Median effective concentration of remifentanil for the inhibition of laryngoscope-induced cardiovascular responses

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Abstract. The aim of this study was to calculate the median effective concentration (EC_{50}) of remifentanil (Rem) for the inhibition of laryngoscope-induced cardiovascular responses, and to observe its effects on the cardiovascular system and stress system. The study included 20 patients, who underwent time-scheduled vocal cord polyp resection with monitoring of heart rate (HR), mean blood pressure (MBP) and auditory evoked potential (AEP)-based A-line ARX Index (AAI). The Rem concentration was initially 5 ng/ml in the first patient, and the concentration selected for each subsequent patient was calculated from the previous case on the basis of whether or not cardiovascular reactions occurred. The HR, MBP and AAI at baseline, after the induction of anesthesia, and before and after the insertion of a self-retaining laryngoscope were recorded, with a change >15% recorded as a positive cardiovascular response. The EC_{50} sequential method was used to calculate the EC_{50} of Rem for the inhibition of laryngoscope-induced responses. Cortisol, interleukin-6 and blood glucose levels before and after laryngoscope insertion were also measured. The target-controlled concentrations for the 20 patients were as follows: 2 cases at 5 ng/ml, 6 cases at 4.2 ng/ml, 6 cases at 3.5 ng/ml, 4 cases at 2.9 ng/ml and 2 cases at 2.4 ng/ml. The EC_{50} of Rem for the inhibition of laryngoscope-induced responses was 3.5 ng/ml with a 95% confidence interval (CI) of 3.47-3.60 ng/ml. A reasonable dose for inhibiting laryngoscope-induced responses was within the range 2.9-4.2 ng/ml. In conclusion, Rem exhibited an EC_{50} of 3.5 ng/ml for the inhibition of laryngoscope-induced cardiovascular responses, with a 95% CI of 3.47-3.60 ng/ml, and a reasonable dose for the inhibition of such responses was 2.9-4.2 ng/ml.

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Introduction

Surgery is currently the most commonly used treatment method for vocal cord polyps; however, the self-retaining laryngoscope used during surgery can cause severe cardiovascular reactions and stress responses, resulting in a series of changes in the nervous, endocrine and metabolic systems (1). This surgical procedure is delicate, with a high requirement for anesthesia; during the surgery, the vocal cord is required to remain stationary, as this should reduce the stress response and throat reflex, and fully relax the muscles, and also enable recovery and rehabilitation from the surgery as quickly as possible to avoid the aspiration of blood and oropharyngeal secretions (2). Therefore, it is vitally important to establish a scientifically confirmed and reasonable amount of anesthetic for use during the surgery.

A combination of the ultra-short-action opioid remifentanil (Rem) and ultra-short-action intravenous anesthetic propofol (Pro) is currently considered the best combination for total intravenous anesthesia (TIVA) (3). Rem has very short half-life, and so the continuous intravenous administration of Rem should not produce cumulative effects (4). In particular, its infusion time-related half-life is only 3-5 min; it is not notably decomposed by plasma cholinesterase; repeated or high-dose application does not affect the recovery time for spontaneous breathing and extubation after its discontinuation; and it can inhibit the decomposition of norepinephrine and corticosteroids (5). Pro is rapidly effective, with a short duration of action and rapid recovery, and it makes sedation easy to control (6-8). These two drugs are suitable for target-controlled infusion (TCI) in a short surgical procedure.

However, at present there have been no definitive studies concerning the dosage of Rem for use in surgery involving a self-retaining laryngoscope. Thus, the aim of the present study was to use the median effective concentration (EC_{50}) sequential test method to calculate the EC_{50} and 95% confidence interval (95% CI) of the Rem-Pro combination for the inhibition of self-retaining laryngoscope-caused cardiovascular responses (SRLCCRs). Through observing changes of heart rate, mean arterial pressure, auditory evoked potential (AEP) index, cortisol, interleukin (IL)-6 and blood glucose prior to and following the induction of anesthesia, as well as prior to and following the self-retaining laryngoscope insertion, this study aimed to observe the inhibitory effects of Rem towards

the cardiovascular system and SRLCCRs, aiming to provide a reference for its clinical use.

Materials and methods

General information. A total of 20 patients, who were subjected to vocal cord polyp resection under general anesthesia in Weifang People's Hospital (Weifang, China) from June 2009 to December 2012, were randomly selected for inclusion in the present study. The exclusion criteria were as follows: Circulation, glucose metabolism and nervous system dysfunctions; preoperative history of long-term application of analgesic or sedative drugs, with medication history that would interfere with glucose metabolism, adrenal function or the sympathetic system, with long-term history of alcohol abuse, long-term application of opioids or allergic response to opioids; endotracheal intubation could not be completed within 1 min; serious cardiovascular reactions occurring during endotracheal intubation and laryngoscope insertion that prevented the surgery from proceeding. This study was approved by the ethics committee of Weifang People's Hospital. Written informed consent was obtained from the patients.

Anesthesia. All study subjects were set up for intravenous access after entry into the surgery room, and connected to a PM-6000 multi-parameter monitor (Mindray Bio-Medical Electronics Co., Shenzhen, China) to show electrocardiogram (ECG), heart rate (HR), pulse oxygen saturation (SpO_2), non-invasive arterial pressure (BP) and Alaris AEP Index (AAI) values. Rem (batch no. 070904; Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, China) and Pro (batch ET763; AstraZeneca SpA, Basiglio, Italy) were infused through a TCI-I type infusion pump (Slgo Medical Technology Co., Ltd., Beijing, China) for TCI. Rem was infused with the plasma target-controlled concentration in accordance with the EC_{50} sequential method; when the plasma concentration and effect-site concentration were in equilibrium [the half-life for equilibration ($T_{1/2}$ Keo) of Rem was 1.32 min (9), with equilibrium of the two concentrations being reached 5-6 min later], the TCI of Pro was initiated. When the patient lost consciousness [Observer's Assessment of Alertness/Sedation (OAA/S) scale score ≤2], 0.1 mg/kg vecuronium (batch no. 070704.1; Xianju Pharmaceutical Co., Ltd., Zhejiang, China) was intravenously injected. Then, connection to the intubation and anesthesia instrumentation was performed and the peak end tidal CO_2 ($PETCO_2$) level was maintained at 35-45 mmHg. After 3 min, the HS2301 self-retaining laryngoscope (Shanghai Hengsheng Medical Instrument Co., Ltd., Shanghai, China) was inserted, and the surgery was conducted. If a reduction in HR or systolic BP occurred during the induction of anesthesia, cardiovascular drug treatment was applied until the patient's HR or blood pressure was stable (observed for 1 min). The laryngoscopic surgery was then conducted, and the monitoring that was initiated prior to treatment was continued, and values were recorded. If the HR or mean arterial BP increased during laryngoscope insertion, the Rem target concentration was adjusted to a higher level for completion of the surgery (while the concentration for next patient was determined on the basis of the initial concentration). The Pro plasma concentration was controlled at 4 μg/ml (Marsh pharmacokinetic parameters) (10). The Rem target-controlled plasma concentration (Minto pharmacokinetic parameters) (11) was determined according to the EC_{50} sequential method, that is, the patient's plasma target-controlled concentration was determined by the previous patient's cardiovascular responses; if the previous patient exhibited SRLCCRs, the next higher concentration level was used; if there were no SRLCCRs, a lower-level concentration was applied. The ratio of two adjacent concentrations was 1.2. The test started from a Rem target-controlled plasma concentration of 5 ng/ml, and the concentration for each case was calculated from the previous case on the basis of whether cardiovascular reactions were exhibited.

Observation items and scoring. The values of HR, mean (arterial) blood pressure (MBP) and the auditory evoked potential (AEP)-based A-line ARX Index (AAI) were recorded. The data acquisition time points were: Baseline value (T0), after anesthesia induction (T1), prior to laryngoscope insertion (T2) and highest value within 3 min after laryngoscope insertion (T3). Each value was recorded three times and averaged. Changes of HR, MBP and/or AAI of >15% were considered as positive cardiovascular responses.

Sedation scoring was initiated after the Pro infusion, and the OAA/S scale score (12) was used to assess the patient's degree of sedation. The scores were recorded at T1, T2 and T3, respectively.

Arterial blood samples (5 ml) were drawn at T2 and T3 for the measurement of stress indicators, namely cortisol and the inflammatory marker interleukin (IL)-6 using radioimmunoassay kits (Fuzhou Maixin Biotechnology Development Co., Ltd., Fuzhou, China). Blood glucose levels were measured using a type II blood glucose meter (Roche Diagnostics (Shanghai) Ltd., Shanghai, China) at T2 and T3.

Statistical analysis. The EC_{50} sequential method was used (13) to calculate the effective plasma concentration of Rem that inhibited SRLCCR in 50% of patients (the EC_{50}). The valid number (r) and invalid number (s) of SRLCCR inhibitions under a specific Rem plasma target concentration were analyzed, and the logarithm of each plasma target concentration (x), the total number of patients (n), efficiency (p) of SRLCCR inhibition, and difference (d) of logarithms of two adjacent concentrations were determined and used to calculate the EC_{50} and 95% confidence interval (CI) by the EC_{50} sequential method. The following formulae were used: Logarithm of EC_{50} ($\lg EC_{50}$) = $\sum nx/\sum n$; standard deviation of the logarithm of EC_{50} ($S \lg EC_{50}$) = $d\sqrt{[p(1-p)/n-1]}$; and 95% CI for the overall EC_{50} = ($\lg EC_{50}$ - 1.96 $S \lg EC_{50}$ to $\lg EC_{50}$ + 1.96 $S \lg EC_{50}$). The EC_{50} and 95% CI values were reported as the anti-logarithm of each logarithmic number. The average values of cortisol, IL-6 and glucose under the Rem plasma target-controlled concentration were determined, and intragroup comparisons were conducted using paired t-tests. Measurement data are expressed as mean ± standard deviation. SPSS software, version 11.5 (SPSS, Inc., Chicago, IL, USA) was used for statistical processing, with $P<0.05$ considered to indicate a statistically significant difference.

Table I. General information of the patients in the five groups.

Variable	Group A	Group B	Group C	Group D	Group E
Age (years)	38	39.6±7.9	42.2±6.8	36.3±5.9	44
Gender (male/female)	2/0	4/2	3/3	2/2	1/1
Weight (kg)	68.4	70.2±11.3	69.6±9.4	65.6±10.6	63.5

Target remifentanil concentration: Group A, 5 ng/ml; group B, 4.2 ng/ml; group C, 3.5 ng/ml; group D, 2.9 ng/ml; group E, 2.4 ng/ml.

Table II. Remifentanil plasma target-controlled concentration.

Plasma target-controlled concentration (ng/ml)	Log plasma target-controlled concentration (x)	Total cases for each plasma target-controlled concentration (n)	Valid cases of SRLCCR inhibition (r)	Invalid cases of SRLCCR inhibition (s)	Valid rate (%) of SRLCCR inhibition (p)
5	0.699	2	2	0	100
4.2	0.623	6	4	2	66.7
3.5	0.544	6	3	3	50.0
2.9	0.477	4	2	2	50.0
2.4	0.398	2	0	2	0

Difference of logarithms of two adjacent concentrations, d=0.07918. SRLCCR, self-retaining laryngoscope-caused cardiovascular response.

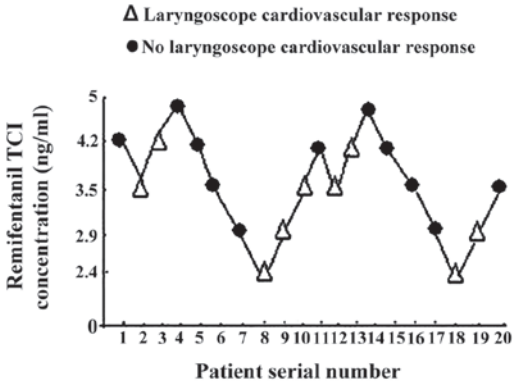

Figure 1. Curve of remifentanil plasma target-controlled concentration for SRLCCR inhibition. TCI, target-controlled infusion.

Results

General patient information and grouping. A total of 20 patients were enrolled in the present study The Rem target concentrations of the selected patients were set as follows: 2 cases at 5 ng/ml, 6 cases at 4.2 ng/ml, 6 cases at 3.5 ng/ml, 4 cases at 2.9 ng/ml and 2 cases at 2.4 ng/ml. The 20 patients were then divided into five groups, for analysis according to the different target concentrations of Rem; Group A, 5 ng/ml; group B, 4.2 ng/ml; group C, 3.5 ng/ml; group D, 2.9 ng/ml; and group E, 2.4 ng/ml. No statistically significant difference in age, weight and gender was observed among the five groups (P>0.05; Table I).

During testing, 1 patient was excluded due to the occurrence of laryngoscope-induced bradycardia (HR, <50 beats/min), but none of the patients exhibited any chest wall stiffness. Postoperative questioning confirmed that no patients experienced intraoperative awareness.

Calculation of the EC_{50}. The valid number (r) and invalid number (s) of SRLCCR inhibitions under each Rem plasma target concentration were analyzed, and the logarithm of each plasma target concentration (x), total number of patients (n), efficiency (p) of SRLCCR inhibition and difference (d) of logarithms of two adjacent concentrations were calculated, and the results are presented in Table II. The EC_{50} value calculated according to the EC_{50} sequential method was 3.5 ng/ml and the 95% CI was 3.47-3.60.

The Rem target-controlled plasma concentrations for SRLCCR inhibition in each patient are shown in Fig. 1.

Changes of HR, MBP and AAI. With regard to HR, the HR at T1 was reduced compared with that at T0 in group A (P<0.05) and group B (P<0.01). In addition, the HRs at T3 were significantly increased compared with those at T2 in groups D and E (P<0.05; Table III).

With regard to blood pressure, the MBP values for groups A and D at T1 were reduced compared with those at T0 (P<0.05); the MBP values at T1 of groups B and C were also reduced compared with those at T0, with a higher level of significance (P<0.01). In groups D and E, the MBP values at T3 were significantly increased compared with those at T2 (P<0.05; Table III).

The AAI value at T1 was reduced compared with that at T0 in group A (P<0.05). In groups B, C and D, the AAI values at T1 were also reduced compared with those at T0, with a higher level of significance (P<0.01). Furthermore, the AAI values in groups D and E at T3 were significantly increased compared with those at T2 (P<0.05; Table III).

Table III. HR, MBP and AAI changes of the five groups at different time points (mean ± standard deviation).

Indices	Time point	Group A	Group B	Group C	Group D	Group E
HR (bpm)	T0	98.0±1.4	88.3±2.8	74.2±6.6	79.2±6.6	76.5±4.3
	T1	68.4±2.3[a]	76.5±6.7[b]	69.7±3.3	78.9±5.8	75.3±2.8
	T2	74.0±4.6	77.0±5.6	72.1±3.6	81.0±5.4	80.3±4.7
	T3	75.3±5.5	80.8±6.2	78.8±5.4	89.0±2.6[c]	113.5±8.3[c]
MBP (mmHg)	T0	102.1±7.6	100.5±5.6	99.4±4.9	95.7±5.2	94.1±2.3
	T1	83.3±5.7[a]	83.8±4.1[b]	83.5±3.8[b]	86.3±6.6[a]	90.5±1.2
	T2	86.8±3.5	87.0±3.6	86.0±3.0	88.2±6.4	94.6±3.2
	T3	91.0±4.4	93.0±6.3	94.3±6.3	100.1±11.4[c]	123.9±5.2[c]
AAI	T0	70.3±2.1	75.3±6.1	76.3±4.4	69.9±5.9	72.4±9.5
	T1	19.9±4.7[a]	21.1±2.5[b]	20.6±3.2[b]	20.8±7.0[b]	24.7±2.8
	T2	21.9±3.8	21.9±2.0	20.6±2.4	25.8±3.4	26.0±5.9
	T3	21.3±4.9	22.6±2.3	23.3±3.0	30.2±2.7[c]	40.2±6.4[c]

HR, heart rate; MBP, mean blood pressure; AAI, A-line ARX Index; Group A, target remifentanil concentration 5 ng/ml; group B, target remifentanil concentration 4.2 ng/ml; group C, target remifentanil concentration 3.5 ng/ml; group D, target remifentanil concentration 2.9 ng/ml; group E, target remifentanil concentration 2.4 ng/ml; T0, baseline; T1, after induction of anesthesia; T2, before laryngoscope insertion; T3, after laryngoscope insertion. [a]P<0.05, [b]P<0.01 vs. T0; [c]P<0.05 vs. T2.

Table IV. Cortisol, IL-6 and blood glucose levels in the five groups at different time points (mean ± standard deviation).

Indices	Time point	Group A	Group B	Group C	Group D	Group E
Cortisol (ng/ml)	T2	180.60±23.76	176.73±13.24	180.45±13.23	184.65±5.85	186.45±10.25
	T3	181.05±12.23	185.78±11.37	188.17±7.66	239.80±24.94[a]	282.05±16.33[a]
IL-6 (ng/ml)	T2	0.71±0.06	0.72±0.06	0.73±0.07	0.86±0.05	0.87±0.06
	T3	0.74±0.08	0.78±0.06	0.79±0.08	0.95±0.07[a]	1.62±0.18
Blood glucose (mmol/l)	T2	4.90±0.28	4.68±0.84	4.97±0.60	4.98±0.85	5.55±0.21
	T3	5.00±0.57	4.80±0.73	5.20±0.39	5.78±0.50[a]	7.70±0.42[a]

IL, interleukin; Group A, target remifentanil concentration 5 ng/ml; group B, target remifentanil concentration 4.2 ng/ml; group C, target remifentanil concentration 3.5 ng/ml; group D, target remifentanil concentration 2.9 ng/ml; group E, target remifentanil concentration 2.4 ng/ml; T2, before laryngoscope insertion; T3, after laryngoscope insertion. [a]P<0.05 vs. T2.

Changes of cortisol, IL-6 and blood sugar levels. When stress indicators were examined, it was observed that the cortisol levels and blood sugar levels at T3 of groups D and E were increased compared with those at T2, and the differences were statistically significant (P<0.05; Table IV). In addition, in group D, the IL-6 level at T3 was increased compared with that at T2 (P<0.05; Table IV).

OAA/S scores. All patients exhibited no response towards the deltoid extrusion pushing examination conducted at T1, T2 and T3, and thus had a corresponding OAA/S score of 1. No significant differences were observed.

Discussion

Vocal cord surgery using a self-retaining laryngoscope involves a short operation with a strong stimulus; although the duration of surgery is short, the requirements of anesthesia are high, as it should not only reduce stress responses and the throat reflex and fully relax the muscles, but also enable the patient to recover and rehabilitate from the surgery as soon as possible (2). Thus, the timely mastering of the depth of anesthesia is very important, and the scientific and rational determination of drug dosage during the anesthesia is essential. The present study was conducted to determine the drug dosage for Rem, and the results are analyzed as follows.

Cortisol has been demonstrated to be a stress indicator; for example, Haussmann *et al* studied healthy human volunteers under three different stressful conditions, and found that the salivary cortisol levels were significantly increased following each type of stress (14). The present study showed that the plasma cortisol values groups A, B and C at T3 were higher than those at T2, but the difference was not significant (P>0.05). However, it could be considered that the intubation affected cortisol production, as the plasma cortisol levels of groups D and E group increased significantly at T3 compared with T2 (P<0.05). These results indicate that when Rem was

≤2.9 ng/ml, it could not effectively inhibit the stress responses caused by the laryngoscope.

IL-6 is an important type of inflammatory cytokine that can mediate the pathophysiological process of stress; the stimulus of surgical trauma could potentially induce the excessive production of IL-6. It is considered that IL-6 is a particularly sensitive inflammatory marker that can reflect tissue damage and the degree of stress (15,16). A prior study suggested that changes of IL-6 levels occur earlier and are more sensitive than those of cortisol (17). In the present study, the IL-6 values of all groups at T3 were higher than those at T2. However, while the changes in groups A, B, C and E were not significant (P>0.05), the plasma IL-6 level of group D was significantly increased following insertion of the laryngoscope (P<0.05). These results indicate that when the Rem concentration was 2.9 ng/ml, it could not inhibit laryngoscope-induced IL-6 induction. The IL-6 levels of group E changed notably between T2 and T3, although not in a statistically significant manner, which might be due to the small number of patients in this group.

A previous study has confirmed that glucose is an effective indicator that can reflect the stress response (18). Testing has shown that following laparoscopic surgery, blood glucose and cortisol values showed significant differences from those preoperatively (19). The present study showed that there was no significant change in the blood glucose values of groups A, B and C before and after laryngoscope insertion (P>0.05), while those of groups D and E at T3 were significantly increased compared with those at T2 (P<0.05), indicating that when the Rem dosage was <2.9 ng/ml, it could not effectively suppress the high metabolic changes caused by laryngoscope insertion.

The results showed that HR at T1 was lower than that at T0 for group A (P<0.05) and group B (P<0.01), and the HRs of groups D and E at T3 were significantly increased compared with those at T2 (P<0.05). One patient received emergency treatment due to the rapid HR reduction during insertion of the laryngoscope (<50 beats/min), and thus was excluded. One patient of group A exhibited a decreased HR following the induction of anesthesia, and thus required atropine treatment; 2 cases from groups D and E, respectively, had an increased Rem target-controlled concentration for the increased HR following laryngoscope insertion. This result indicated that when the Rem plasma target-controlled concentrations were 4.2 and 5 ng/ml, the patients might exhibit induced cardiovascular responses, while at these concentrations, it would be difficult to achieve effective inhibition of laryngoscope-induced changes in HR. This result is essentially consistent with the EC_{50}, calculated by the EC_{50} sequential method, and the above analysis.

Rem can expand the arteries to various degrees (20), and excessive medication could cause the lowering of blood pressure. The results of the present study showed that the patients of each group exhibited a reduction in MBP at T1 compared with that at T0, which might be considered to be associated with the blood pressure-lowering effects of Pro. However, the reduction of group E was not significant (P>0.05), whereas the reductions at T1 compared with those at T0 were significant for groups A and D (P<0.05) and groups B and C (P<0.01). The MBPs of groups D and E at T3 were significantly increased compared with those at T2 (P<0.05), among which 1 case of groups A, B and C, respectively, received ephedrine treatment because of blood pressure reduction at T1, and 1 case of group D and 2 cases of group E underwent adjustment of the Rem target concentration at T3 due to the increase in blood pressure. These results indicate that when the Rem target concentrations were 2.9 and 2.4 ng/ml it was difficult to effectively suppress the elevated blood pressure caused by the insertion of the laryngoscope. This result is essentially consistent with the above analysis. Whether Rem and Pro had a synergistic effect in lowering the blood pressure requires further investigation.

AAI is the AEP index derived from the usage of an A-line monitoring instrument; AEP can accurately reflect the situations of sedation and analgesia, as well as the prediction of short-term body movements (21). AAI values are normally in the range 0-100. Generally, it is considered that AAI 60-100 represents the normal waking state, 40-60 represents the sleep state, 30-40 represents the light anesthesia state, <30 represents the clinical anesthesia state and <10 represents the deep anesthesia state (22). It has been suggested that AAI can much more sensitively reflect the depth of anesthesia than the bispectral index in Pro-fentanyl anesthesia (23). The present study showed that the AAI of group A at T1 was decreased compared with that at T0 (P<0.05), and those of groups B, C and D at T1 were significantly lower than those at T0 (P<0.01); those of groups D and E at T3 were significantly increased compared with those at T2 (P<0.05). Kreuer *et al* (24) studied the AAI changes during anesthesia with Pro and Rem, and hypothesized that in Pro and Rem anesthesia, a large variation in the AAI values might exist when the patient is awake, which might explain the reduction of AAI values of groups A, B and C after the induction of anesthesia.

In this study, sedation/alert scoring was performed from the initiation of Pro TCI, and the results showed that the OAA/S scores at three time points of all the patients were 1, indicating that the patients were in the deep sleep state.

EC_{50} is a new concept for target-controlled intravenous infusion drugs, with its meaning equivalent to the minimum effective concentration of alveolar gas in inhalation anesthesia. In this study, the EC_{50} sequential method was used to calculate the EC_{50} of Rem-inhibited SRLCCR, so the patient selection was conducted in accordance with the requirements of the EC_{50} sequential method, with a total number of between 12 and 20.

It was calculated that the EC_{50} of Rem for the inhibition of SRLCCRs was 3.5 ng/ml, with a 95% CI of 3.47-3.60 ng/ml. This study suggested that when the Pro target-controlled concentration was 4 μg/ml and the concentration of Rem was 5 or 4.2 ng/ml obvious inhibition of the cardiovascular system could be achieved; while Rem target concentrations of 2.9 and 2.4 ng/ml may be insufficient to effectively inhibit SRLCCRs. When all patients were anesthetized, the OAA/S scores prior to and following laryngoscope insertion were 1, indicating that the patients were in the deep sleep state. From the above analysis, it could be concluded that a Pro concentration of 4 μg/ml could maintain adequate sedation, and the increase of HR, MBP and AAI in certain patients before the insertion was associated with the Rem dose.

In conclusion, the EC_{50} sequential method was used to calculate the EC_{50} (3.5 ng/ml) and 95% CI (3.47-3.60 ng/ml)

of Rem towards SRLCCR inhibition. The test results showed that a Pro concentration of 4 μg/ml could maintain adequate sedation. The dose of Rem that was able to effectively inhibit SRLCCRs while not causing a serious Rem-induced inhibition response was between 2.9 and 4.2 ng/ml. This result is consistent with the results of calculation by the EC_{50} sequential method.

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