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Optimal Propofol Plasma Concentration during Upper Gastrointestinal Endoscopy in Young, Middle-aged, and Elderly Patients

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Background: **Suitable propofol plasma concentrations during gastroscopy have not been determined for suppressing somatic and hemodynamic responses in different age groups.**

Methods: **Propofol sedation at target plasma concentrations from 0.5 to 4.0 μg/ml were performed randomly in three groups of patients (23 per group) who were undergoing elective outpatient gastroscopy: ages 17–49 yr (group 1), 50–69 yr (group 2), and 70–89 yr (group 3). Plasma propofol concentration in which 50% of patients do not respond to these different stimuli were determined by logistic regression: verbal command (Cp_{50}ls), somatic response to gastroscopy (Cp_{50}endo), and gag response to gastroscopy (Cp_{50}gag). Hemodynamic responses were also investigated in the different age groups.**

Results: **Cp_{50}ls concentrations were 2.23 μg/ml (group 1), 1.75 μg/ml (group 2), and 1.40 μg/ml (group 3). The Cp_{50}endo values in groups 1 and 2 were 2.87 and 2.34 μg/ml, respectively, which were significantly higher than their respective Cp_{50}ls values. Cp_{50}endo value in group 3 was 1.64 μg/ml, which was close to its Cp_{50}ls value. Because of a high degree of interpatient variability, Cp_{50}gag could not be defined. Systolic blood pressure response decreased with increasing propofol concentrations.**

Conclusions: **The authors determined the propofol concentration necessary for gastroscopy and showed that increasing age reduces it. Propofol concentration that suppresses somatic response induces loss of consciousness in almost all young patients. (Key words: Monitored anesthesia care; sedation; target-controlled infusion.)**

OUTPATIENT gastrointestinal endoscopy necessitates reliable sedation involving rapid onset, short predictable duration of action, and rapid elimination without side effects.[1,2] Because of its favorable pharmacokinetic characteristics and recovery profile, propofol has increasingly become the drug of choice for maintaining adequate sedation during monitored anesthesia care,[3,4] including upper gastrointestinal endoscopy.[5] However, inappropriate sedation with propofol can cause apnea and hemoglobin oxygen desaturation.[6,7] Therefore, the narrow therapeutic range of propofol must be determined and carefully maintained. Target controlled infusion (TCI) has theoretical advantages over manual controlled infusion in sustaining the narrow therapeutic range of propofol,[8] and TCI provides satisfactory sedation conditions for upper gastroscopy.[6] However, little is known about the plasma concentration suitable to suppress somatic and hemodynamic responses during gastroscopy.

In endoscopy, sedation may make the procedure more tolerable for the patient but may contribute to cardiorespiratory risk, especially in elderly patients.[9–13] The propofol plasma concentration necessary for gastroscopy and the effects on somatic and hemodynamic responses to this stimulus has not been investigated precisely. This study was designed (1) to determine the plasma propofol concentrations at which somatic or gag responses to insertion of a gastroscope are suppressed in 50% of patients (Cp_{50}endo and Cp_{50}gag); (2) to compare those responses with the plasma propofol concentration

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at which 50% of patients do not respond to verbal command (Cp_{50}ls); and (3) to measure the hemodynamic responses to insertion of a gastroscope in young, middle-aged, and elderly patients.

Materials and Methods

The study was approved by the District Hamamatsu University Hospital Ethics Committee. After obtaining written informed consent from all subjects, we studied three groups of 23 patients each, aged 17–49 yr (group 1), 50–69 yr (group 2), and 70–89 yr (group 3), who were undergoing elective outpatient upper gastrointestinal endoscopy. All subjects were unpremedicated American Society of Anesthesiologists physical status I or II with no known or suspected cardiac, pulmonary, liver, renal, or metabolic diseases. Patients with significant obesity (body mass index $>$ 30) or with neurologic dysfunction were excluded from the study. No topical pharyngeal anesthesia was used before the experiments.

Stable blood concentrations of propofol were achieved using a pharmacokinetic model-driven infusion device designed for computer-assisted continuous infusion, which was described precisely in our previous report.[14] The pharmacokinetic parameters used in TCI for propofol were reported previously by Gepts *et al.*[15] For each pair of predicted and measured values, the prediction error and absolute prediction error[16] were calculated.

An intravenous cannula was placed in the left antecubital vein for the infusion of propofol. A 22-gauge radial artery catheter, for blood sampling only, was also inserted. Parameters that were monitored included noninvasive blood pressure (1-min intervals), heart rate, electrocardiogram, and pulse oximeter. Within each group, patients were randomized to receive predetermined target concentrations of propofol ranging from 0.25 to 4.0 μg/ml (fig. 1). These values were selected on the basis of our previous experience with propofol Cp_{50} values.[14] To ensure equilibration between plasma and effect compartment, the predetermined target concentration (fig. 1) was maintained for 15 min before verbal command and insertion of an endoscope. Arterial blood samples for plasma propofol concentration were taken 10 and 14 min after the start of infusion. Only paired samples that had concentrations within ±30% of each other were analyzed statistically.

After a 15-min equilibration period of the predetermined propofol blood concentration (set by TCI), a verbal command to open their eyes was given to the

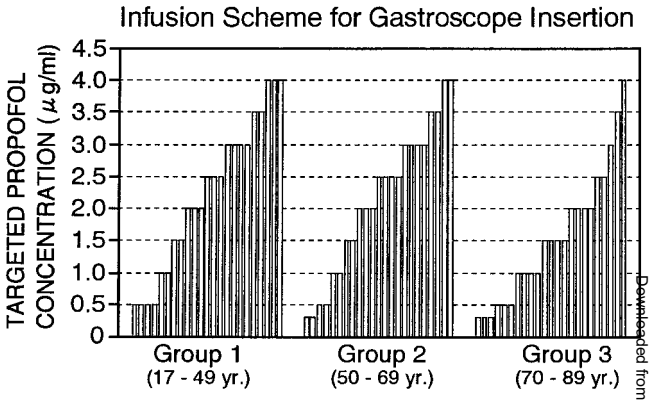

Fig. 1. Target concentrations of propofol to which patients were randomized for assessment of responses.

patients one or two times. One minute after giving the verbal command, the endoscopist, who was blinded to the target propofol concentration, performed the gastroscopy with an Olympus endoscope (GIF-Q200; Olympus, Tokyo, Japan). Somatic response was noted and classified as positive if the patient showed a gross purposeful movement of the head or extremities. The presence or absence of gagging was also noted when the endoscope was inserted. Coughing during insertion was not considered a positive response. The responses to verbal command and to insertion of gastroscopy at one predetermined propofol concentration as shown in figure 1 were measured to obtain Cp_{50} values.

When gag or somatic response was positive, target concentration was increased by 0.5 or 1.0 μg/ml after a 10- or 20-mg propofol bolus dose. When it was impossible to insert an endoscope at that dose, the target concentration was increased further by 0.5 or 1.0 μg/ml after another 10- or 20-mg propofol bolus dose. When gag or somatic response was negative, target concentration was decreased if hypotension or bradycardia occurred. The bolus infusion doses given by the TCI device in the manual mode were taken into consideration in the model. During examination by gastroscope, the target propofol concentration of each patient was continually adjusted within a range of 1 and 3 μg/ml. The data of no response and response during gastroscopy after gastroscope insertion were not used to determine Cp_{50} values. Adjustments were made to ensure that the patient did not show inappropriate movements, was resting comfortably, had stable cardiovascular and respiratory functions, and could be examined using an endoscope.

Systolic blood pressure (SBP) and heart rate were recorded before insertion of an endoscope. The mean value during the 2 min before insertion was considered

Table 1. Patient Characteristics of the Three Age Groups

Group	Group 1 (17–49 yr)	Group 2 (50–69 yr)	Group 3 (70–89 yr)
Sex (M/F)	23 (13/10)	23 (12/11)	23 (11/12)
Age (yr)	36 ± 8	58 ± 5	75 ± 6
Height (cm)	165 ± 9	161 ± 6	150 ± 7
Weight (kg)	64 ± 8	54 ± 7	47 ± 9
Duration of gastroscopy (min)	9.1 ± 2.7	8.7 ± 2.8	9.6 ± 2.9
Total infusion dose of propofol (mg)	239 ± 54	197 ± 27	110 ± 35
Mean target concentration during gastroscopy	2.61 ± 0.32	2.17 ± 0.39	1.36 ± 0.36

Data are mean ± SD.

the prestimulation value. For the poststimulation value, the maximum value during the 2 min after insertion of the gastroscope was recorded. Linear regression analysis was used to correlate the SBP and heart rate values of all patients with the propofol concentrations. The numeric increase values at insertion of a gastroscope were obtained at the Cp_{50}endo and the Cp_{95}endo with linear regression.

Somatic and autonomic responses were identified by the same attending anesthesiologist, who was blinded to the target concentration. All patients breathed room air throughout the procedure. Patients with 3 min of persistent oxygen saturation nadir $< 90\%$, as monitored by a pulse oximeter, were given nasal oxygen (3 l/min). If hypotension (< 80 mmHg systolic arterial pressure) or bradycardia (< 45 beats/min) persisted, the patient's blood pressure was restored by a combination of fluid, ephedrine, and decreasing of target propofol concentration, and heart rate was restored by atropine (0.25 mg administered intravenously). The incidents of complications and untoward events requiring intervention were documented. These included respiratory depression, excessive pain, inappropriate movements, and inability to examine the patient.

For responses to verbal command and insertion of an endoscope, each patient's clinical state was categorized as "responsive" or "nonresponsive" based on the aforementioned criteria. Within the three response categories, data for all patients were pooled. For determination of Cp_{50} values, we only used the data of responses at the predetermined equilibrated propofol concentration, as shown in figure 1. The response–nonresponse data overlapped and was related to the propofol concentration according to following equation:

$$\text{Probability of no response} = Cp^{\gamma}/(Cp_{50^{\gamma}} + Cp^{\gamma})$$

where Cp is the measured propofol concentration in plasma, Cp_{50} is the plasma concentration of propofol that results in a 50% probability of no response, and γ is a dimensionless power function that determines the steepness of the slope of the probability *versus* concentration curve. Cp_{50}ls, Cp_{50}endo, and Cp_{50}gag were calculated by logistic regression (Microsoft Excel 8.0; Microsoft Co., Seattle, WA). To investigate the relation between continuous age values and Cp_{50} values, the age-dependent concentration at which 50% of the patients show no responses to verbal command or insertion of a gastroscope was calculated by applying the following formula:

$$Cp_{50} = a + b \cdot age$$

where the parameters a and b were estimated by all 69 observations.[17]

Blood samples were kept on ice and stored at 5°C until extraction and assay. Plasma concentrations of propofol were determined using high-performance liquid chromatography with fluorescence detection at 310 nm after excitation at 276 nm (CTO-10A, RF550, and C-R7A; Shimazu, Kyoto, Japan).[18] For each batch of blood samples (representing one patient), a separate standard curve was computed by adding pure propofol emulsion to human plasma to concentrations of 1.0, 5.0, and 10.0 μg/ml. Linear regression (method of least squares) was used with the plasma propofol concentration as the dependent variable. Propofol concentrations in this study were calculated with the derived regression equation. The lower limit of detection was 14 ng/ml, and the coefficient of variation was 7.6%.

One-way analysis of variance was used to determine if a significant difference ($P < 0.05$) existed between the mean values of Cp_{50} for the various responses within each group. Multiple two-tailed unpaired *t* tests with Bonferroni correction were performed to determine significance ($P < 0.05$) between groups.

Results

All 69 patients (23 per group) completed the study. Demographic characteristics for the three groups are shown in table 1. There were no statistically significant differences between the groups in gender or duration of endoscopy. Total propofol infusion dose and mean target concentration during endoscopic procedure was significantly lower in groups 2 and 3 than in group 1. In our protocol, all patients were examined easily by endoscopy and showed no inappropriate movements.

Transient hypotension was observed in three patients in group 3. In two of these patients, normotension was restored by insertion of an endoscope without any treatment. The hypotension of the other patient was alleviated by a combination of fluid infusion and decrease in target propofol concentration. No patients suffered from bradycardia, and none showed electrocardiographic changes from baseline. In two patients from group 3, oxygen saturation decreased $< 90\%$ transiently after insertion of the endoscope but was restored to normal within a few minutes without treatment. No patients developed laryngospasm on insertion of the endoscope. In the present study, the average duration of a procedure was approximately 9 min (table 1), and all patients were awake and coherent in < 10 min after the end of the procedure. There were no other adverse effects during this study.

Median prediction error and median absolute prediction error for TCI administration of propofol were 5.4% and 8.4%, respectively. Responses to verbal command, somatic response to gastroscope insertion, and gag response to gastroscope insertion and concentration–effect curves in each age group are shown in figure 2. Cp_{50}ls and Cp_{50}endo were decreased significantly with increasing age ($P < 0.05$; table 2), and they were calculated as $Cp_{50}ls = 2.95 - 0.021 \cdot age$ and as $Cp_{50}endo = 3.74 - 0.026 \cdot age$. In both the young and middle-aged groups, Cp_{50}endo values were significantly higher ($P < 0.05$) than their Cp_{50}ls values. However, the Cp_{50}ls and Cp_{50}endo values were similar in the elderly group. The percent probabilities of no response to verbal command at Cp_{50}endo of groups 1, 2, and 3 were 99%, 93%, and 73%, respectively, *i.e.*, the propofol concentration that suppressed somatic response induced loss of consciousness in almost all patients in groups 1 and 2.

The concentration–effect curve of gag response was not particularly steep, and it was impossible to define a threshold at which propofol suppressed gag response. Average target concentrations during gastroscopy in groups 1, 2, and 3 were 2.61, 2.17, and 1.36 μg/ml, respectively (table 1), which were lower than the respective values of Cp_{50}endo. These results demonstrate that insertion of a gastroscope was the most intense stimulus during intestinal gastroscopy.

The dose-dependent increase in sedation produced by propofol was paralleled by a decrease in SBP just before

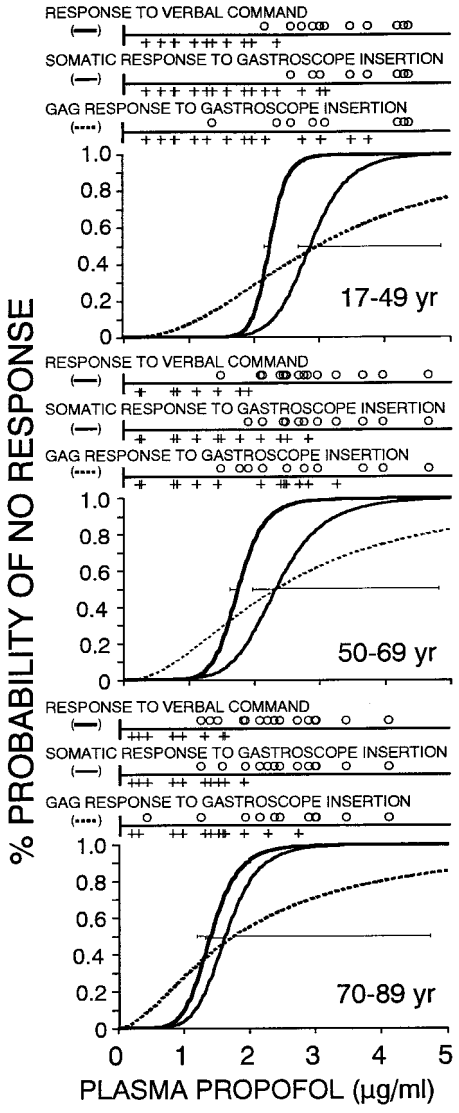

Fig. 2. Relation between the propofol plasma concentration and response to verbal command, somatic response to gastroscopy, and gag response to gastroscopy in various age groups. The diagrams show the propofol plasma concentration of every patient associated with (plus sign = positive response) or without (unfilled circles = negative response) each of these three responses. The concentration–effect curves were defined from the data shown in the upper diagrams of each age group using logistic regression. Straight line indicates ± SE of Cp_{50}.

Table 2. Cp_{50}s and Slopes of Propofol Plasma Concentration-Effect Curves for Responses to Verbal Command and Gastroscope Insertion

	Cp50 (μg/ml)			Steepness (γ)		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Response to verbal command (Cp_{50}ls)	2.23 ± 0.02*	1.75 ± 0.06*	1.40 ± 0.10*	16.56	8.75	6.64
95% Confidence limits of Cp_{50}ls	(2.19–2.27)	(1.63–1.87)	(1.20–1.61)			
Somatic response to gastroscope insertion (Cp_{50}endo)	2.87 ± 0.09*†	2.34 ± 0.17*†	1.64 ± 0.15*	9.88	6.52	6.72
95% Confidence limits of Cp_{50}endo	(2.68–3.05)	(1.98–2.70)	(1.33–1.94)			
Gag response to gastroscope insertion (Cp_{50}gag)	2.98 ± 0.89	2.35 ± 1.19	1.77 ± 1.41	2.29	2.04	1.68
95% Confidence limits of Cp_{50}gag	(1.12–4.84)	(−0.12–4.80)	(−1.17–4.72)			

Data are mean ± SE.

Cp50 = propofol plasma concentration at which there is a 50% chance of response.

Steepness = dimensionless exponent that determines the steepness of the plasma concentration–effect curve.

95% Confidence limits = 95% confidence limits defined as $Cp_{50} \pm t_{0.05,n-2} \times SE$.

* Significantly different from all other groups.

† Significantly different from response to verbal command.

insertion of the gastroscope. SBP response on insertion decreased with increasing propofol plasma concentrations (fig. 3). SBP response at Cp_{50}endo in patients older than 70 yr was 36.9 mmHg, which was higher than the 21.4-mmHg average in young patients. Heart rate response to gastroscope insertion was minimal (fig. 4).

Discussion

Although endoscopy can be performed without intravenous sedation, tolerance is lower in unsedated patients than in sedated patients, especially during a prolonged procedure. In addition, endoscopy necessitates relative immobility throughout, which can be difficult for an unsedated patient to maintain. Propofol provides rapid onset, short predictable duration of action, and rapid elimination. However, if patients are not sedated appropriately, propofol may cause apnea and hemoglobin oxygen desaturation.[6,7] Avramov and White[4] described safe, effective anesthesia procedures for outpatient monitored anesthesia care with carefully titrated propofol and alfentanil. Recognition of exactly what propofol concentration will be safe for gastrointestinal endoscopy is crucial. To enable precise, correct concentrations for different age groups, we determined various Cp_{50} values related to the insertion of a gastroscope, which is thought to be one of the strongest stimuli encountered during endoscopy.

For Cp_{50}ls, we previously reported that equilibrated awakening propofol concentration was 2.2 μg/ml.[19] Schnider *et al.*[17] reported increasing sensitivity to propofol in elderly patients, with Cp_{50}ls at 2.35, 1.8, and 1.25 μg/ml, in patients aged 25, 50, and 75 yr, respectively. Smith *et al.*[20] showed that the Cp_{50}ls was decreased by increasing age. These values are consistent with our Cp_{50}ls values in the present study. Church *et al.*[6] demonstrated that TCI of propofol provided satisfactory sedation conditions during upper gastrointestinal endoscopy. They reported that the median predicted blood propofol concentration necessary for gastroscope insertion in 20- to 76-yr-old patients was 2.5 μg/ml. Although they did not examine the relation between age and propofol concentration necessary for gastroscope insertion, their reported median value was close to the 2.34 μg/ml of our Cp_{50}endo in 50- to 69-yr-old patients. In the present study, we determined that both Cp_{50}ls and Cp_{50}endo decreased significantly ($P < 0.05$) in the elderly patients.

There has been no previous precise report of the relation between Cp_{50}ls and Cp_{50}endo. According to our findings of Cp_{50}ls and Cp_{50}endo in various age groups, Cp_{50}ls was significantly lower than Cp_{50}endo in 17- to 69-yr-old patients. In the patients aged 17–49 yr, Cp_{95}ls (propofol concentration at which 95% of patients did not respond to verbal command) was 2.67 μg/ml, a level at which somatic response to gastroscope insertion was suppressed in only 30% of group 1 patients (fig. 2). In other words, the propofol concentration necessary to suppress somatic response to gastroscope insertion produced loss of consciousness in most 17- to 49-yr-old patients. If conscious sedation is defined as when a patient is resting comfortably but is easily arousable and alert enough to obey commands, conscious sedation may be inappropriate for gastroscopy in patients within

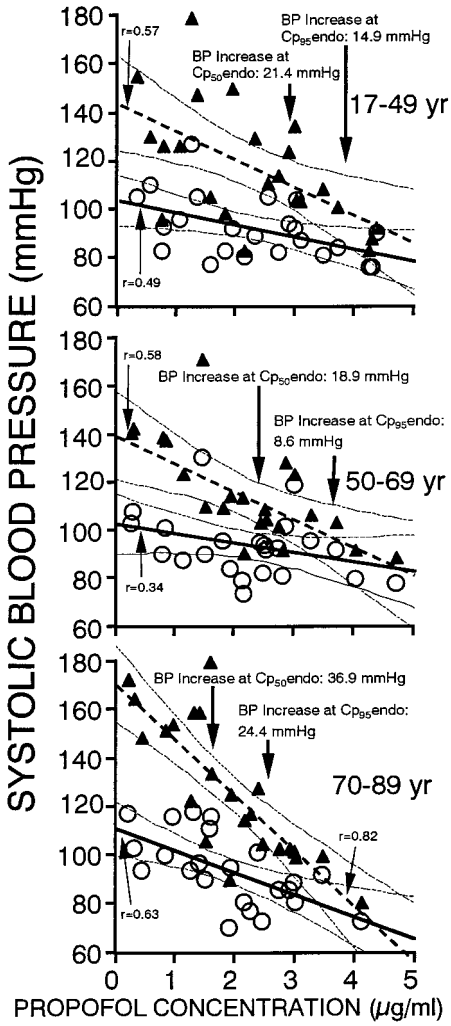

Fig. 3. Response of systolic blood pressure (SBP) to gastroscope insertion in various age groups as a function of propofol plasma concentration. Filled circles = SBP values before insertion; open circles = SBP values after insertion. Solid lines show concentration–response regressions and 95% confidence intervals for SBP before insertion, and dotted lines indicate those after insertion. The correlation coefficient, r, to these lines is indicated. Vertical arrows indicate Cp_{50endo} and Cp_{95}endo values of propofol for various age groups.

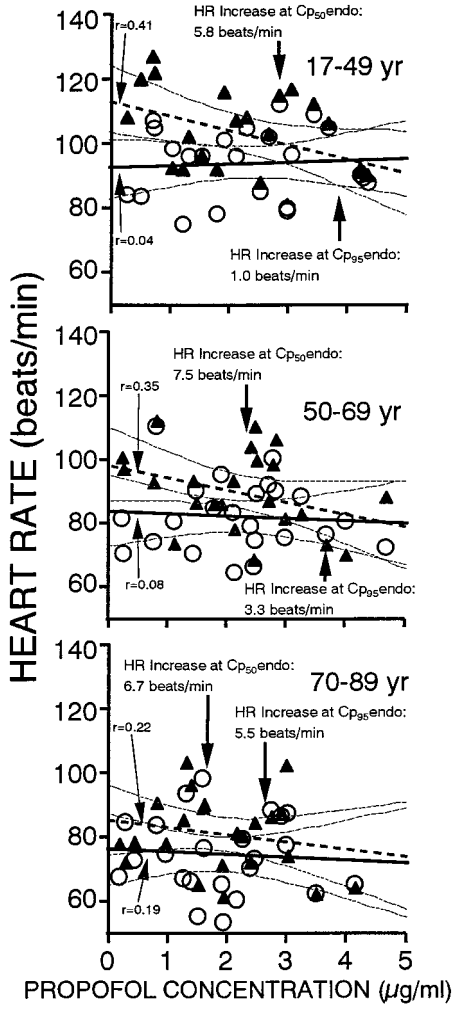

Fig. 4. Response of heart rate (HR) to gastroscope insertion in various age groups as a function of propofol plasma concentration. Filled circles = HR values before insertion; open circles = HR values after insertion. Solid lines show concentration–response regressions and 95% confidence intervals for HR before insertion, and dotted lines indicate those after insertion. The correlation coefficient, r, to these lines is indicated. Vertical arrows indicate Cp_{50}endo and Cp_{95}endo values of propofol for various age groups.

this age range. In patients aged 70–89 yr, the Cp_{50}ls value was close to the Cp_{50}endo value. That means conscious sedation can be performed easily in these patients.

We speculate that gag reflex, similar to cough reflex, is originally a variable reflex depending on individual patient and that propofol concentration to block the gag response is also variable compared with response to verbal command or purposeful somatic response to insertion of a gastroscope in our study. No topical pharyngeal anesthesia was used in this study, which might have given emphasis on gag reflex.

Previous reviews of major complications during gastrointestinal endoscopy point out that cardiopulmonary problems account for 50% of morbidity and 60% of deaths.[11,21,22] Carter *et al.*[10] reported that more than 60% of deaths occurring after gastrointestinal endoscopy are related to cardiorespiratory complications. In our study, SBP response on insertion of an endoscope decreased with increasing propofol plasma concentration

(fig. 3), and preventing such SBP responses may decrease the incidence of cardiopulmonary complications. However, in elderly patients, SBP increased by 37% at the propofol Cp_{50}endo level (1.64 μg/ml). By the use of higher propofol concentrations, the SBP response can be suppressed even when elderly patients show indications before the beginning of gastroscopy that they may be susceptible to a potentially dangerous SBP decrease during the procedure.

Furthermore, the insertion may cause a decrease in oxygen saturation. Blouin *et al.*[7] reported that a propofol concentration as low as 2.0 μg/ml decreased the hypoxic ventilatory response in even young volunteers. When titrating propofol concentration during gastroscopy, it is necessary to consider both sedative action and influence on cardiorespiratory function. Compared with SBP response, heart rate response to gastroscope insertion was minimal in the present study. In a previous report, propofol was associated with a significantly slower heart rate than was midazolam.[1] This effect of propofol has been demonstrated by other investigators and may be beneficial because it reduces myocardial oxygen demand.[23] Our results will enable the endoscopist to select, with a greater degree of confidence, a target blood concentration that should produce adequate sedation while at the same time minimizing the risk of hypertension or hypotension in various age groups.

The risk of arrhythmias may be increased during periods of arterial desaturation.[12] Lieberman *et al.*[9] found that diazepam sedation during endoscopy represents a potential danger to patients with marginal arterial oxygen saturation, and they concluded that diazepam should be used cautiously, if at all, in this population. There is a reduction in oxygen saturation after sedation for endoscopy, which compounds that which occurs after endoscopic intubation alone.[13,24,25] In our study, oxygen saturation decreased to $< 90\%$ transiently after gastroscope insertion in only two patients from group 3, and this reduction was reversed in a few minutes without treatment. Although few elderly patients suffered transient oxygen desaturation in our study, its clinical importance is obvious. If sedation is necessary in elderly patients with marginal arterial oxygen saturation, supplemental oxygen should be used.[9,26]

In conclusion, Cp_{50}ls and Cp_{50}endo decreased significantly as age increased. To suppress the somatic response to gastroscope insertion in young and middle-aged patients, higher plasma propofol concentration than the Cp_{50}ls value is necessary. In elderly patients, the plasma propofol concentration for Cp_{50}ls is sufficient to suppress somatic response during insertion of a gastroscope. SBP response on gastroscope insertion decreased with increasing propofol plasma concentration. SBP response in elderly patients was higher than that in young and middle-aged patients.

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