Sedation-Analgesia with Propofol and Remifentanil: Concentrations Required to Avoid Gag Reflex in Upper Gastrointestinal Endoscopy

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BACKGROUND: The purpose of this study was to identify optimal target propofol and remifentanil concentrations to avoid a gag reflex in response to insertion of an upper gastrointestinal endoscope.

METHODS: Patients presenting for endoscopy received target-controlled infusions (TCI) of both propofol and remifentanil for sedation-analgesia. Patients were randomized to 4 groups of fixed target effect-site concentrations: remifentanil 1 ng·mL^{-1} (REMI 1) or 2 ng·mL^{-1} (REMI 2) and propofol 2 μg·mL^{-1} (PROP 2) or 3 μg·mL^{-1} (PROP 3). For each group, the other drug (propofol for the REMI groups and vice versa) was increased or decreased using the "up-down" method based on the presence or absence of a gag response in the previous patient. A modified isotonic regression method was used to estimate the median effective $C_{e,50}$ from the up-down method in each group. A concentration-effect (sigmoid E_{max}) model was built to estimate the corresponding $C_{e,90}$ for each group. These data were used to estimate propofol bolus doses and remifentanil infusion rates that would achieve effect-site concentrations between $C_{e,50}$ and $C_{e,90}$ when a TCI system is not available for use.

RESULTS: One hundred twenty-four patients were analyzed. To achieve between a 50% and 90% probability of no gag response, propofol TCIs were between 2.40 and 4.23 μg·mL^{-1} (that could be achieved with a bolus of 1 mg·kg^{-1}) when remifentanil TCI was fixed at 1 ng·mL^{-1}, and target propofol TCIs were between 2.15 and 2.88 μg·mL^{-1} (that could be achieved with a bolus of 0.75 mg·kg^{-1}) when remifentanil TCI was fixed at 2 ng·mL^{-1}. Remifentanil ranges were 1.00 to 4.79 ng·mL^{-1} and 0.72 to 3.19 ng·mL^{-1} when propofol was fixed at 2 and 3 μg·mL^{-1}, respectively.

CONCLUSIONS: We identified a set of propofol and remifentanil TCIs that blocked the gag response to endoscope insertion in patients undergoing endoscopy. Propofol bolus doses and remifentanil infusion rates designed to achieve similar effect-site concentrations can be used to prevent gag response when TCI is not available. (Anesth Analg 2015;121:90–6)

Gastrointestinal endoscopy is one function of nonoperating room anesthesia in which anesthetic services have expanded most. Upper gastrointestinal procedures sometimes require sedation and analgesia in cases where a long diagnostic or therapeutic procedure is anticipated or when the patient will not tolerate the introduction of the endoscopy probe.[1] Gag reflex response to the introduction of the tube is common in this setting.[2]

In addition to having discomfort and pain, patients[3] who experience a gag response can be at risk for significant hemodynamic changes and, on rare occasions, esophageal rupture.[4] Although the gag reflex has been estimated to be absent in around 30% of healthy subjects, its presence cannot be predicted.[2] Adequate sedation and analgesia may be helpful for managing patient stress on endoscope placement. Propofol and remifentanil are powerful but titratable anesthetic drugs that can be administered by means of a target-controlled infusion (TCI) system. Previous work from our group has reported combinations of propofol and remifentanil target effect-site concentrations that achieve and maintain moderate sedation (arousable with verbal and tactile stimuli) during upper gastrointestinal endoscopy.[5]

Under the hypothesis that adequate sedation and analgesia could prevent the occurrence of gag, the purpose of the present study is to determine propofol and remifentanil effect-site concentrations that can predictably block the gag reflex in patients undergoing upper gastrointestinal endoscopic procedures.

METHODS

Patients in this study were part of a larger project to evaluate the influence of a specific genetic polymorphism, A118G, on

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the requirements for remifentanil during sedation-analgesia using the bispectral index of the electroencephalogram.[6]

The protocol was approved by the investigational review board of Hospital Clinic de Barcelona. All patients gave their written informed consent to participate in this study. Patients undergoing an ultrasonographic endoscopy of the upper gastrointestinal tract were randomized to 4 groups depending on the fixed target effect-site concentration of either propofol or remifentanil administered: remifentanil 1 ng•mL^{-1}, remifentanil 2 ng•mL^{-1}, propofol 2 μg•mL^{-1}, or propofol 3 μg•mL^{-1}. The groups were named REMI 1, REMI 2, PROP 2, or PROP 3, respectively.

Patient Monitoring

Patients were noninvasively monitored with continuous electrocardiography, arterial blood pressure, pulse oximetry, respiratory rate analysis based on thoracic bioimpedance, and transcutaneous continuous carbon dioxide measurement using a SenTec Digital Monitoring System (SenTec AG, Therwil, Switzerland). The degree of sedation was monitored by the attending anesthesiologist using the Ramsay Sedation Score to maintain a Ramsay Sedation Score of 4.[7] Before starting drug administration, patients were lying on their left side in a quiet environment for 5 minutes.

Drug Administration and End Point Evaluation

Propofol and remifentanil were administered by TCI system (Base Primea; Fresenius Kabi, Brezins, France) by using published pharmacokinetic models for propofol[8,9] and remifentanil.[10]

The study used up-and-down sequential allocation design.[11,12] For the REMI 1 and REMI 2 subjects, the initial target effect-site concentrations of propofol were 3.5 and 2.5 μg•mL^{-1}, respectively. For the PROP 2 and PROP 3 subjects, the initial target effect-site concentration of remifentanil was 1.5 ng•mL^{-1}. The 4 groups as well as the initial targets to allocate the patients or the magnitude of changes in targets were selected based on work published previously by our laboratory.[5]

The main outcome measure was the presence or absence of a gag response to insertion of an endoscope probe. Gag response was determined by the same endoscopist for all patients. The presence of a gag response was defined as retching, cough, and/or patient refusal with introduction of the endoscopy probe. Target concentrations of the nonfixed drug were individually adjusted based on the presence or absence of gag in the previous patient.

For groups REMI 1 or REMI 2, the target concentration of propofol in the next patient of the group was increased by 0.5 μg•mL^{-1} if the gag response was present indicating ineffective concentration, and it was decreased by the same concentration if there was no gag response indicating effective concentration.

For groups PROP 2 or PROP 3, the target concentration of remifentanil in the next patient of the group was increased by 0.5 ng•mL^{-1} when gag was present and was decreased by the same concentration when a gag response was absent. After an assessment of gag response, the drug target concentrations were adjusted at the discretion of the anesthesiologist for the remainder of the procedure.

Using the up-down method, each group required the inclusion of >20 subjects to provide stable estimates of target concentrations.[12,13]

Data Collection

Physiologic and drug infusion data were recorded using a computerized data acquisition system (Rugloop, Demed, Belgium, and Hyperterminal®, Windows; Microsoft, Redmond, WA) at 1-second intervals and stored for data analysis. The exact time at the introduction and extraction of the endoscopy probe, when a gag response was observed, and any other event considered relevant to the study by the attending anesthesiologist were manually entered into the data acquisition system.

Data Analysis

The presence or absence of a gag response was recorded at each target concentration. Observations at a given concentration were reported as an observed response rate. The observed response rate was defined as the number of blocked gag responses over the total number of assessment at a given target concentration. The concentration data for each group was further analyzed using a modified isotonic regression method consisting of an up-and-down sequential allocation design to determine the median effective concentration ($C_{e,50}$).

Isotonic regression is a well-described variant of restricted least-squares regression based on the implicit assumption that drug effect increases with an increasing dose or concentration. However, this assumption is not always accurate when the observed response rate is computed from the sequential dose-responses, which could present unexpected ups and downs because of patient variability, among other causes. To minimize the influence of patient variability, an adjusted response probability was calculated, using a pooled-adjacent-violators algorithm (PAVA),[12] to ensure a monotonic response rate. Accordingly, estimated $C_{e,50s}$ using the isotonic regression method are always monotonic increasing (never decreasing) or monotonic decreasing (never increasing), showing favorable statistical properties. An isotonic point may be constant over some range of target effect-site concentrations. At each assigned dose, an adjusted response probability is easily calculated by the PAVA. The modified isotonic method as described by Stylianou and Flournoy[14] was used because of its efficiency in estimating $C_{e,50s}$ (i.e., requires fewer up-down assessments to reach a stable value than other approaches).

A comparison of $C_{e,50}$ between groups REMI 1 and REMI 2 or groups PROP 2 and PROP 3 was made using the overlapping confidence intervals (CIs) method.[15] This highly conservative approach assesses overlap of the 83% CI between groups. If there is overlap, then the null hypothesis of equal $C_{e,50}$ is rejected at a significance level α of approximately 0.05.

Pharmacodynamic Model Development

Based on the $C_{e,50}$ values estimated from the isotonic method, and effect-site concentration—gag response data, the steepness of the curve, γ, was estimated by fitting the

Table 1. Anthropometric Characteristics of Patients in Each Group

Groups	N	Gender (M/F)	Age (years)	Weight (kg)	Height (cm)
REMI 1	26	14/12	65 (25–88)	70 (41–100)	164 (146–180)
REMI 2	27	17/10	66 (30–84)	65 (40–92)	163 (140–182)
PROP 2	42	33/9	64 (25–84)	71.5 (35–102)	166.5 (149–186)
PROP 3	29	19/10	59 (22–83)	73 (44–104)	166 (148–190)

Values expressed as median (min–max) except for gender (M/F).
REMI 1 = remifentanil 1 ng·mL^{-1}; REMI 2 = remifentanil 2 ng·mL^{-1}; PROP 2 = propofol 2 μg·mL^{-1}; PROP 3 = propofol 3 μg·mL^{-1}.

logistic regression model to the observations in all 4 groups, as follows:

$$P = \frac{C_e^{\gamma}}{C_e^{\gamma} + C_{e,50}^{\gamma}} \quad (1)$$

Where P is the probability of absence of gag response, C_e is the predicted propofol concentration (for groups REMI 1 and REMI 2) or remifentanil concentration (for groups PROP 2 and PROP 3), and maximum likelihood function was the objective function to be minimized. This model was used to estimate the $C_{e,90}$, the predicted effect-site concentration associated with a probability of absence of gag of 0.9.

Dosing Simulations

Using simulation software (PKPD tools for Excel[a]) and published pharmacokinetic models for propofol[8,9] and for remifentanil,[10] simulations were conducted to identify propofol bolus doses and remifentanil infusion rates that would result in effect-site concentrations between the $C_{e,50}$ and $C_{e,90}$ for loss of gag response in each group.

RESULTS

The sample size in each group was previously determined in a study exploring the prevalence of the single nucleotide polymorphism A118G in general population. From 160 patients randomized for inclusion in this analysis, 124 were included in this study. With 12 patients, the endoscopist was not a member of the research team and was not familiar with the criteria defining gag response. With 5 patients, evaluation of the gag response was unclear. With 6 patients, there was an error in programming the correct dose. With 6 patients, there was an error in entering the events correctly into the data collection software. With 7 patients, there were technical problems related to data collection software.

No episodes of apnea or intolerable respiratory depression, defined as a decrease in oxygen saturation <90% or a respiratory rate <4 breath•min^{-1} requiring interruption of the procedure or manual or assisted ventilation, were observed. Administration of atropine or ephedrine because of hemodynamic changes was not required. No patient complained of nausea and/or vomiting in the postanesthesia care unit.

Table 1 summarizes the characteristics of the patient for groups REMI 1, REMI 2, PROP 2, and PROP 3.

Figure 1 shows the up-and-down sequences for the 4 study groups. The estimation of the median effective concentration $C_{e,50}$ (solid line) and the 95% CIs (dashed line), using the modified isotonic regression method, are also represented in these figures. There is a clear reduction of the $C_{e,50}$ in the group REMI 2 in relation with the group REMI 1. Similarly, the $C_{e,50}$ in the group PROP 3 tends to be lower than in the group PROP 2 as can be seen in Figure 1, but there is an overlapping between the CIs of both groups.

Table 2 presents the propofol and remifentanil $C_{e,50s}$ and their accompanying 83% and 95% CIs from the modified isotonic regression method. Based on the 83% CIs, the differences in propofol $C_{e,50}$ for groups REMI 1 and REMI 2 are significant ($P < 0.05$), whereas differences in remifentanil $C_{e,50}$ for groups PROP 2 and PROP 3 are not.

The observed response rates for each concentration of propofol or remifentanil and the predicted response based on the PAVA of the isotonic regression are presented in Figure 2. For groups REMI 1 and PROP 3, the observed response rate is not monotonically increasing with increasing concentration. By contrast, with the PAVA algorithm, the predicted response rate is monotonically increasing with increasing concentration.

Pharmacodynamic Model Development

Figure 3 presents the concentration-effect model predictions for each group and the 0.5 and 0.9 probabilities of no gag response. Table 3 presents the parameter values for γ and $C_{e,90}$ estimated by logistic regression by using a sigmoid E_{max} model structure.

Propofol bolus (mg•kg^{-1}) and remifentanil infusion rates (μg•kg^{-1}•min^{-1}) were identified that achieved predicted concentrations that would have between a 50% and 90% probability of blocking a gag response. For a target remifentanil concentration of 1 ng•mL^{-1}, the infusion rate is 0.05 μg•kg^{-1}•min^{-1} and is combined with a propofol bolus of 1 mg•kg^{-1}. For a remifentanil target concentration of 2 ng•mL^{-1}, the remifentanil infusion rate is 0.1 μg•kg^{-1}•min^{-1} and is combined with a propofol bolus of 0.75 mg•kg^{-1}. The remifentanil continuous infusions will reach approximately 75% of steady-state concentration 5 minutes after the start of the infusion.

DISCUSSION

The present work provides a set of clinically relevant C_e targets for propofol or remifentanil TCIs to avoid a gag response with insertion of an upper gastrointestinal endoscope. It also provides propofol bolus and remifentanil infusion rate recommendations that achieve and maintain the similar effect-site concentrations of propofol and remifentanil when TCI systems are unavailable and a bolus or constant continuous infusion must be used.

The $C_{e,50}$ value for propofol or remifentanil in combination with selected TCI of the other drug allowed for an exploration of various dosing options and for a starting point for drug administration. One drawback to the $C_{e,50}$,

[a]Available at: http://www.pkpdtools.com. Accessed August 29, 2014.

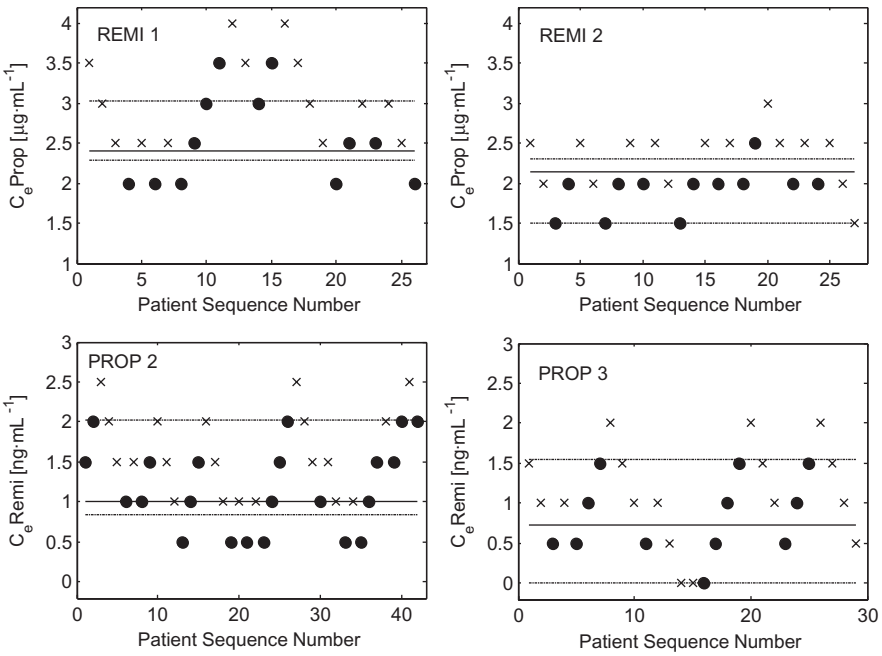

Figure 1. Sequential allocation graph to show the series of effective and ineffective concentrations in groups: REMI 1, REMI 2, PROP 2, and PROP 3. Effective concentration (absence of gag) is denoted by "x" and ineffective concentration (presence of gag response) is denoted by a solid circle. The $C_{e,50}$ (solid line) and the 95% confidence intervals (dashed line) are also indicated. REMI 1 and REMI 2 indicate remifentanil target effect-site concentrations of 1 and 2 ng·mL^{-1}, respectively, and PROP 2 and PROP 3 indicate propofol target effect-site concentrations of 2 and 3 μg·mL^{-1}, respectively.

Table 2. Median Effective Concentration ($C_{e,50}$) of Propofol for Groups REMI 1 and REMI 2 and Remifentanil for Groups PROP 2 and PROP 3

Groups	Fixed target	Median effective concentration	95% CI	83% CI
REMI 1	Remifentanil 1 ng·mL^{-1}	$C_{e,50}$ Prop = 2.40 μg·mL^{-1}	2.28–3.02	2.30–2.50
REMI 2	Remifentanil 2 ng·mL^{-1}	$C_{e,50}$ Prop = 2.15 μg·mL^{-1}	1.50–2.30	1.96–2.25*
PROP 2	Propofol 2 μg·mL^{-1}	$C_{e,50}$ Remi = 1.00 ng·mL^{-1}	0.84–2.03	0.87–1.68
PROP 3	Propofol 3 μg·mL^{-1}	$C_{e,50}$ Remi = 0.72 ng·mL^{-1}	0.00–1.56	0.00–1.26

Values are given as mean (95% CI) (83% CI).
REMI 1 = remifentanil 1 ng·mL^{-1}; REMI 2 = remifentanil 2 ng·mL^{-1}; PROP 2 = propofol 2 μg·mL^{-1}; PROP 3 = propofol 3 μg·mL^{-1}; CI = confidence interval.
*$P < 0.05$ ($C_{e,50}$ propofol between REMI 1 and REMI 2).

however, is that it assumes that half of the patients will still have a gag response. To provide a more clinically relevant target, we used the logistic model to estimate the $C_{e,90}$, a target concentration more likely to lead to a loss of a gag response in most patients.

The results presented here are consistent with previous work from our group. In a previous study, we found that in the absence of remifentanil, a C_e of propofol of 2.7 μg•mL^{-1} was required to maintain moderate sedation where patients would respond to tactile, but not to verbal, stimulation. When combining the propofol with remifentanil TCI set to 1.5 ng•mL^{-1}, the propofol target concentration was decreased to 1.8 μg•mL^{-1} to achieve the same level of sedation.[5] In the present work, we found that drug requirements to achieve a loss of gag response were higher than those required for sedation reflecting the increase in noxious stimulation associated with endoscope insertion compared with maintaining moderate sedation in an unstimulated state (responsive to tactile stimulation).

The $C_{e,50}$ of propofol used alone to blunt movement response to laryngoscopy has been estimated to be 5.6 μg•mL^{-1}. As expected, propofol target concentrations can be decreased to 3 μg•mL^{-1} when the remifentanil concentration is increased to 2 ng•mL^{-1}. Our propofol $C_{e,50}$ estimate for the REMI 2 group is 2.15 μg•mL^{-1}, again reflecting the difference in intensity of stimulation between laryngoscopy, a more stressful stimuli than endoscope insertion.

Our results are also consistent with those reported in volunteers. LaPierre et al.[16] measured the response to esophageal instrumentation at various pairs of propofol and remifentanil target effect-site concentrations and built an interaction pharmacodynamic model. Based on their model, the 50% and 95% probability of no response to esophageal instrumentation were target propofol-remifentanil effect-site concentrations of 2 μg•mL^{-1} and 2 ng•mL^{-1} for 50% and 3 μg•mL^{-1} and 3 ng•mL^{-1} for 95%, respectively. Our estimates for $C_{e,50}$ and $C_{e,90}$ are very close to the $C_{e,50}$ and $C_{e,95}$ of their isobolograms (isoeffect lines).

Previous work has also explored requirements of propofol alone to avoid a gag response in different adult age groups. Kazama et al.[17] estimated that a propofol $C_{e,50}$ of 2.98 μg•mL^{-1} is necessary to block the gag response in patients 17 to 49 years old although these authors reported a high degree of variability. Based on their findings, it could be argued that propofol dosing would be enough, without any requirement for remifentanil. This was not the case in any of the groups we studied. There were 2 consecutive patients with a remifentanil target of 0 in the PROP 3 group, but the trend subsequently increased to higher remifentanil target concentrations.

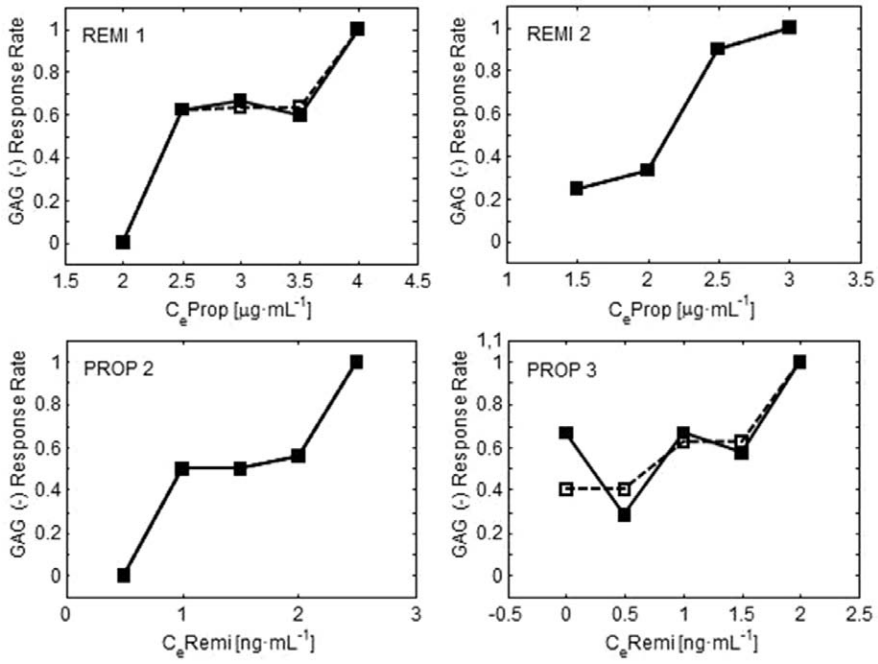

Figure 2. Graphical representation of observed and predicted response rate in groups. Observed (solid line and solid square) and pooled-adjacent-violators algorithm (dashed line, open square) response rate in groups: REMI 1, REMI 2, PROP 2, and PROP 3. REMI 1 and REMI 2 indicate remifentanil target effect-site concentrations of 1 and 2 ng·mL^{-1}, respectively, and PROP 2 and PROP 3 indicate propofol target effect-site concentrations of 2 and 3 µg·mL^{-1}, respectively.

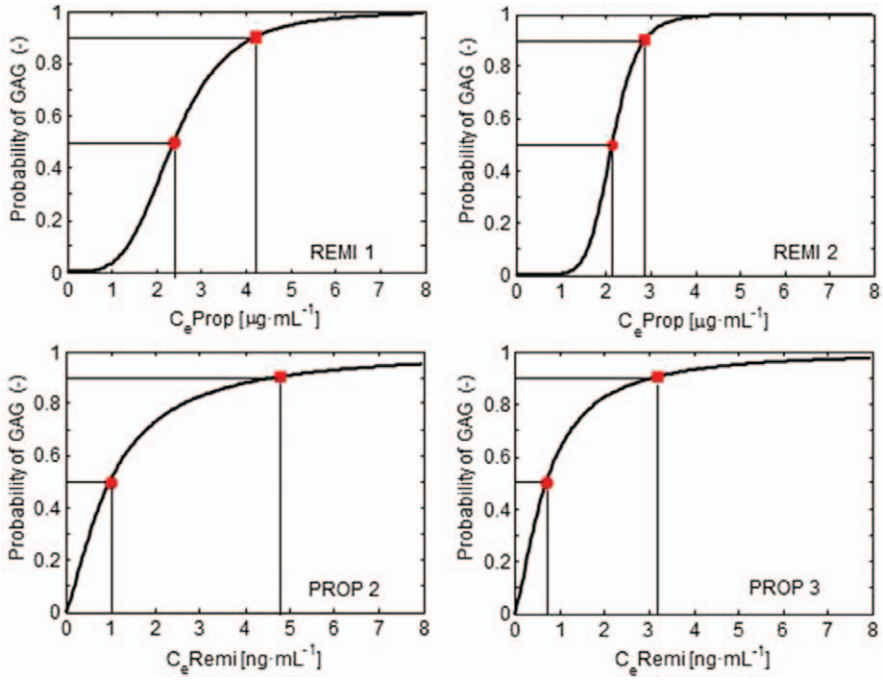

Figure 3. Estimation of $C_{e,50}$ (circle) and $C_{e,90}$ (square) values associated with a probability of absence of gag response of 0.5 and 0.9, respectively. Each group depicted in REMI 1, REMI 2, PROP 2, and PROP 3. REMI 1 and REMI 2 indicate remifentanil target effect-site concentrations of 1 and 2 ng·mL^{-1}, respectively, and PROP 2 and PROP 3 indicate propofol target effect-site concentrations of 2 and 3 µg·mL^{-1}, respectively. $C_{e,90}$ = predicted effect-site concentration associated with a probability of absence of gag of 0.9; $C_{e,50}$ = median effective concentration associated with a probability of absence of gag of 0.5.

From the present analysis, we can only state that both drugs work well together, a fact that we already described for a different pharmacodynamic end point in a previous publication.[5] It is important to point out that propofol by itself has no analgesic properties and thus requires high effect-site concentrations to blunt responses, usually rendering patients unresponsive. With the addition of a modest dose of opioid, patients are profoundly analgesic yet often remain responsive to verbal or tactile stimuli.

The 2 consecutive patients with a remifentanil target of 0 in the PROP 3 group may have contributed to the lack of a statistical difference in the remifentanil $C_{e,50}$ between the PROP 2 and PROP 3 groups. Although there was no difference in $C_{e,50}$, the estimates for $C_{e,90}$ in the same groups were substantially different.

One potential issue with the up-down method is the sample size necessary to identify the $C_{e,50}$. Previous works by other authors have used similar sample size design to our work.[12,13] In a methods article, Stylianou and Flournoy explored identifying a toxic dose in as few subjects as possible using the up-down method. They compared 5 different estimators and reported reaching an equilibrium point after

Table 3. Values of Gamma and $C_{e,90}$ Concentration-Effect (Sigmoid E_{max}) Model Estimated Using Concentration-Effect (E_{max}) and Simulation Software (PKPD Tools) Models, Respectively

Groups	Gamma	$C_{e,90}$
REMI 1	3.9	$C_{e,90}$ Prop = 4.23 μg·mL^{-1}
REMI 2	7.5	$C_{e,90}$ Prop = 2.88 μg·mL^{-1}
PROP 2	1.4	$C_{e,90}$ Remi = 4.79 ng·mL^{-1}
PROP 3	1.5	$C_{e,90}$ Remi = 3.19 ng·mL^{-1}

Groups are (REMI 1) remifentanil 1 ng·mL^{-1}, (REMI 2) remifentanil 2 ng·mL^{-1}, (PROP 2) propofol 2 μg·mL^{-1}, or (PROP 3) 3 μg·mL^{-1}.

$C_{e,90}$ = predicted effect-site concentration associated with a probability of absence of gag of 0.9; $C_{e,50}$ = median effective concentration associated with a probability of absence of gag of 0.5.

20 or so subjects.[14] After 40 subjects, the estimators showed minimal change from the previous 20. Thus, we concluded that our group sizes of 25 patients were adequate in identifying $C_{e,50s}$ in each group.

We observed no significant ventilatory depression in patients enrolled in our study. This is in contrast to the observations made by LaPierre et al. in volunteers. In their study, escalating TCIs of propofol and remifentanil were administered to identify effect-site concentrations that would block the response to esophageal instrumentation. Some subjects developed intolerable respiratory depression at higher effect-site concentrations.[17] In our study, no patient required manual or assisted ventilation. This may have been attributed to the ongoing endoscopy procedure with its associated esophageal and gastric stimuli that preserved respiratory function.

The study design used in the present work did not offer a wide range of propofol and remifentanil concentrations as would be provided in an interaction study. However, it did provide a set of propofol and remifentanil effect-site concentration targets that an anesthesiologist could choose from that have a high probability of blocking a gag response during endoscopy. Although our results were based on responses during upper gastrointestinal endoscopy, they could easily be extrapolated to other procedures associated with a gag response, such as fiberoptic endotracheal intubation or bronchoscopy.

In summary, we measured the presence or absence of a gag response in patients undergoing upper endoscopy procedures anesthetized with various propofol/remifentanil TCIs. Using a sequential method analysis, we estimated the $C_{e,50}$ for propofol in the presence of a background TCI infusion of remifentanil and the $C_{e,50}$ for remifentanil in the presence of background TCI infusion of propofol to block a gag responses for 4 different target-controlled dosing regimens. From that data, using a combined pharmacokinetic-pharmacodynamic model, we also estimated the $C_{e,90}$ necessary to block a gag response for the same 4 dosing regimens. Finally, we estimated propofol bolus doses and remifentanil infusions rates that would achieve target effect-site concentrations between the $C_{e,50}$ and $C_{e,90}$ for blocking a gag response.

To conclude, we identified a set of propofol and remifentanil TCIs that blocked the gag response to endoscope insertion in patients undergoing endoscopy. Propofol bolus doses and remifentanil infusion rates designed to achieve similar effect-site concentrations can be used to achieve a loss of gag response when TCI is not available.

DISCLOSURES

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Attestation: Xavier Borrat has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
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Contribution: This author helped design the study, analyze the data, and write the manuscript.
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REFERENCES

1. Abraham N, Barkun A, Larocque M, Fallone C, Mayrand S, Baffis V, Cohen A, Daly D, Daoud H, Joseph L. Predicting which patients can undergo upper endoscopy comfortably without conscious sedation. Gastrointest Endosc 2002;56:180–9
2. Davies AE, Kidd D, Stone SP, MacMahon J. Pharyngeal sensation and gag reflex in healthy subjects. Lancet 1995;345:487–8
3. Campo R, Brullet E, Montserrat A, Calvet X, Moix J, Rué M, Roqué M, Donoso L, Bordas JM. Identification of factors that influence tolerance of upper gastrointestinal endoscopy. Eur J Gastroenterol Hepatol 1999;11:201–4
4. Püschel K. An unusual case of Boerhave syndrome. Esophageal rupture during preparation for gastroscopy. Dtsch Med Wochenschr 1985;110:726–8
5. Gambús PL, Jensen EW, Jospin M, Borrat X, Martínez Pallí G, Fernández-Candil J, Valencia JF, Barba X, Caminal P, Trocóniz IF. Modeling the effect of propofol and remifentanil combinations for sedation-analgesia in endoscopic procedures using an Adaptive Neuro Fuzzy Inference System (ANFIS). Anesth Analg 2011;112:331–9
6. Borrat X, Trocóniz IF, Valencia JF, Rivadulla S, Sendino O, Llach J, Muñoz J, Castellví-Bel S, Jospin M, Jensen EW, Castells A, Gambús PL. Modeling the influence of the A118G polymorphism in the OPRM1 gene and of noxious stimulation on the synergistic relation between propofol and remifentanil: sedation and analgesia in endoscopic procedures. Anesthesiology 2013;118:1395–407
7. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974;2:656–9
8. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998;88:1170–82
9. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90:1502–16
10. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL. Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil. I. Model development. Anesthesiology 1997;86:10–23
11. Dixon WJ. Staircase bioassay: the up-and-down method. Neurosci Biobehav Rev 1991;15:47–50
12. Pace NL, Stylianou MP. Advances in and limitations of up-and-down methodology: a précis of clinical use, study design, and dose estimation in anesthesia research. Anesthesiology 2007;107:144–52
13. Gupta PK, Pace NL, Hopkins PM. Effect of body mass index on the ED50 volume of bupivacaine 0.5% for supraclavicular brachial plexus block. Br J Anaesth 2010;104:490–5
14. Stylianou M, Flournoy N. Dose finding using the biased coin up-and-down design and isotonic regression. Biometrics 2002;58:171–7
15. Payton ME, Greenstone MH, Schenker N. Overlapping confidence intervals or standard error intervals: what do they mean in terms of statistical significance? J Insect Sci 2003;3:34:1–6
16. LaPierre CD, Johnson KB, Randall BR, White JL, Egan TD. An exploration of remifentanil-propofol combinations that lead to a loss of response to esophageal instrumentation, a loss of responsiveness, and/or onset of intolerable ventilatory depression. Anesth Analg 2011;113:490–9
17. Kazama T, Takeuchi K, Ikeda K, Ikeda T, Kikura M, Iida T, Suzuki S, Hanai H, Sato S. Optimal propofol plasma concentration during upper gastrointestinal endoscopy in young, middle-aged, and elderly patients. Anesthesiology 2000;93:662–9