |            |
| Propofol      | 0.50 (0.27–0.93)*  | 4.16 (3.00–5.40)   | 0.75 (0.25)†   | 1.34 (0.66) |
| Remifentanil  | 0.72 (0.42–1.27)*  | 5.99 (4.66–8.49)*  | 0.94 (0.19)    | 1.29 (0.37) |
| Group P₁R₂    |            |            |             |            |            |
| Propofol      | 0.42 (0.30–0.59)*  | 2.97 (2.01–3.80)*  | 0.99 (0.40)    | 0.89 (0.22)† |
| Remifentanil  | 1.21 (0.80–1.85)*  | 8.56 (6.80–10.36)* |             |            |            |
| Group P₂R₁    |            |            |             |            |            |
| Propofol      | 0.89 (0.42–1.85)   | 3.34 (2.02–4.20)*  |             |            |            |
| Remifentanil  | 0.64 (0.34–1.18)*  | 2.41 (1.41–3.32)*  |             |            |            |

Values are mean (95% confidence limit) or (SD). EC₅₀: Median effective dose, EC₉₀: 90% effective dose, CI: combination index. P₁R₁: propofol : remifentanil 1 : 1 potency, P₁R₂: propofol : remifentanil 1 : 2 potency, P₂R₁: propofol : remifentanil 2 : 1 potency. *P < 0.05 compared to the single drug administration. †P < 0.05 compared to the P₁R₂ and P₂R₁ groups, ‡P < 0.05 compared to the P₁R₁ and P₁R₂ groups.

Fig. 2. The dose-effect curve of propofol of the P₁R₁, P₁R₂, and P₂R₁ groups. The effect site concentration of propofol in the P₁R₁, P₁R₂, and P₂R₁ groups and the hypnotic effect are shown as the X and Y axes, respectively. The P₂R₁ group required the lowest effect site concentration of propofol for EC₉₀. P₁R₁: propofol : remifentanil 1 : 1 potency, P₁R₂: propofol : remifentanil 1 : 2 potency, P₂R₁: propofol : remifentanil 2 : 1 potency, EC₉₀: 90% effective dose.

Fig. 3. The dose-effect curve of remifentanil of the P₁R₁, P₁R₂, and P₂R₁ groups. The effect site concentration of remifentanil in the P₁R₁, P₁R₂, and P₂R₁ groups and the hypnotic effect are shown as the X and Y axes, respectively. The P₂R₁ group required the lowest effect site concentration of remifentanil for EC₉₀. P₁R₁: propofol : remifentanil 1 : 1 potency, P₁R₂: propofol : remifentanil 1 : 2 potency, P₂R₁: propofol : remifentanil 2 : 1 potency, EC₉₀: 90% effective dose.
we administered 66% N₂O to all groups to reflect our clinical practice. There have been controversies regarding the effect of N₂O on BIS. Some insisted that N₂O up to 70% does not affect the BIS [19]. However, addition of N₂O to propofol and remifentanil co-administration deepened anesthesia and prevented movement without affecting BIS [20]. In the contrary, others demonstrated significant changes on BIS by N₂O [21]. Therefore, N₂O might have influenced our results, however, with keeping the N₂O concentrations similar among three groups, the focus of our study-interaction of propofol and remifentanil on BIS is still considered valid.

In conclusion, the propofol dominant-infusions are recommended for a BIS guided hypnosis and the addition of high dose-remifentanil might not result in synergistic dose reduction on BIS guided anesthesia.

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