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Determination of Plasma Concentrations of Propofol Associated with 50% Reduction in Postoperative Nausea

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Background: **Subhypnotic doses of propofol possess direct antiemetic properties. The authors sought to determine the plasma concentration of propofol needed to effectively manage postoperative nausea and vomiting.**

Methods: **Patients aged 18–70 yr who were classified as American Society of Anesthesiologists physical status 1 or 2 and had surgery during general anesthesia were approached for the study. Only patients who had nausea (verbal rating score > 5 on a 0- to 10-point scale), retching, or vomiting in the postanesthetic care unit participated. Propofol was administered to these patients to achieve target plasma concentrations of 100, 200, 400, and 800 ng/ml using a computer-assisted continuous infusion device. Target concentrations were increased every 15 min until patients described at least a 50% reduction in symptoms on the verbal rating score. An arterial blood sample was obtained at each step. The measured plasma propofol concentrations were used to analyze data. Blood pressure, heart and respiratory rates, arterial blood saturation, sedation score, and overall satisfaction with treatment were recorded.**

Results: **Of the 89 patients who consented to the study, 15 patients met entry criteria and were enrolled. Five of these patients also had retching or vomiting when they entered the study. Fourteen patients responded successfully to treatment. One patient did not achieve the required response at plasma concentrations of 830 ng/ml. Hence the success rate for the treatment of postoperative nausea and vomiting was 93%. Among patients who responded, the median plasma concentration associated with an antiemetic response was 343 ng/ml. There was no difference in sedation scores from baseline and no episodes of desaturation. Hemodynamic parameters were stable during the study.**

Conclusions: **Propofol is generally efficacious in treating postoperative nausea and vomiting at plasma concentrations that do not produce increased sedation. Simulations indicate that to achieve antiemetic plasma propofol concentrations of 343 ng/ml, a bolus dose of 10 mg followed by an infusion of approximately 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ are necessary. (Key words: Propofol; plasma concentration. Postoperative nausea; treatment. Vomiting. Computer-assisted continuous infusion.)**

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PROPOFOL used to maintain anesthesia has been associated with a lower incidence of postoperative nausea and vomiting (PONV)[1–5] compared with patients anesthetized with inhalational agents. More recently, propofol in subhypnotic doses has been used successfully to manage chemotherapy-induced emesis[6] and PONV.[7] It was further shown that the antiemetic action of propofol was not due to the intralipid emulsion in the formulation.[8] The doses that have been used in these studies[6,7] were chosen empirically and not based on any systematic dose–response analysis. In this study, we determined the effective plasma concentration of propofol when used to manage postoperative nausea, retching, and vomiting using a computer-assisted continuous infusion device.

Methods

After we received institutional review board approval of our study design, we approached male or nonpregnant female patients between the ages of 18 and 70 yr who were classified as American Society of Anesthesiologists physical status 1 or 2 and who were scheduled to have surgery during general anesthesia. We excluded

from the study patients who had received drugs with an antiemetic effect within 24 h before anesthesia, were allergic to propofol, had received an investigational drug within the past 30 days, had vomited or retched within the preceding 24 h, or were twice their ideal body weight. Informed consent was obtained from all potential study drug recipients before initiating any premedication or anesthesia. The various anesthetic drugs used during surgery include thiopental or propofol for induction, fentanyl with nitrous oxide, oxygen and isoflurane, neuromuscular blocking drugs (no restriction), and neostigmine and glycopyrrolate/atropine. While in the postoperative anesthesia care unit, those patients who developed symptoms of severe nausea, as judged by the verbal rating score (VRS) score >5, retching, or vomiting and who requested an antiemetic agent were formally studied.

A computer-assisted continuous infusion device was used to deliver the propofol.[9] A pump-control algorithm used a simulation of the model, computed at frequent intervals, to determine the infusion rates required to theoretically achieve and maintain the specified plasma drug concentration.[10]. The pharmacokinetic data set used in this study was based on that by Gepts *et al.*[11] Plasma concentrations of propofol were achieved in an incremental step-up fashion, with the first target plasma concentration of propofol at 100 ng/ml, followed by 200, 400, and 800 ng/ml if the preceding concentrations of propofol did not adequately relieve symptoms. Each target concentration was maintained for a minimum of 15 min. Propofol administered during operation was not considered in the dosing regimen.

When the patients consented for the study, they were told that they would first receive propofol if they had symptoms of nausea, retching, or vomiting in the recovery period and would like to have an antiemetic to relieve or treat their symptoms. However, they could request rescue antiemetic at any time during the study period. The 11-point VRS, 0–10 whole number linear scale to assess their severity of symptoms was also explained to them. Zero (0) described "no nausea" and 10 described "nausea as bad as it could be."

Before the beginning of the propofol infusion, a baseline VRS for nausea was assessed. A radial arterial cannula was inserted if it had not already been placed for surgical indications. An arterial blood sample was taken to determine the baseline plasma propofol concentration. The propofol infusion was set at a target plasma concentration of 100 ng/ml. Fifteen minutes after achieving each target concentration, the patient was assessed on a VRS for nausea and further arterial blood samples were obtained. Episodes of retching and vomiting were recorded. Treatment was considered successful if there was a 50% or more reduction of symptoms on the VRS. Otherwise, the next-higher plasma concentration was targeted until 800 ng/ml was reached. Successfully treated patients had the infusion continued at that target concentration for a further 2 h. If the patients' VRS scores increased during the study period, the next-higher target propofol concentration was delivered up to a maximum of 800 ng/ml.

Table 1. Sedation Scores

0	Completely awake
1	Awake but drowsy
2	Asleep but responds to verbal commands
3	Asleep but responds to physical stimulus
4	Unarousable

Blood pressure, heart and respiratory rates, arterial blood saturation measured using a pulse oximeter, and observer assessment of sedation score (table 1) were recorded before beginning the study, 15 min after each target plasma concentration, and at every 30 min during the study. An overall rating of their satisfaction with treatment was sought from the patients 24 h after the study.

Steady-state plasma concentrations were correlated with nausea scores for each patient. These data were examined for plasma concentrations that bracketed the transition from "no response" to "response." The mean of the resulting two plasma concentrations was computed for each patient. The median and percentiles of the individual means were taken to represent the study population. All calculations were performed with an Excel spreadsheet (Excel 7.0; Microsoft Corp., Redmond, WA).

Results

Of the 89 patients who consented to the study, 15 (17% of the total) met entry criteria and were enrolled in the study. Fourteen patients completed the study. Five of these patients also experienced retching or vomiting at entry into the study, and no patient had retching or vomiting at the end of the study. One patient did not achieve the required response at a plasma propofol level of 830 ng/ml and was not included in the analysis. Thus the success rate was 93%. There were 2 men and

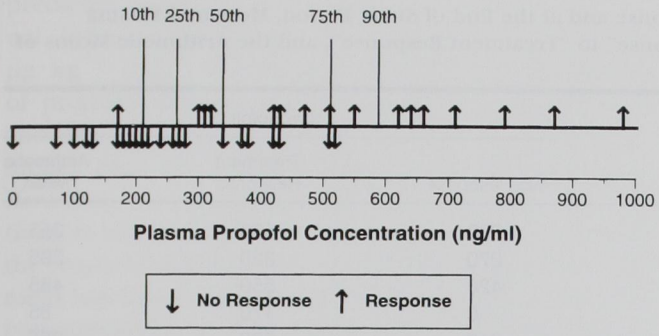

Fig. 1. Individual plasma propofol concentrations at no response (↓) and response (↑). Also shown are the plasma propofol concentrations (derived from the individual mean response concentrations) calculated to provide successful treatment response in various percentages of the population.

12 women. The mean ± SD for age was 41.2 ± 12 yr, for weight it was 78.8 ± 15.4 kg, and for intraoperative fentanyl use it was 454 ± 187 μg. Nine patients received propofol during operation.

The median plasma concentration associated with antiemetic response was 343 ng/ml. Figure 1 shows other concentrations and associated study population percentiles. Figure 2 presents data on measured plasma propofol concentrations that bracketed the transition from "no response" and "response" *versus* VRS for nausea. Table 2 shows nausea VRS at various time periods and plasma propofol concentrations immediately before response, at response, and their arithmetic means for each patient. Raw data on individual propofol concentrations are shown in figure 2. Only one patient had breakthrough nausea after initial control at a plasma propofol concentration of 200 ng/ml, but symptoms were controlled when the next-higher plasma concentration (400 ng/nl) was achieved. Thirteen of 14 patients rated the treatment as satisfactory or very satisfactory. One patient rated it as not satisfactory.

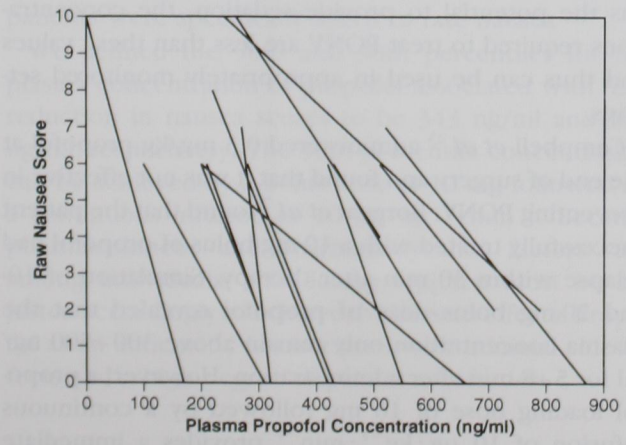

Fig. 2. Raw nausea score *versus* measured plasma propofol concentrations that bracketed the transition from "no response" to "response" for each patient.

There were no requests for rescue antiemetic during the study period, and no patient had a sedation score > 2 or an episode of desaturation. There were no significant changes with respect to time in sedation score (table 3), hemoglobin oxygen saturation, systolic and diastolic blood pressures, and heart rate during the study.

Discussion

Propofol was used recently as an antiemetic agent to treat PONV[7] and chemotherapy-induced nausea and vomiting.[6] Borgeat *et al.*[6,7] used a 17 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol infusion in a group of patients receiving cisplatinum chemotherapy in whom ondansetron and steroid treatment previously was ineffective during their initial chemotherapeutic treatment cycle. They found an incidence of 89% success in these patients. Schulman *et al.*[12] determined the plasma concentration of propofol for the successful treatment of nausea in a postoperative patient to be 197 ng/ml.

Propofol-based anesthetics were associated with a lower incidence of PONV compared with enflurane,[3,13,14] isoflurane,[15] or desflurane anesthesia.[16,17] The findings from these studies showed a low incidence of PONV only when propofol was used throughout the procedure. The protective effect of propofol against PONV was not evident when it was used as an induction drug only. In these studies, the authors did not measure the plasma concentrations of propofol during the recovery period. However, the findings may not be surprising if we consider that there is a therapeutic range of propofol to prevent PONV successfully. We systematically defined this therapeutic range in the current study. In a recent study of the incidence of PONV after breast surgery when propofol was used in various regimens during operation, we found that when propofol was given throughout the procedure, it was more efficacious in preventing PONV than when it was given at induction only, or at induction and toward the end of surgery as a replacement for the isoflurane used to maintain anesthesia.[18] We subsequently performed pharmacokinetic simulation in these groups of patients

Table 2. Individual Data on Baseline VRS, VRS at Treatment Response and at the End of Study Period, Measured Plasma Propofol Concentrations at Bracketed Transition from "No Response" to "Treatment Response", and the Arithmetic Means of the Two Propofol Concentrations

Patient No.	Baseline VRS	Treatment Response VRS	Final VRS (2 h)	[Propofol]		
				No Response	Treatment Response	Arithmetic Mean
1	6	0	0	280	430	355
2	7	0	0	270	320	295
3	6	1	0	420	550	485
4	10	3	0	0	170	85
5	6	2	2	210	300	255
6	6	0	0	100	310	205
7	7	2	2	200	300	250
8	7	0	0	200	660	330
9	10	0	0	220	420	320
10	10	5	4	260	510	385
11	7	0	0	520	870	595
12	8	1	2	430	620	525
13	10	2	2	240	790	585
14	6	0	2	510	710	610

[Propofol] = plasma propofol concentration in ng/ml.

based on the kinetic parameters by Gepts *et al.*[11] The median plasma concentration of propofol in the group who experienced a significant effect on PONV (propofol throughout surgery) was 424 ng/ml, compared with 178 ng/ml in the group (propofol at induction and toward the end of surgery) in whom the incidence of PONV was high.

We also performed a simulation based on Borgeat *et al.*'s[6] propofol dosing regimen of 17 $\mu g \cdot kg^{-1} \cdot min^{-1}$, which resulted in a high degree of efficacy in patients receiving chemotherapy. The plasma concentrations of propofol were 400–540 ng/ml for most of the 24-h period. Pavlin *et al.*[19] recently studied the clinical effects of sedative doses of propofol and alfentanil, alone and in combination. No patient experienced nausea or vomiting during the study in the propofol and the propofol/alfentanil groups. However, there was an incidence of nausea of 50% in the alfentanil-only group. The plasma propofol concentrations in their patients ranged from 150 to 600 ng/ml. In both of these studies, the propofol concentrations are nearly identical to our results of the 90% confidence level of the antiemetic action of propofol. These ranges are much lower than the propofol concentrations needed for sedation (1,500–2,000 ng/ml)[20] and maintenance of general anesthesia (3,000–10,000 ng/ml).[21,22] None of the patients in this study became sedated. Thus although propofol has the potential to provide sedation, the concentrations required to treat PONV are less than these values and thus can be used in appropriately monitored settings.

Table 3. Sedation Scores at Various Propofol Concentrations

Target Plasma Propofol Concentrations (ng/ml)	No. of Patients	Median Sedation Scores	25–75th Percentile Sedation Scores
0	15	1	0–2
100	15	1	0–1
200	15	1	0–1
400	10	1	0–1
800	5	1	0–1
End of study	15	0	0–1

Campbell *et al.*[23] administered 0.3 mg/kg propofol at the end of surgery and found that it was not effective in preventing PONV. Borgeat *et al.*[7] found that the patient successfully treated with a 10-mg bolus of propofol had relapse within 30 min after therapy. Simulation of 10- and 20-mg bolus dose of propofol revealed that the plasma concentration only remain above 300–500 ng/ml for 5–8 min after administration. However, a propofol loading dose of 10 mg followed by a continuous infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ provides a immediate relief of symptoms and subsequent maintenance of an effective plasma concentration to treat PONV. This

predicted infusion rate was close to our observed actual infusion rates, which ranged from 8 to 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$. We did not consider the administration of propofol during operation in the dosing regimen, and thus some measured propofol concentrations were higher than the computer-predicted concentrations. However, we used the measured propofol concentrations in the analysis. One patient did not experience the required response and we considered that the treatment had failed. This patient's highest plasma propofol concentration was 830 ng/ml. Thus it is important to note that high concentrations of propofol may not be effective in some patients in the treatment of PONV.

The mechanism of action of propofol as an antiemetic agent is not known. It has been postulated that propofol may act *via* an antidopaminergic pathway.[24] However, two recent studies have not substantiated this claim.[25,26] Several mechanisms have been postulated. Propofol may have a direct depressant effect on the chemoreceptor trigger zone, the vagal nuclei, and other centers implicated in nausea and vomiting. Propofol has also been shown to decrease synaptic transmission in the olfactory cortex, suggesting a decrease in the release of excitatory amino acids such as glutamate and aspartate, which may be related to its antiemetic activity.[27] More recently research showed that prolonged propofol infusion (333–417 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 6 h) causes a decreased concentration of serotonin in the area postrema,[28] and this may be mediated through a gamma-aminobutyric $acid_A$ receptor mechanism.[29]

Propofol has mood-altering properties.[30] It is conceivable that during the study patients' subjective moods may be influenced by propofol. However, this is unlikely to influence the nausea VRS scores because the patients were specifically asked to rate nausea.

We defined the 50th and 90th percentiles for the plasma concentration of propofol associated with 50% reduction in nausea scores to be 343 ng/ml and 592 ng/ml, respectively. The 50th percentile concentration can be achieved by a bolus dose of 10 mg followed by a continuous infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Because pharmacokinetic and pharmacodynamic factors vary among individuals, this dosing regimen must be adjusted accordingly to achieve the desired effects. Propofol as an antiemetic is associated with minimal side effects and a high degree of patient satisfaction.

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