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Effects of Subhypnotic Doses of Propofol on Gastric Emptying in Volunteers

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Background: **Drugs which accelerate gastric emptying (GE) decrease nausea and vomiting. This could contribute to the antiemetic potential of subhypnotic doses of propofol. On the contrary, subhypnotic doses of propofol used for sedation could decrease GE and thus favor regurgitation and pulmonary inhalation. Therefore, the aim of this study was to assess the effect of low-dose propofol infusion on GE.**

Methods: **On three separate occasions, 10 volunteers received either a propofol infusion at a rate set to achieve a target plasma concentration of 0.5 μg/ml or equivalent volumes of 10% Intralipid® or 0.9% saline. GE for solids was measured by using the octanoic acid breath test. An acetaminophen absorption technique measured the GE rate for liquids. Blood samples were assayed for acetaminophen and propofol. Breath samples were analyzed for $^{13}CO_2$ concentration by isotope-ratio mass spectrometry. Carbon dioxide production ($\dot{V}CO_2$) was measured instead of calculated by indirect calorimetry. Sedation was evaluated by the Bispectral Index of the electroencephalogram.**

Results: **Propofol blood concentrations were 0.32 ± 0.20 and 0.45 ± 0.18 μg/ml at 60 and 165 min, respectively. These concentrations were not sedative. Propofol or its solvent did not modify GE for solids or liquids. In all groups, differences in GE were obtained if measured $\dot{V}CO_2$ was integrated in the formula instead of calculated $\dot{V}CO_2$ ($P < 0.002$).**

Conclusions: **Subhypnotic doses of propofol known to be antiemetic do not inhibit GE. These results suggest that the antiemetic properties of propofol are not peripheral and that propofol cannot be considered as a prokinetic agent. $\dot{V}^{13}CO_2$ must be measured instead of calculated to accurately determine GE.**

PROPOFOL was first introduced as an induction agent and for maintenance of anesthesia. Subsequently, the nonhypnotic therapeutic applications of propofol were developed.[1–3] Thus, it has been shown that subhypnotic doses of propofol possess antiemetic properties by decreasing the occurrence of chemotherapy-induced emesis.[2,3] It is also used to prevent or to treat postoperative nausea and vomiting.[4,5]

Delayed gastric emptying (GE) *per se* is associated with nausea and vomiting.[6] Thus, it has been shown that patients with gastroparesis, such as during diabetes mellitus, pregnancy, and other systemic diseases, may have an increase risk of nausea and vomiting.[7,8] It has been also suggested that gastroparesis may contribute to postchemotherapy nausea and vomiting.[8] On the contrary, the prokinetic drugs metoclopramide and cisapride have been shown to be effective both in eliminating the symptoms of gastroparesis and in enhancing the rate of GE.[9] Although propofol is used for control of nausea and vomiting, its mechanism of action remains unknown, and there are limited data on the effects of propofol on gastrointestinal motility. Only one study has shown that propofol has no influence on GE of liquids, but the influence of propofol of GE rate for solids has not been evaluated.[10] Accordingly, the present study was conducted to determine the effect of an antiemetic dose of propofol on GE in volunteers after ingestion of a nutrient meal. GE for solids was measured by a noninvasive breath test technique, and GE for liquids was measured by the acetaminophen absorption technique.

Material and Methods

Subjects

With approval of the University of Lyon Committee on Human Research (Lyon, France), we evaluated 10 healthy volunteers (5 men and 5 women; mean age, 29 yr, range, 23–42 yr). All volunteers gave written informed consent before the study. The subjects had no history of diabetes mellitus, previous gastrointestinal surgery, or use of medication effecting gastric motility. Volunteers attended three separate studies sessions, each at least 2 weeks apart. In this double-blind study, volunteers were randomly allocated by coded envelopes to the following groups: placebo (0.9% saline), 2% propofol, or fat emulsion (10% Intralipid®; Pharmacia-Upjohn, St Quentin en Yvelines, France; the solvent for propofol).

Experimental Protocol

The experimental protocol is summarized in figure 1. Routine physiologic values were recorded throughout the study, including heart rate (HR), noninvasive arterial blood pressure (systolic, diastolic and mean), and arterial oxygen saturation (Spo_2).

After the patients were given local anesthesia, a peripheral venous catheter was inserted on the dorsal face of the hand. The hand was heated in a hot blanket to obtain arterialized blood samples. On the opposite arm,

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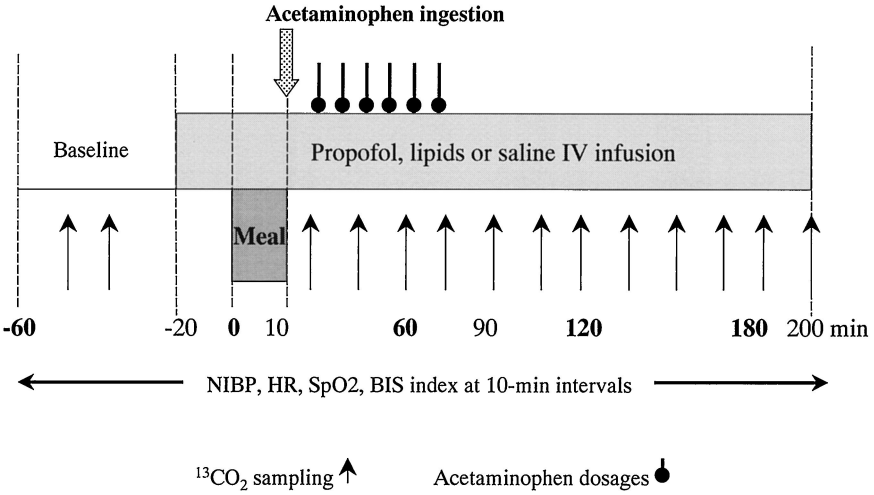

Fig. 1. Schematic drawing of experimental protocol.

a cannula was inserted into an antecubital vein for the infusion of propofol, lipids, or saline at the same volume. This infusion was started after 40-min baseline measurements. Twenty minutes after the start of the infusion, a test meal was ingested over 10 min to measure GE. The infusion was continued 200 min after the end of the test meal (fig. 1).

Blood samples were regularly drawn and subsequently separated by centrifugation. The plasma was stored at −20°C until analyzed for acetaminophen and propofol concentrations (fig. 1). After each blood sample was taken, the intravenous catheter was flushed with 1 ml heparinized saline.

Measuring Techniques for Gastric Emptying of Solids

A breath test for the measurement of GE of solids labeled with ^{13}C-octanoic acid was used in this study, as previously established by Ghoos *et al.*[11] This is based on the fact that disintegration of the labeled solid phase of the test meal, with subsequent absorption and oxidation of ^{13}C-octanoic acid to $^{13}CO_2$, takes place once the meal reaches the duodenum.

The test meal consisted of a scrambled egg with the yolk labeled with 100 mg ^{13}C-octanoic acid (Euriso-top, Saint Aubin, France). The egg was ingested with two slices of white bread and 5 g margarine, followed immediately by 150 ml water. The yolk and the egg white were baked separately but were administered together with the bread. The total caloric value of the meal was 250 kcal. All test meals were consumed in less than 10 min.

Measured carbon dioxide production instead of estimated carbon dioxide production was used for calculations. Measurements of oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) were performed by the open-circuit method of indirect calorimetry (Deltatrac; Datex, Helsinki, Finland), regularly calibrated. Expired air was collected in Douglas bags for 2 min at the

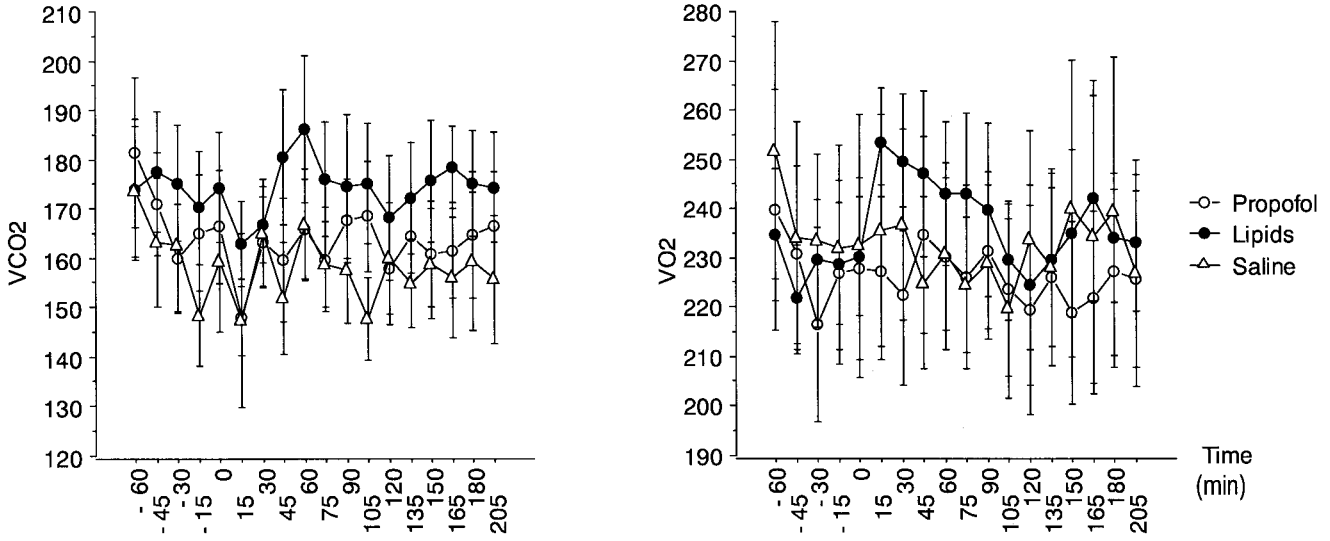

Fig. 2. Effects of intravenous propofol at antiemetic dosage, 10% lipids, and saline at the same infusion rate on CO_2 production and O_2 consumption in ml/min (indirect calorimetry) in volunteers while studying gastric emptying rate. Results are mean ± SE.

Table 1. Gastric Emptying for Solids as Measured by Octanoic Acid Breath Test Method

	Saline	Lipids	Propofol
GE coefficient	2.44 ± 0.11 2.43 (1.92–3.17)	1.84 ± 0.20 1.74 (1.04–2.83)	2.06 ± 0.15 2.05 (1.40–2.83)
Half emptying time $t_{1/2\beta}$ (min)	116.80 ± 17.13 110.50 (60–25.60)	117.30 ± 7.55 115.00 (87–160)	137.90 ± 24.57 112.50 (64–306)
Lag time (min)	77.70 ± 14.26 68 (20–185)	80.40 ± 9.21 92 (32–125)	91.40 ± 17.27 82 (39–21.60)

Data are expressed as mean ± SE, median, minimum–maximum. No statistically differences were noted.

GE = gastric emptying.

end of each $\dot{V}CO_2$ measurement, and samples of expired gas in duplicate were then transferred into evacuated tubes (Vacutainer; Beckton Dickinson, Grenoble, France) for further analysis. Measurements were taken with patients lying in a semi-recumbent position (20°), breathing room air in a ventilated hood. The subjects became accustomed to the hood of the indirect calorimeter during 30 min before the test.

Breath samples were taken before ingestion of the meal and at regular 20-min intervals thereafter for 200 min and were analyzed for $^{13}CO_2$ concentration by isotope-ratio mass spectrometry (SIRA 10; VG Isogas, Middlewich, United Kingdom) as previously described.[12,13] Breath CO_2 isotopic enrichments were calculated *versus* breath CO_2 obtained prior to labeled octanoic ingestion. Using nonlinear regression methods, the $^{13}CO_2$ excretion curves were fitted to calculate three GE parameters, *i.e.*, the gastric emptying coefficient (GEC), the gastric half emptying time ($t_{1/2\beta}$), and the lag phase (tlag).[11] GEC gives an overall index of GE, and $t_{1/2\beta}$ indicates the time on which half of the dose of $^{13}CO_2$ is excreted of the cumulative $^{13}CO_2$ excretion when time is infinite. The lag phase corresponds to the time when the peak of the $^{13}CO_2$ excretion curve is reached. These calculations were made using a homemade Excel 4.0 macro program (Microsoft Corp., Redmond, WA) by a physician not involved in the collection of data (F. M.).

Table 2. Gastric Emptying for Liquids as Measured by the Acetaminophen Technique

	Saline	Lipids	Propofol
$AUC_{0-90\ min}$	42.90 ± 5.01 43.20 (18.40–72)	53.22 ± 9.60 43.70 (9.70–121.10)	45.50 ± 6.98 42.20 (11.80–91.70)
Peak (μg/ml)	14.40 ± 1.40 12.70 (9.70–22.60)	13.04 ± 1.90 13.20 (3.90–24.40)	13.55 ± 2.11 11.50 (6.00–24.40)
Time to peak (min)	19.20 ± 2.80 21 (6–30)	25.20 ± 6.05 15 (12–60)	30.00 ± 4.56 33 (12–60)

Data are expressed as mean ± SE, median, minimum–maximum. No statistically differences were noted.

Administration and Dosage of Propofol

Twenty minutes before the test meal, each volunteer received a 220-min infusion of propofol (Astra Zénéca, Cergy, France) to a target level of 0.5 μg/ml *via* a target-controlled infusion (TCI) device (Vial Medical Master TCI Diprifusor, Lyon, France). The concentration of propofol was selected based on a report by Gan *et al.*[14] who showed that a serum concentration of 0.5 μg/ml propofol was able to decrease the incidence of nausea and vomiting. The Diprifusor device was also used for lipids or saline administration. For this purpose, the syringe was emptied of propofol and filled with 10% Intralipid® or 0.9% saline (Fresenius, Louviers, France). A target concentration was set at 0.5 μg/ml to ensure the same volume delivery as with propofol.

Plasma concentrations of propofol were determined using high-performance liquid chromatography with fluorescence detection at 310 nm after excitation at 276 nm (Wisp Injector 715, Pump 590, Detector 470; Waters, Milford, MA). For each batch of blood samples, a standard curve was computed by adding pure propofol liquid to drug-free human plasma to achieve concentrations of 0.1, 0.5, 1.0, and 2.0 μg/ml. Linear regression (least-squares method) was used with plasma propofol concentration as the dependent variable. Propofol concentrations in this study were calculated using the obtained regression equation. The lower limit of detection was 15 ng/ml, and the coefficient of variation was 7.4%.

The ^{13}C enrichment of propofol or lipids was determined by using an isotope-ratio mass spectrometer (SIRA 10; VG Isogas, Middlewich, United Kingdom) on-line with an elemental nitrogen and carbon analyzer (NA 1500; Carlo Erba, Massy, France), as previously described.[12,13]

Gastric Emptying Calculation for Liquids

The appearance of acetaminophen in the systemic circulation is an indirect method of determining the rate of GE for liquid because acetaminophen is not absorbed from the stomach but is rapidly absorbed by the intestine.[15] This test has been validated using radionucleotide techniques that quantitatively measure GE.[16] Acetaminophen (1 g in 150 ml water) was given by mouth at the end the test meal. Blood samples for acetaminophen analysis were collected at 5, 10, and 15 min and then at 15-min intervals during 90 min.

Acetaminophen concentrations were measured in the plasma by high-performance liquid chromatography (Wisp auto injector 717, Pump 600 E, PDA 996). The limit of quantification of the assay was 100 ng/ml. The calibration curve showed a linear response ($r < 0.99$) for the concentration range (100–20.000 ng/ml) tested. The coefficient of variation for the calibration range was less than 5%.

Estimation of Pharmacokinetic Parameter Values for Acetaminophen

Three groups of patient files (propofol, lipids, saline) were made using the file manager program (PASTRX) included in the USC*PACK software.[17] Each file contained anthropometric and treatment data, such as age, weight, administered amounts of acetaminophen, time of administration, infusion duration, blood sampling times, and drug serum concentration measurements. Pharmacokinetic parameter values were estimated in each group using the nonparametric EM algorithm NPEM2 implemented within the USC*PACK software NPEM program. It computed the discrete joint probability density function (PDF) of pharmacokinetic parameters without making any assumption on the shape of the distribution. The population parameter values obtained for each group were then used to estimate individual pharmacokinetic parameter values by using a MAP (Maximum A Posteriori) Bayesian method also implemented in USC*PACK.[18] Several parameters of GE, including time to reach the peak serum concentration (Tmax), the maximum serum concentration (Cmax), and the area under the acetaminophen serum concentration-*versus*-time curve (AUC), were then calculated.

Statistical Analysis

Results are expressed as mean ± SE, range, and minimum–maximum values. For all calculations, the Statview computer software package was used (SAS Institute, Cary, NC). Comparisons for GE parameters were performed by analysis of variance. Continuous variables (Spo_2, HR, Bispectral Index, mean arterial pressure) were analyzed by a repeated-measures analysis of variance followed by a *post hoc* test (Bonferroni adjusted comparisons) when appropriate. Measured and calculated GE parameters for each solution tested were compared using a Wilcoxon test. A P value less than 0.05 was considered to be statistically significant.

Consistently with a prospective and descriptive study, power analysis was calculated subsequently to determine relevance of the results. Then, with at least 10 volunteers (assuming $\alpha = 0.05$), the power of the analysis of variance reached 98% with a goal of a 25% difference in GEC and a 30% difference in AUC among the three groups.

Results

Isotope-ratio mass spectrometry showed that the ^{13}C enrichment for propofol and Intralipid® were similar with values of 1.0790 Atom % and 1.0794 Atom %, respectively. Measured propofol concentrations were 0.32 ± 0.20 and 0.45 ± 0.18 μg/ml at 60 and 165 min, respectively. These concentrations were well tolerated. No significant difference was observed between groups for mean arterial blood pressure, HR, and Spo_2.

Indirect calorimetry showed similar results between groups concerning $\dot{V}co_2$ and $\dot{V}o_2$ (fig. 2). When compared, GEC was statistically different in each group if measured $\dot{V}co_2$ was integrated in the formula instead of calculated $\dot{V}co_2$ ($P < 0.002$). GEC calculations using measured $\dot{V}co_2$ were 2.44 ± 0.11, 1.84 ± 0.20, and 2.06 ± 0.47 for saline, lipids, and propofol, respectively (table 1). GEC calculations using calculated $\dot{V}co_2$ were 2.60 ± 0.10, 2.02 ± 0.19, and 2.26 ± 0.48 during saline, lipids, and propofol, respectively. Accordingly, the difference reached 10% in the propofol group.

No significant difference was observed between groups for half emptying time ($t_{1/2\beta}$) and for the lag phase (tlag). GE for liquids as measured by the acetaminophen technique was similar between groups (table 2).

Discussion

This study showed in volunteers that subhypnotic doses of propofol known to be antiemetic do not inhibit GE. These results suggest that the antiemetic properties of propofol are not peripheral and that propofol cannot be considered as a prokinetic agent.

Little is known of the gastrointestinal effects of propofol. Freye *et al.*[19] showed that a hypnotic dose of propofol (0.11 mg · kg^{-1} · min^{-1}) does not alter gastrointestinal tract motility more than a standard isoflurane anesthesia. Other research groups showed that the delay in GE for liquids was similar between propofol alone compared to propofol–enflurane or to propofol–fentanyl.[20,21] In lightly sedated human volunteers, GE for liquids was uninfluenced by propofol over a 30-min period (0.04 mg · kg^{-1} · min^{-1}).[10] An *in vitro* study showed a dose-dependent depression of gastric muscle to various concentrations of propofol.[22] At a concentration of 1.7×10^{-6} M, a concentration corresponding to clinical light sedation, propofol has no effect on the spontaneous and contractile response of gastric muscles to acetylcholine. Thus, those previous works with our study suggest that low doses of propofol do not decrease gastric muscle contractility, and propofol is not a prokinetic drug.

Although low doses of propofol are commonly used to treat nausea and vomiting in various settings, propofol's exact mechanism of action remains unclear. A direct depressant effect on the chemoreceptor trigger zone has been postulated. Previous studies have demonstrated that propofol does not act *via* an antidopaminergic pathway but may have a 5-HT_3 antagonistic effect.[23–26] Gan *et al.*[14] showed that the plasma concentration of propofol associated with a 50% reduction of nausea score was 343 μg/ml. Although plasma concentrations of propofol measured in our study were close to these values, GE was unchanged. Thus, our data suggest that the antiemetic properties of propofol might be related to a central effect rather than a prokinetic one.

Scintigraphy is regarded as the "gold standard" technique for GE studies. Simultaneous radioscintigraphic and breath test measurements showed an excellent correlation between the GE results of the scintigraphic method and those of the breath test when using a solid standard test meal of 250 kcal.[11] However, reported values for GE vary widely depending on age and clinical status of the subjects and on test meal and methods. Maes *et al.*[27] obtained a GEC mean value of 3.31 ± 0.6. Ghoos *et al.*[11] reported mean values of the breath test methods of 3.25 ± 0.30 for GEC, 72 ± 22 min for $t_{1/2\beta}$, and 32 ± 20 min for tlag, while Choi *et al.*[28] found median values for $t_{1/2\beta}$ close to 210 min (range, 160–360) and 80 for tlag (range, 60–110). In healthy volunteers, Duan *et al.*[29] reported a mean value for $t_{1/2\beta}$ of 148 ± 35 min. The difference in the duration of $t_{1/2\beta}$ and tlag observed between studies may result from several factors. First, both liquid and solid GE were simultaneously studied in some studies, while in others, GE for solids was studied alone. It is possible that a portion of the medium-chain lipid in the test meal was liquid and that it may empty from the stomach with the liquid phase.[30] Second, an undigested, previous meal residing in the ileal reservoir may contribute to the early increase in $^{13}CO_2$ in breath.[31] Third, $t_{1/2\beta}$ and tlag can change by varying the total duration of $^{13}CO_2$ sampling. Thus, it has been shown that a 4-h sampling period compared with a 6-h period overestimated $t_{1/2\beta}$.[28]

The results of the current study showed that GEC calculations changed if $\dot{V}_{CO_2}$ is measured instead of calculated. The percentage recovered in breath depends on the CO_2 production rate. Usually, CO_2 production is calculated from a formula integrating the body surface and a fixed rate of CO_2 production by square meter of this surface. However, $\dot{V}_{CO_2}$ production varies during the day, and this variation should be taken in account when stable isotopic tracers are used for metabolic studies. For this reason, $\dot{V}_{CO_2}$ production was measured by indirect calorimetry, and the result was integrated in the calculation.

Because every exogenous substrate has a particular $^{13}CO_2$ abundance, it may change $^{13}CO_2$ enrichment even in the absence of tracer infusion. Previous studies showed that small differences in ^{13}C between substrates moderately affect the results of isotopic studies.[32] Because we found that the ^{13}C contents of propofol and lipids were quite similar and the amount of each solution perfused was very small, no correction was judged as necessary in the present study.

As Hammas *et al.*[10] showed, we found that low-dose propofol does not inhibit GE for liquids. Previous studies showed a wide range for Cmax and AUC depending on the dose of acetaminophen ingested.[10] The timing of Cmax has been reported to range from 20 to 180 min. Although similar values were found in the current study, comparison of our results with previous works must take several facts into account. First, a population pharmacokinetics model was used to analyze the data. Second, the presence of a solid phase probably influenced the acetaminophen pharmacokinetics, but this has not been evaluated until now.

Previous studies showed that duodenal infusion of lipids strongly inhibit GE.[33,34] Our findings showed that intravenous infusion of long-chain lipids did not influence GE for solids and liquids. No previous data reported the effects of intravenous lipids on GE. However, the amount of lipids infused throughout the current study was low. Therefore, further studies are needed to explore the effects of intravenous lipids on GE. This is particularly important because numerous patients receive parenteral nutrition, which contains a large amount of lipids.

The potential limiting factor in the use of propofol as an antiemetic agent is the appearance of significant adverse effects, especially sedation. The plasma propofol concentrations obtained in our study were around 0.5 μg/ml. These values are lower than the propofol concentrations needed for sedation (1–1.5 μg/ml) or maintenance of general anesthesia (3–5 μg/ml). None of the patients in this study became sedated. Thus, target-controlled propofol infusion can be used safely to treat nausea and vomiting in appropriately monitored settings.

The limitation of this study is that we studied volunteers without nausea and vomiting. Because propofol has been proposed for both prophylactic and curative treatment of nausea and vomiting, our data investigating the mechanism of action of propofol could be applied in patient suffering for postoperative nausea and vomiting.

In conclusion, this study showed that subhypnotic doses of propofol known to be antiemetic do not inhibit GE. These findings suggest that the mechanism of the antiemetic properties of propofol is not peripheral and that propofol cannot be considered as a prokinetic agent. Target-controlled propofol infusion can avoid adverse side effects linked to the sedative property of this anesthetic agent and can be considered in acute emesis episodes.

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