

Determination of the Pharmacodynamic Interaction of Propofol and Remifentanil during Esophagogastroduodenoscopy in Children

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Background: **Propofol is commonly used to anesthetize children undergoing esophagogastroduodenoscopy. Opioids are often used in combination with propofol to provide total intravenous anesthesia. Because both propofol and remifentanil are associated with rapid onset and offset, the combination of these two drugs may be particularly useful for procedures of short duration, including esophagogastroduodenoscopy. The authors previously demonstrated that the median effective concentration (C_{50}) of propofol during esophagogastroduodenoscopy in children is 3.55 μg/ml. The purpose of this study was to describe the pharmacodynamic interaction of remifentanil and propofol when used in combination for esophagogastroduodenoscopy in pediatric patients.**

Methods: **The authors studied 32 children aged between 3 and 10 yr who were scheduled to undergo esophagogastroduodenoscopy. Propofol was administered *via* a target-controlled infusion system using the STANPUMP software based on a pediatric pharmacokinetic model. Remifentanil was administered as a constant rate infusion of 25, 50, and 100 ng · kg^{-1} · min^{-1} to each of three study groups, respectively. A sigmoid Emax model was developed to describe the interaction of remifentanil and propofol.**

Results: **There was a positive interaction between remifentanil and propofol when used in combination. The concentration of propofol alone associated with 50% probability of no response was 3.7 μg/ml (SE, 0.4 μg/ml), and this was decreased to 2.8 μg/ml (SE, 0.1 μg/ml) when used in combination with remifentanil.**

Conclusion: **A remifentanil infusion of 25 ng · kg^{-1} · min^{-1} reduces the concentration of propofol required for adequate anesthesia for esophagogastroduodenoscopy from 3.7 to 2.8 μg/ml. Increasing the remifentanil infusion yields minimal additional decrease in propofol concentration and may increase the risk of side effects.**

BECAUSE of its desirable pharmacokinetic and pharmacodynamic properties, propofol is widely used for induction and maintenance of anesthesia in both adults and children. The pharmacokinetics of propofol are characterized by a rapid distribution into peripheral tissues as well as rapid clearance. This results in a rapid decrease in plasma propofol concentration after the infusion is terminated.[1–3] The pharmacodynamic properties of propofol include early return of alertness and decreased nausea and vomiting.[4,5] As a result, propofol is appropriate for intravenous anesthesia for outpatient procedures, including esophagogastroduodenoscopy. In clinical practice, propofol is commonly combined with an opioid to produce complete anesthesia while substantially reducing the propofol dose.[6–8]

Because remifentanil, like propofol, is associated with rapid onset and offset, the combination of propofol and remifentanil may be particularly useful for procedures of short duration, including esophagogastroduodenoscopy. Nevertheless, appropriate dosing regimens for the combination of propofol and remifentanil in children have not been characterized. Accordingly, we conducted this study to describe the pharmacodynamic interaction of remifentanil and propofol when used in combination for esophagogastroduodenoscopy in pediatric patients.

Materials and Methods

Clinical Trial Design

After approval was obtained by the institutional review board (Stanford University, Stanford, California) and written, informed consent was obtained from parents, we studied 32 children aged between 3 and 10 yr who were scheduled to undergo esophagogastroduodenoscopy. This age range was selected because propofol pharmacokinetics have been published for this pediatric population.[9] Exclusion criteria were lack of informed consent; allergy to propofol; obesity (weight for height $>$ 95th percentile)[10]; and significant cardiac, metabolic, hepatic, or renal disease. All patients received nothing per mouth according to the Department of Anesthesia guidelines ($\geq$ 8 h for milk/solid food, $\geq$ 3 h for clear liquids). No premedication was administered. Lidocaine and prilocaine cream (EMLA®; AstraZeneca Pharmaceuticals LP, Wilmington, DE) was applied to the skin of upper or lower extremity sites to facilitate placement of an intravenous catheter before administration of propofol. No topical pharyngeal anesthesia was used.

All patients were monitored with continuous electrocardiography and pulse oximetry. Noninvasive blood pressure measurements were made at 1- to 2.5-min intervals throughout the study period. Oxygen (2 l/min) was administered *via* nasal cannula beginning just before or immediately after initiation of propofol infusion,

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Table 1. Patient Demographics, Assigned Group, Remifentanil and Propofol Dose and Response/No Response Result Data

Patient No.	Group	Age, yr	Weight, kg	Remifentanil, ng · kg^{-1} · min^{-1}	Propofol, μg/ml	Response/No Response
1	1	8	33	0	1.0	R
2	1	4	20	0	1.25	R
3	1	8	23.5	0	1.60	R
4	1	10	52.8	0	2.0	R
5	1	9	29.1	0	2.5	R
6	1	10	27.7	0	3.2	R
7	1	4	12.3	0	4.0	R
8	1	10	25	0	5.0	NR
9	1	9	31.7	0	4.0	NR
10	1	6	19.9	0	3.2	NR
11	1	5	19.2	0	2.5	R
12	1	3	9.7	0	3.2	R
13	2	9	24.7	25	2.0	R
14	2	6	21.5	25	2.5	R
15	2	10	57.4	25	3.2	NR
16	2	10	26.6	25	2.5	R
17	2	4	16.5	25	3.2	NR
18	2	9	28.1	25	2.5	R
19	2	8	27	25	3.2	NR
20	3	9	52.2	50	2.5	R
21	3	9	31.4	50	3.2	NR
22	3	8	25.5	50	2.5	R
23	3	7	22.2	50	3.2	NR
24	3	9	48.6	50	2.5	NR
25	3	8	22.7	50	2.0	R
26	3	9	28.8	50	2.5	R
27	4	10	21.2	100	2.5	R
28	4	8	54.5	100	3.2	NR
29	4	10	30	100	2.5	NR
30	4	8	29	100	2.0	R
31	4	10	25.4	100	2.5	R
32	4	3.5	15	100	3.2	R

Group number denotes the dose of remifentanil. All responses were patient movement.
NR = no response; R = response (see text for definition of response).

depending on patient cooperation. All episodes of bradycardia (heart rate < 80% of baseline), tachycardia (heart rate > 120% of baseline), hypotension (blood pressure < 80% of baseline), hypertension (blood pressure > 120% of baseline), and oxygen desaturation (Spo_2 < 94%) were recorded.

Patients were enrolled into four groups in a consecutive manner. Group 1 patients were given anesthesia with propofol as the sole anesthetic agent. Groups 2, 3, and 4 were given anesthesia with a combination of propofol and remifentanil. The dose of remifentanil for groups 2, 3, and 4 was a constant rate infusion of 25, 50, and 100 ng · kg^{-1} · min^{-1}, respectively. Propofol was administered *via* a target-controlled infusion system using the STANPUMP software‖ based on a pediatric pharmacokinetic model.[9] Because the median effective concentration (C_{50}) of propofol in the presence of remifentanil was not known, the sample size for each group was calculated using the up-and-down experimental design described by Dixon.[11–13] For purposes of this study, a patient was considered to have no response to stimuli if there was minimal movement and the heart rate and blood pressure remained at 120% of baseline or less during the procedure. Patients who moved excessively, *i.e.*, requiring more than gentle restraint, or who manifested heart rate and blood pressure greater than 120% of baseline were considered to have had a response to stimuli. The study was terminated as soon as excessive movement or increase of heart rate and blood pressure were noted, and the propofol infusion was increased at the discretion of the anesthesiologist.

Group 1 (propofol only) was completed first. These results have been published.[14] The target plasma propofol concentration for the first patient studied in group 1 was 1.0 μg/ml. The target plasma propofol concentration for each subsequent patient was determined by the response of the previous patient. If a patient was adequately anesthetized (*i.e.*, had no response to stimuli), the target plasma propofol concentration for the subsequent patient was decreased by 0.1 log interval. If a patient had a response to stimuli, the target plasma propofol concentration for the subsequent patient was increased by 0.1 log interval (table 1). Taking into consideration the results of the analysis of group 1, the

‖ STANPUMP. Available at: http://anesthesia.stanford.edu/pkpd. Accessed September 14, 2003.

target plasma propofol concentration for the first patient in group 2 was 2.0 μg/ml and in groups 3 and 4 was 2.5 μg/ml; subsequent concentrations were determined as described above for group 1.

To allow for equilibration between plasma and effect compartment, the propofol and remifentanil infusions were initiated 5 min before insertion of the endoscope (Olympus GIF P140 or GIF XQ140 endoscope; Olympus, Tokyo, Japan). Propofol was given by a target-controlled infusion to rapidly attain the desired plasma concentration of propofol and to provide an induction of anesthesia comparable to routine practice. In contrast, remifentanil was given by a fixed rate infusion to avoid a "bolus effect" of this potent opioid and because remifentanil effect concentration reaches equilibrium rapidly. The propofol and remifentanil infusions were started simultaneously.

Deriving the Interaction from the Study Data

The clinical effects of an individual anesthetic drug may be described by relating drug effect (E) to drug concentration (C) using a sigmoid mathematical model:

$$E = E_0 + (Emax - E_0)\frac{C^{\gamma}}{C_{50}^{\gamma} + C^{\gamma}}, \quad (1)$$

where E_o is the baseline effect, Emax is the maximal drug effect, C is the drug concentration, C_{50} is the drug concentration that produces 50% of maximal effect, and γ describes the sigmoidicity of the relation. When the drug concentration is altered and a clinical response is measured, this allows for estimation of a single sigmoid curve to characterize the relation between drug concentration and drug effect. When more than one drug is administered to produce an anesthetic effect, as in clinical practice, multiple sigmoid curves can be generated for each concentration of a particular drug.[15,16] Propofol and remifentanil were infused together to produce the measured anesthetic endpoint, which is "response" or "no response" to the stimulus of the procedure. Several pharmacodynamic models were considered to first determine whether there was a significant interaction between the two drugs; subsequently, models were considered that would best characterize the interaction between the two drugs. The basic models considered were a simple sigmoid Emax model as described above for all data, multiple sigmoid curves for each concentration of remifentanil, and a surface response interaction model.[16] The above equations were implemented into NONMEM version V (NONMEM Project Group, University of California, San Francisco, California) such that response data with estimated plasma concentrations and infusion rates were analyzed by nonlinear regression. The pharmacodynamic parameters were estimated using a first-order method with likelihood estimation. SEs were calculated by NONMEM with the parameter estimates. Best fits to the data were assessed using the NONMEM log likelihood (likelihood ratio test); the *P* value was calculated from the chi-square distribution.

Results

Thirty-two subjects aged 3–10 yr were enrolled, and all subjects completed the study protocol. No patient had bradycardia or hypotension. Three patients in group 4 (100 ng · kg^{-1} · min^{-1}) had oxygen desaturation and required positive pressure ventilation before insertion of the endoscope. All three patients improved with stimulation (*e.g.*, jaw thrust) and insertion of the endoscope. The patient demographics, group number, propofol and remifentanil doses, and response/no response measurements are included in table 1. All responses of the subjects were movement responses; hemodynamic variables always remained within 120% of baseline.

When all propofol and remifentanil data, taken together, were initially analyzed with a simple model, the fit was significantly different ($P < 0.05$) than when the propofol group was fit separately. This difference showed that when remifentanil was present, the 50% effect concentration was different than when propofol was used alone, and the quality of the fit was not as good when only one value for the 50% effect concentration was assumed. Sigmoid curves were then fit for each of the four groups; although the remifentanil curves were different from the propofol sigmoid curve, they were not significantly different ($P > 0.05$) from each other. The data were fit again using four groups: the first group as propofol alone and the second group as propofol with all doses of remifentanil. The fit to the data with two curves was significantly improved compared with previous models. The steepness (γ) of the two curves, propofol alone *versus* propofol plus remifentanil, was not significantly different ($P > 0.05$). Thus, the two curves were fit simultaneously with one parameter for the steepness (γ). The data were further fit using a surface response interaction model with the four patient groups entering into the model. Although the interaction model revealed a significant synergistic interaction based on SE criteria, the model was not significantly ($P > 0.05$) superior to the model with a single curve for propofol and another curve for all remifentanil groups together.

From the fit of the best model, the concentration of propofol alone associated with 50% probability of no response was 3.7 μg/ml (SE, 0.4 μg/ml), and the concentration of propofol associated with 50% probability of no response when used with remifentanil was 2.8 μg/ml (SE, 0.1 μg/ml). Figure 1 shows the sigmoid curves for propofol alone and for the combination of remifentanil and propofol. The steepness parameter was very steep (11.2; SE, 3.6), which is typical of the intravenous anesthetics and represents the rapid transition from inadequate to adequate anesthesia as the dose of these drugs is increased.

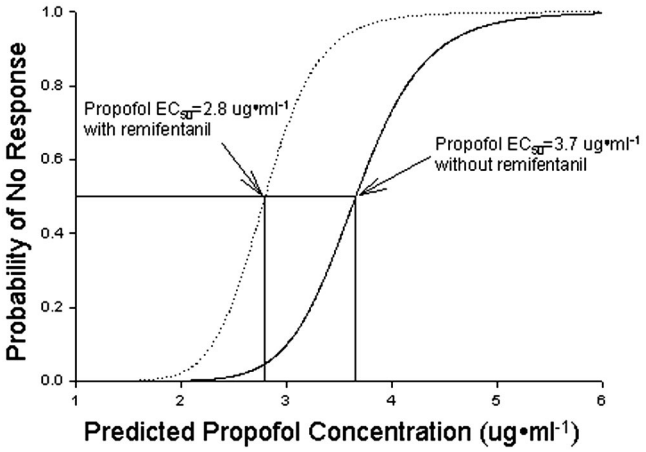

Fig. 1. The probability of response curves for propofol when used alone and when used with remifentanil.

Discussion

The purpose of this study was to describe the pharmacodynamic interaction of remifentanil and propofol when used in combination for esophagogastroduodenoscopy in pediatric patients. Because of episodes of respiratory depression requiring assisted ventilation with a remifentanil dose of 100 ng · kg^{-1} · min^{-1}, a starting dose of 25 ng · kg^{-1} · min^{-1} may be more appropriate. There was a pharmacodynamic interaction between remifentanil and propofol such that using remifentanil decreased the EC_{50} of propofol from 3.7 μg/ml when used alone to 2.8 μg/ml when used with remifentanil. Doses of remifentanil above 25 ng · kg^{-1} · min^{-1} did not improve interaction with propofol and would not be recommended in this setting.

In clinical practice, propofol is usually combined with an opioid to produce complete anesthesia. Because of its favorable pharmacokinetic properties, including rapid onset, rapid equilibration between plasma and effect site concentrations, and rapid offset, remifentanil is well suited for use in ambulatory surgery.[17,18] Remifentanil reduces the propofol plasma concentrations associated with loss of consciousness and response to surgical stimulation.[6,19] The use of remifentanil with propofol for ambulatory anesthesia and the dose-sparing effect of remifentanil on propofol in adult patients have been previously described.[20] A study in spontaneously breathing adult patients receiving propofol infusions for ambulatory surgery noted decreased responses to surgical stimuli with increased doses of remifentanil.[21] However, the interaction of propofol and remifentanil has not been studied in pediatric patients.

We used target-controlled infusions of propofol for induction and maintenance of anesthesia to rapidly achieve and then maintain a constant plasma concentration. Propofol was infused with a target-controlled infusion device and the STANPUMP software, using a pediatric pharmacokinetic model for children aged between 3 and 11 yr.[9] Because administration of remifentanil results in rapid equilibration with the effect site, use of boluses or target-controlled infusion may not be required because a static infusion rate allows a consistent concentration of remifentanil in the effect site in 5 min.[22–24] Although a steady state concentration is not obtained in 5 min, we timed the stimulus to occur at 5 min to improve consistency between patients while avoiding the undesired effect of an intravenous bolus of remifentanil.

We previously demonstrated that the C_{50} of propofol during esophagogastroduodenoscopy in children is 3.55 μg/ml.[14] This previous report used Dixon's methodology[11–13] for the calculation of the C_{50}. The current analysis reports a C_{50} of 3.7 μg/ml for the same data, which is a small and nonsignificant difference (based on SE) from that reported previously. The discrepancy can arise from a different method of analysis (Dixon's method *vs.* logistic regression) and the simultaneous fitting of the propofol data with the remifentanil data using only one value for the steepness variable (γ).

For purposes of simplicity and to avoid the need for phlebotomy, we did not measure plasma concentrations of propofol or remifentanil during this study. It is acknowledged that direct measurement of plasma concentrations may be desirable in a pharmacodynamic study because of pharmacokinetic variability between patients. A previous study of the interaction of propofol and remifentanil, however, showed no difference in results regardless of whether plasma concentrations, predicted concentrations, or infusion rates were used in the calculations.[25] A pharmacokinetic interaction of propofol and remifentanil has been noted, but this only seemed to affect the pharmacokinetics of remifentanil given as a bolus dose.[26] Because remifentanil was not given by bolus dose during this investigation, the interaction noted here was most likely solely a pharmacodynamic interaction.

In summary, we found that there was an interaction between remifentanil and propofol when used in combination and that the 50% effective concentration of propofol was reduced from 3.7 μg/ml (SE, 0.4 μg/ml) to 2.8 μg/ml (SE, 0.1 μg/ml). Clinicians may wish to choose a starting remifentanil dose of 25 ng · kg^{-1} · min^{-1} to minimize episodes of oxygen desaturation because increasing the dose of remifentanil does not diminish the propofol requirements and does increase the risk of opioid-related side effects.

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