Experimental and Clinical Studies on the Antiemetic Effects of Propofol

BY

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Postoperative nausea and vomiting (PONV) is still a clinical problem and its incidence is unacceptably high. After the introduction of propofol as an agent for induction and maintenance of anesthesia, it was reported that the incidence of PONV was lower. It was also proposed that propofol possesses antiemetic effects. Dopamine, serotonin and opioids may contribute to PONV. Therefore the purpose of these investigations was to evaluate if propofol has dopamine, serotonin or opioid antagonistic effects and if a subhypnotic infusion of propofol decreases the incidence of PONV.

Nausea and vomiting were induced in volunteers by a dopamine agonist, apomorphine, and by ipecacuanha which releases serotonin from the enterochromaffin cells in the gut. The effects of propofol on gastric emptying and orocecal transit time were evaluated in volunteers with the paracetamol method and by measuring the endtidal hydrogen concentration after ingestion of the trisaccharide raffinose. The effects of morphine on gastric emptying and gastric tone were studied in patients before surgery with the paracetamol method and with an electronic barostat, respectively. The effects of low dose propofol for prophylaxis of PONV were studied in 172 patients undergoing breast and abdominal surgery. Propofol prophylaxis was compared with a multidrug regimen consisting of dexamethasone and three antiemetic drugs, ondansetron, droperidol and metoclopramide.

Propofol did not abolish apomorphine-induced vomiting but reduced the number of retchings induced by ipecacuanha. Propofol sedation did not influence gastric emptying of liquids but it slightly prolonged orcecal transit time. Gastric relaxation induced by morphine was abolished by propofol but propofol did not abolish morphine-induced delay of gastric emptying. Propofol in a low dose infusion reduced the incidence of PONV but nausea and especially vomiting increased significantly after termination of the infusion. Prophylaxis with the multidrug regimen was very effective in preventing PONV.

These studies have shown that propofol does not have any dopamine antagonistic effect but may have a weak serotonin antagonistic effect. Propofol cannot abolish morphine-induced delay of gastric emptying. Low dose propofol infusion was effective in preventing PONV as long as the infusion was ongoing but after termination of the infusion nausea and especially vomiting substantially increased. The multidrug regimen (dexamethasone, ondansetron, droperidol, metoclopramide) was very effective in preventing PONV and can be recommended as prophylaxis in patient groups with a known high risk for PONV.

Key words: Gastric emptying, gastric tone, orocecal transit time, Propofol, dopamine, serotonin, morphine, Postoperative nausea and vomiting.

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I  **Hvarfner A, Hammas B, Thörn S-E, Wattwil M**  
   The influence of propofol on vomiting induced by apomorphine.  

II  **Hammas B, Hvarfner A, Thörn S-E, Wattwil M**  
   Effects of propofol on ipecacuanha-induced nausea and vomiting.  

III  **Hammas B, Hvarfner A, Thörn S-E, Wattwil M**  
    Propofol sedation and gastric emptying in volunteers.  

IV  **Hammas B, Thörn S-E, Wattwil M**  
    Propofol and gastric effects of morphine.  
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V  **Hammas B, Thörn S-E, Wattwil M**  
    Prophylaxis of postoperative nausea and vomiting – comparison of a combination of four antiemetic drugs and a subhypnotic infusion of propofol.  
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INTRODUCTION

Propofol, 2,6 di-isopropylphenol, was introduced in the late 1980s as an intravenous anesthetic agent with a rapid onset and short duration (1, 2). The mechanism by which propofol acts as a general anesthetic is poorly understood. Propofol appears to exert its action on central nervous system functions by a potentiation of gamma-aminobutyric acid (GABA) transmission and by modulating the binding of GABA to its receptor complex. Propofol might exert its pharmacological effects by enhancing the function of GABA activated chloride channels linked to the GABA-receptor. This effect is similar to that induced by pentobarbital and benzodiazepines (3-6). All central nervous system structures are affected by these actions, which are rapidly reversible. However, we still do not know if this is the main mechanism by which anesthesia is produced by propofol (7). It has also been shown that propofol acts directly on nicotinic acetylcholine receptors in the frontal cortex and hippocampus. This impairment of cholinergic neurons may mediate the sedative and hypnotic effects of propofol (8, 9). In addition to its effects on the CNS, propofol also impairs acetylcholine-dependent gastrointestinal contractile activity during the experimental situation (10), and has also been shown to have other non-hypnotic therapeutic applications such for cholestatic pruritus and for pruritus that is induced by spinal opioids (11).

In addition to being used for induction of anesthesia, propofol has become the drug of choice for maintenance of total intravenous anesthesia. Intravenous anesthesia was described as early as 1665 by Sigismond Elsholtz, who anesthetized a dog by intravenous administration of opium. However, this subject received no further attention until 1822, when Oré described anesthesia in animals by means of the intravenous administration of a solution of chloral hydrate. The first use of chloral hydrate in humans was reported in 1874. Barbiturates were introduced in 1924 and sodium thiopentone (pentothal sodium), which is still in use, was introduced in 1934. However, it was not until after the introduction of propofol and opioids of short and predictable duration that the necessary conditions for modern, total intravenous anesthesia were created (12).

Soon after the introduction of propofol, it was reported that the incidence of postoperative nausea and vomiting (PONV) was low after propofol anesthesia and it was also proposed that propofol possesses antiemetic effects (13-21). PONV has been a problem since the introduction of general anesthesia. The sequelae of anesthesia and surgery involving nausea and vomiting was first described in 1846 by Dr John Snow, who reported that, “Narcotism by chloroform or ether occasionally leave
some effects after the immediate influence of the vapor has subsided. These sequelae were sickness, headache, nausea and vomiting” (22).

Despite the introduction of less invasive surgical procedures and new anesthetic agents, PONV is still a clinical problem. The incidence remains unacceptably high. The reason for this is that the genesis is multifactorial and there is still no ultimate effective pharmacological monotherapy. PONV has been described as “the big little problem”(23), and from the patient perspective PONV is the most distressing complication of anesthesia and surgery (24). The incidence of PONV varies greatly in different studies (8-92 %) (25), and in order to evaluate and compare these studies it is necessary to know which anesthesia techniques and regimens were used and which surgical procedures were performed. In addition, it is important to know the length of time during which PONV was registered. Some patients can feel fine, without any problems during the initial period in the postoperative care unit, and then start to feel nauseated and possibly even vomit several hours later.

**Physiology of nausea and vomiting**

The chemoreceptor trigger zone is situated within the area postrema, dorsal in the medulla oblongata, outside the blood-brain-barrier, and it can react to toxic agents present both in the circulating blood and in cerebrospinal fluid. The impulses are then transferred to the vomiting center (26-32). Several neurotransmitters, such as dopamine, histamine, acetylcholine and endogenous opioid receptors, have been identified in the chemoreceptor trigger zone. During recent years it has been shown that 5-hydroxytryptamine (5-HT, serotonin) is an important mediator of emetic stimuli. 5-HT is located both in central and peripheral neurons, but 90 % of it is located in the enterochromaffin cells of the mucosa in the small intestine (33, 34). Thus, postoperative nausea and vomiting may also be induced from the gastrointestinal tract.

It is not surprising that the gastrointestinal tract is important, as its main function in this respect is to protect the body from accidental oral intake of poisonous substances and toxic agents in food (35). The vagus nerve is the main nerve for detection and mediation of emetic stimuli, and in the abdominal part of this nerve 80-90 % of the fibers are afferent. Two different kinds of vagal afferents are involved, some in the mechanoreceptors in the muscular wall and some in the chemoreceptors in the mucosa of the small intestine (36). In animal studies, vomiting induced by intragastric administration of hypertonic saline, copper sulfate and bacterial toxins can be abolished by vagotomy (26).
Postoperative nausea and vomiting are distressing and frequent adverse events after abdominal surgery performed under general anesthesia (28). Surgical manipulation of the gut may influence the mechanoreceptors and probably also irritate the mucosa of the small intestine, with release of 5-hydroxytryptamine (5-HT) from the enterochromaffin cells. 5-HT stimulates peripheral 5-HT receptors on the afferent vagal nerve ends in the mucosa, and via the vagal nerve the impulses are transferred to the vomiting center (31). Simultaneously, circulation of 5-HT may also effect receptors in the chemoreceptor trigger zone. Although it has not been clearly shown, some agents such as nitrous oxide (37-39), inhalation anesthetics (40), cholinesterase inhibitors (41) and atropine (42), probably release 5-HT indirectly by distension of the gut, thereby activating afferent vagal nerve endings (43, 44).

Although these peripheral mechanisms are speculative, release of 5-HT from the enterochromaffin cells during anesthesia and surgery is very likely, as 5-HT3 antagonists have some effect against postoperative nausea and vomiting. It is of interest to note that ipecacuanha syrup, which is used at emergency departments for inducing vomiting (45), releases 5-HT (46-50). Ipecacuanha-induced vomiting can be prevented by ondansetron, a 5-HT3 antagonist (46-51). Intravenous apomorphine, a potent dopamine agonist, exerts its effect on the dopamine receptors (D2) in the chemoreceptor trigger zone, and apomorphine has been used in anesthesia for inducing vomiting (53, 59). The majority of drugs used today for prophylaxis or treatment of PONV are dopamine or serotonin antagonists, but it is also important to avoid opioids as much as possible in order to decrease the incidence of PONV (52). As the antiemetic effects of propofol have not been clearly demonstrated, the aims of the present studies were to investigate if propofol has dopamine or serotonin antagonistic effects, and if propofol abolishes the negative effects of opiates on the gastrointestinal tract.
PURPOSE OF THE STUDY

The aims of the investigations were:

* To study if propofol abolishes nausea and vomiting induced by a dopamine agonist, apomorphine (I).
* To study if propofol abolishes nausea and vomiting induced by serotonin that is released by ipecacuanha syrup (II).
* To study the effects of propofol on gastric emptying and orocecal transit time (III).
* To study if propofol effects morphine-induced gastric relaxation (IV).
* To study if propofol abolishes morphine induced delay of gastric emptying (IV).
* To study if a subhypnotic infusion of propofol decreases the incidence of postoperative nausea and vomiting after breast and abdominal surgery (V).
SUBJECTS

All studies were approved by the Ethics Committee of Örebro County Council, and the volunteers and patients gave their informed consent to participate after receiving verbal and written information.

In study I, the dopamine antagonistic effects of propofol were evaluated in 10 healthy male volunteers, aged 30.4 (23-35) years (mean and range), to see if propofol has dopamine antagonistic effects.

In study II, the antagonistic effects of propofol were evaluated in 10 healthy male volunteers, aged 27.4 (20-37) years, to see if propofol has serotonin antagonistic effects.

In study III, the effects of a low dose of propofol on gastric emptying and orocecal transit time were evaluated in 10 healthy male volunteers, aged 30.4 (23-35) years. These volunteers were the same as in study I.

In study IV, if propofol abolishes the morphine-induced decrease in gastric tone was evaluated in 20 ASA I-II patients (9 females/11 males), aged 64.8 (33-79) years, and if propofol abolishes the morphine-induced delay in gastric emptying was evaluated in 20, ASA I-II patients (11 females/9 males, aged 54.3 (29-81) years.

In study V, the effects of propofol on postoperative nausea and vomiting were evaluated in 172 ASA I-II patients (106 females/66 males), aged 52.5 (20-82) years.
METHODS

Dopamine-induced vomiting

_In study I_, the dopamine agonist apomorphine was used for inducing vomiting. The amount of apomorphine needed to induce vomiting was recorded.

Serotonin-induced vomiting

_In study II_, ipecacuanha syrup, which releases serotonin in the gut, was used to induce nausea and vomiting. The intensity of nausea was estimated by the volunteers by using a Visual Analog Scale (VAS) and the number of retchings was recorded (54).

Gastric emptying

_In studies III and IV_, the paracetamol absorption method was used to determine gastric emptying. Paracetamol given by mouth is not absorbed from the stomach but is easily absorbed from the upper small intestine. The rate of absorption of oral paracetamol is therefore an indirect measure of gastric emptying (55). Venous blood samples were taken and the plasma concentrations of paracetamol were determined by an immunologic method including fluorescence polarization (TDx paracetamol, Abbott Laboratories, North Chicago). The maximum paracetamol concentration (C\text{max}), the time to reach the maximum concentration (T\text{max}), and the area under the plasma paracetamol concentration curves from 0 to 60 min (AUC\text{60}) were calculated (55-57).

Orocecal transit time

_In study III_, orocecal transit time was assessed by oral ingestion of the trisaccharide raffinose. Raffinose is fermented by bacteria in the caecum and the colon, thereby producing hydrogen. The rise in end-expiratory hydrogen level represents the arrival of the trisaccharide in the caecum, and the time taken from oral ingestion of raffinose to the rise in the end-expiratory hydrogen level is an estimate of the orocecal transit time. The hydrogen concentration in expired air was measured by a hydrogen monitor (Exhaled Hydrogen Monitor, GMI, Medical Ltd, Innchinnan estate, Renfrew, Scotland) (57, 58, 69).

Serotonin analysis

_In study II_, blood samples for analysis of plasma serotonin concentration were taken. The 5-HT (5-hydroxytryptamine) and 5-HIAA (5-hydroxyindoleacetic acid) plasma concentrations were determined by high-pressure liquid chromatography with electrochemical detection (HPLC) (60, 61).
**Estimation of sedation level**

In studies I, II and III, the grade of sedation was estimated by observers on a 5-grade scale according to Wilson et al, where 1 = fully awake and oriented, 2 = drowsy, 3 = eyes closed but arousable upon command, 4 = eyes closed but arousable upon mild physical stimulation, and 5 = eyes closed and not arousable using physical stimulation (62).

**Gastric tone measurement**

In study IV, gastric tone was measured by an electronic barostat (SVS, Synetics Medical AB, Stockholm, Sweden). The barostat is an instrument with an electronic control system that maintains a constant preset pressure within an air-filled, flaccid intragastric bag by means of continual changes in the volume of air in the intragastric bag. When the stomach contracts, the barostat aspirates air to maintain the constant pressure within the bag, and when the stomach relaxes air is injected. The pressure in the bag was set at 2 mmHg above the basal intragastric pressure. The pressure change at which respiration is perceived on the pressure trace, without an increase or decrease in the average volume, is the intra-luminal pressure of the stomach. The bag, which is made of ultra-thin polyethylene and has a volume capacity of 900 ml, was connected to the barostat by a double-lumen gastric tube (Salem Sump tube 16 ch, diameter 5.3 mm, Sherwood Medical, Petit Rechain, Belgium). The barostat measurements followed the recommendations presented in a review article by an international working team, and the barostat instrument fulfilled the criteria determined by this group (63). The volume changes were calculated by the computer comparing the area under the curve (AUC).

**Assessment of nausea and vomiting**

The intensity of nausea and the intensity of postoperative nausea were assessed in studies II and V, respectively, by means of using a visual analog scale (VAS) (0-10 cm), where 0 = no feeling of nausea at all and 10 = maximum nausea ever felt (54). The incidence of retchings or vomiting was recorded. Retching is by definition a vomiting reflex without expulsion of gastric contents. Retchings were considered to be the same entity as vomiting.
PROCEDURES

In study I, the influence on vomiting induced by apomorphine was evaluated in volunteers on four different occasions, separated by at least one week. The subjects were randomly allocated to receive 1) a propofol infusion, 2.4 ± 0.7 mg/kg/h (mean ± SD), 2) a midazolam infusion (0.13 ± 0.4 mg/kg/h), 3) a single, non-sedating bolus dose of propofol 0.4 mg/kg, and 4) an infusion of normal saline. During the propofol and midazolam infusions the doses were titrated so that the volunteers were sedated to grade 2-3 on the 5-grade sedation scale. The infusion of apomorphine was started when the volunteers reached grade 2-3 of sedation, or after the single dose of propofol and after the infusion of normal saline. The exact amount of apomorphine needed to induce vomiting during the different experimental situations was noted.

In study II, the influence of propofol on vomiting induced by ipecacuanha syrup was evaluated. The volunteers were studied on three occasions and were randomly allocated to receive a concomitant infusion of propofol (initial bolus 0.1 mg/kg, then 1 mg/kg/h), ondansetron (initial bolus 0.11 mg/kg, then 14 µg/kg/h) or placebo on each occasion. The infusions started 30 min before oral ingestion of 30 ml of ipecacuanha syrup and continued until 150 min after intake. The number of retchings was recorded and the intensity of nausea was estimated by the subjects on a Visual Analog Scale (VAS). The grade of sedation was estimated by observers. Blood samples for analysis of the plasma concentration of serotonin were taken before intake and every 30 min up to 150 min, and finally at 300 min after intake of ipecacuanha syrup.

In study III, gastric emptying and orocecal transit time were studied in volunteers on two occasions, with an interval of at least one week, and the volunteers were randomly allocated to receive either propofol sedation or i.v. saline as a control. During propofol sedation the volunteers were sedated to grade 2-3 on a 5-grade scale. This was achieved by an initial propofol infusion of 5 mg/kg/h, which was titrated down to a dose of 2.4 ± 0.7 mg/kg/h. The paracetamol absorption test was used to determine the rate of gastric emptying, and orocecal transit time was determined by the use of the hydrogen breath test. Two grams of paracetamol and 10 g of raffinose dissolved in 200 ml of water were ingested. Before ingestion, a standardized meal of unsweetened rice flour pancakes (170 g) was given to change the inter-digestive pattern in the gastrointestinal tract to post-prandial activity. Venous blood samples for determination of plasma paracetamol concentration were taken at 5, 10 and 15 minutes, and then at 15-min intervals during a period of 120 min after the oral ingestion of
paracetamol. The hydrogen concentration in end-expiratory samples of expired air was measured every 15 min until the hydrogen level increased at least 10 ppm above the baseline level.

*In study IV*, gastric tone and gastric emptying were evaluated in 40 ASA I-II patients before anesthesia. Gastric tone was measured in 20 patients by an electronic barostat. Volume changes were registered continuously in an intragastric flaccid bag with a constant preset pressure. The intragastric bag was placed in the gastric fundus during light sedation. Thereafter the patients rested for 30 min. During the registrations the patients were positioned on their right side with their head raised 15° and were asked to relax comfortably. All patients received i.v. morphine 0.1 mg/kg before the measurement, and in a randomized order 10 patients also received a bolus dose of propofol 1 mg/kg before the morphine. The measurement was completed 10 min after the administration of morphine.

Gastric emptying was studied with the paracetamol absorption test in 20 patients. All patients received morphine 0.1 mg/kg i.v. 10 min before oral ingestion of paracetamol 1.5 g in 200 ml of water, and in a randomized order 10 of the patients also received a 0.3 mg/kg bolus of propofol before the morphine, followed by an infusion of 1 mg/kg/h during the whole study (2 h). Venous blood samples were taken for determination of serum paracetamol concentration before ingestion and at each 15-min interval during a period of 120 min after the intake of paracetamol.

*In study V*, prophylaxis for postoperative nausea and vomiting was studied in two patient groups with a known high incidence. Through a stratified randomization, 60 patients undergoing breast surgery and 120 patients undergoing abdominal surgery were randomized to three groups of equal size, the propofol group (P), the multidrug group (M) and the control group (C). All patients received general anesthesia, induction with propofol and maintenance with sevoflurane. After induction, patients in the P-group received a continuous infusion of propofol 1 mg/kg/h during the operation and the first four postoperative hours. Patients in the M-group received dexamethasone 4 mg and three antiemetics, ondansetron 4 mg, droperidol 1.25 mg, and metoclopramide 10 mg i.v. In the C-group no prophylaxis was given. Nausea and pain were evaluated during 24 h postoperatively by means of a Visual Analog Scale, (0-10 cm). All emetic episodes were observed by the staff during the first four hours and by the patients during the next 20 h.
STATISTICS

In study I, the results are presented as mean ± SD. Comparisons of means were performed by analysis of variance and were tested for statistical significance by Bonferroni’s test.

In study II, the results are presented as medians and ranges. The Wilcoxon signed rank test was used for statistical analysis of the results.

In study III, Student’s t-test for paired samples was used for statistical analysis of the results, which are presented as means ± SD.

In study IV, the results are presented as means ± SEM. In the gastric tone study analysis of variance (ANOVA) was used for statistical analysis of the results. The unpaired Student’s t-test was used for statistical analysis of the results in the gastric emptying study.

In study V, the number of patients experiencing nausea and/or vomiting in the different groups, and during different time intervals, are presented. The Chi-square test was used for statistical analysis of these results. Other data are presented as means or medians and the ranges are given. Student's t-test or the Mann-Whitney test was used for these calculations.

A p-value less than 0.05 was considered statistically significant.
RESULTS

Study I
There was no difference in the sensitivity to apomorphine between the sedative regimens. The amount of apomorphine needed to induce vomiting was increased after sedation with propofol (4.3 ± 1.2 mg, p < 0.005) as well as midazolam (4.7 ± 2.3 mg, p < 0.001) in comparison to saline infusion (2.5 ± 0.5 mg). The non-sedating single bolus of propofol did not change the sensitivity to apomorphine (3.1 ± 1.1 mg) compared to saline infusion.

Study II
During the first 150 min after ingestion of ipecacuanha there were no retchings during the infusion of ondansetron (p < 0.01 vs placebo, p < 0.02 vs propofol) and significantly fewer retchings during the propofol infusion compared to the placebo infusion (p < 0.02). There was no nausea during the infusion of ondansetron (p < 0.01 vs placebo and propofol) and no difference in mean or maximal VAS for nausea during the propofol infusion compared to the placebo infusion.

The number of retchings after the infusions were stopped was significantly higher after propofol infusion as compared to ondansetron and placebo (p < 0.05). Some volunteers, most of them in the placebo group, vomited during the first 1 h after the intake of ipecacuanha, so less ipecacuanha was left in the gastrointestinal tract compared to the other two groups.

The basal level of the plasma 5-HT concentration did not increase after intake of ipecacuanha in either group.

Study III
There was no statistically significant difference in paracetamol absorption between the two study situations (III). During the propofol sedation the AUC$_{60}$ was 4793 ± 1538 µmol · min/L compared to 3897 ± 1310 µmol · min/L during the control situation (n.s.). Orocecal transit time was significantly shorter during the control study 180 ± 32.4 min than during propofol sedation 217 ± 64.9 min (p < 0.05).
Study IV

The volume in the intragastric bag increased in all patients receiving morphine without propofol. In the group that received propofol before morphine, the volume in the intragastric bag decreased in all patients. The volume differences between the groups were statistically significant (p < 0.01). There were no statistically significant differences in the AUC$_{60}$, C$_{max}$ and T$_{max}$ of serum paracetamol concentrations between the morphine and propofol-morphine groups.

Study V

In study V, the overall incidence of PONV during the first 24 h postoperatively was significantly lower in the multidrug group than in either the propofol group (p < 0.01) or the control group (p < 0.001). The incidence of PONV was significantly lower in the propofol group than in the control group (p < 0.05). The incidence of PONV was high both in patients in the control group who underwent breast surgery (84 %) and in those who underwent abdominal surgery (63 %). In abdominal surgery patients the overall incidence of PONV was significantly higher in females (67 %) than in males (38 %) (p < 0.01). The multidrug groups showed the lowest incidence of PONV both in the breast surgery patients and the abdominal surgery patients. However, in the breast surgery patients there was a non-significant difference between the propofol group and the multidrug group, and in the abdominal surgery patients the propofol group showed a statistically significant difference compared to the multidrug group (p < 0.05). The amount of opioid equivalents was numerically higher in the abdominal surgery group, but without statistical significance compared to the breast surgery group.

The incidence of PONV, postoperative nausea (PON) and postoperative vomiting (POV), increased significantly after the termination of propofol in the abdominal surgery patients (p < 0.05), and the incidence of PONV increased significantly (p < 0.05) in the breast surgery patients without a significant increase in PON and POV. In the multidrug group the number of patients who had an emetic event was significantly lower, both in patients undergoing breast surgery and those undergoing abdominal surgery. The maximum VAS scores for these patients who experienced nausea showed no statistical differences between the breast surgery and the abdominal surgery patients in either of the drug groups.
Postoperative nausea and vomiting (PONV) is still a clinical problem, and its incidence is unacceptably high (25, 28). Soon after the introduction of propofol, it was reported that the incidence of PONV was low after propofol anesthesia, and it was also proposed that propofol possesses antiemetic effects (17-21, 64, 65). In the present studies it was shown that a low dose infusion of propofol decreases the incidence of PONV (V), but the effect was of short duration (66-68). Possible antiemetic mechanisms of propofol were studied in papers I-IV, but the antiemetic effects remain unclear.

**Study I.** The purpose was to evaluate if propofol can abolish vomiting induced by apomorphine, a dopamine agonist. Dopamine is present in the human nervous system and acts directly on specific central and peripheral receptors (70). There are significant amounts of dopamine in the gastrointestinal tract, accounting for up to 20% of the free catecholamine content in the stomach (71). Studies in dogs and volunteers have shown that dopamine decreases stomach muscle tone, and it has been proposed as a possible neurotransmitter in gastric relaxation (72-74). Apomorphine is a morphine derivative with structural similarities to dopamine, and it stimulates dopamine receptors both in the chemoreceptor trigger zone and peripherally. Apomorphine has been used clinically to induce vomiting in patients before anesthesia (53, 59).

A non-sedating dose of propofol did not influence apomorphine-induced vomiting (75-77), but during propofol sedation a greater amount of apomorphine was needed to induce vomiting. However, this was probably an effect of sedation, as the same results were achieved with midazolam. Propofol, like other anesthetics, exerts a general depressant effect on the central nervous system (3), and although it seems to have a gamma-aminobutyric acid-(GABA-) mimetic action (7) in common with benzodiazepines such as midazolam, there are no reports on a relationship between GABA and emesis. So if PONV is induced by stimulation of dopamine receptors, it is better to use dopamine antagonists such as droperidol (78-88) or metoclopramide (89-95) for treatment.

**Study II.** The purpose was to evaluate if propofol has serotonin antagonistic effects. Ipecacuanha syrup was used to induce nausea and vomiting (45). Ipecacuanha releases serotonin (5-HT) from the enterochromaffin cells in the mucosa of the gastrointestinal tract. Serotonin stimulates 5-HT receptors at the afferent vagal nerve endings, which mediate stimulation of the vomiting center, but serotonin may also stimulate receptors in the chemoreceptor trigger zone (27, 30) via circulation (29,
32). By administration of ondansetron, a 5-HT$_3$ antagonist, it was clearly shown that ipecacuanha induces nausea and vomiting by release of serotonin, as the volunteers did not experience any nausea and vomiting when ondansetron was administered. Propofol significantly reduced the number of retchings induced by ipecacuanha, but the intensity of nausea was not significantly different from the control situation. There were no significant differences in sedation between the study groups that could influence the results. An interesting finding reported by others (66, 67) and also seen in study V was that the incidence of vomiting was higher after the termination of propofol. The results indicate that propofol may have some effect on vomiting induced by serotonin, and therefore propofol may have a weak 5-HT$_3$ antagonistic effect. However, if PONV is induced by serotonin, a 5-HT$_3$ antagonist is more effective for prophylaxis or treatment than a low dose of propofol. Today 5-HT$_3$ antagonists are used frequently for prophylaxis or treatment of PONV (35, 51, 97, 98).

**Study III.** Gastrointestinal disturbances with delayed gastric emptying and prolonged transit times may induce nausea and vomiting (99-101). The purpose of this study was to evaluate the influence of propofol on gastric emptying and orocecal transit time in volunteers. Gastric emptying was studied with the paracetamol method. This is an indirect method for measuring gastric emptying. Scintigraphy is considered the golden standard for measuring gastric emptying (103-106), but the area under the plasma paracetamol concentration curve from 0-60 min, AUC$_{60}$, correlates very well with scintigraphic methods for evaluating the liquid phase of gastric emptying (102-106). As the paracetamol method is very good for measuring the liquid phase of gastric emptying, it has been used for this both in postoperative and ICU patients (107-111). Orocecal transit time was assessed by measuring the end-expiratory hydrogen concentration after ingestion of the trisaccharide raffinose (57, 58, 69). The disaccharide lactulose is commonly used for measurement of orocecal transit time, but lactulose may stimulate motility, resulting in a shorter orocecal transit time, and therefore raffinose is to be preferred (112).

In this study propofol sedation did not influence gastric emptying, but it prolonged orocecal transit time slightly. This prolongation is probably of no clinical significance, and spinal and systemic opioids have a much greater influence on orocecal transit time (100, 101, 113). There are few reports on the gastrointestinal effects of propofol, but an in vitro study by Lee et al. showed that propofol exhibits inhibitory acetylcholine-induced contractions in human gastric and colonic smooth muscle (10).
Propofol is frequently used for sedation in ICU patients. Other drugs such as opioids probably have a more negative influence on gastrointestinal function in these patients than propofol (100-102).

**Study IV.** Both systemically and spinally administered opioids have negative effects on the gastrointestinal tract (113-115), with delayed gastric emptying (100, 101, 116-117), decreased gastric tone and prolonged orocecal transit time (118, 123). Opioids may also act centrally at the chemoreceptor trigger zone and thereby induce nausea and vomiting (27, 28). The use of opioids contributes greatly to postoperative nausea and vomiting (120). The purpose of study IV was to evaluate whether propofol abolishes morphine-induced effects on gastric emptying and gastric tone. The study was performed before anesthesia in patients scheduled for abdominal surgery. The gastric tone was measured by an electronic barostat. This device has been validated in other studies and found to be a reliable and practical instrument for monitoring changes in gastric tone (63, 119, 121). The pressure in the intragastric bag was set at 2 mmHg above the basal intragastric pressure. The pressure in the balloon must be greater than the pressure in the stomach, because otherwise the gastric pressure would deflate the intragastric bag. Morphine decreased gastric tone in all patients, but when morphine was administered after propofol, gastric tone increased (IV). Even if propofol abolished the negative effects of morphine on gastric tone, it did not abolish the delayed gastric emptying induced by i.v. morphine. Gastric emptying is dependent on a pressure gradient between the stomach and the duodenum (122, 124-127, 160). We also know that the pylorus has a rich enkephalinergic innervation, and stimulation of these receptors results in increased pyloric pressure, thereby causing delay of gastric emptying (128, 130). From this study it can be concluded that negative effects of opioids on gastrointestinal motility in postoperative ICU patients cannot be avoided by the use of propofol for anesthesia or ICU sedation.

**Study V.** The purpose of this study was to evaluate the effects of a per- and postoperative low dose infusion of propofol for prophylaxis of PONV in patients undergoing breast and abdominal surgery. As the genesis of PONV is so multifactorial, propofol prophylaxis was compared with a multidrug regimen consisting of dexamethasone and three antiemetic drugs. These drugs were ondansetron, a 5-HT₃ antagonist, droperidol, a dopamine antagonist, and metoclopramide, a dopamine antagonist that is also a motility-stimulating drug (153, 154). During the last decade several studies have shown that the combination of two or more antiemetic drugs is more effective than single drug therapy (88, 94, 130-142).
In chemotherapy treatment today it is standard to add dexamethasone to 5-HT\textsubscript{3} antagonists for prophylaxis of nausea and vomiting (138, 143-147, 157, 159). Some studies have also shown beneficial effects of dexamethasone for prophylaxis of PONV (148-152, and even better effects when dexamethasone is combined with droperidol (143) or 5-HT\textsubscript{3} antagonists (143, 156, 161). The results from study V demonstrated that propofol was as effective as the multidrug prophylaxis during the first four postoperative hours when the propofol infusion was ongoing. However, after termination of the propofol infusion the incidence of nausea, and especially the incidence of vomiting, substantially increased. It can be concluded that postoperative propofol infusion is not an appropriate routine prophylaxis for PONV due to its rebound effects and a more complicated method of administration. There is also a risk of sedation, and therefore propofol infusion can only be used in the recovery area. However, in isolated cases of intractable PONV propofol may be an alternative (17), as this has been reported during chemotherapy treatment (158, 163, 164)). The incidence of postoperative nausea and vomiting has decreased since the introduction of propofol, but it is still unacceptably high. From these studies it can be concluded that propofol as a low dose infusion reduces the incidence of PONV, but as soon as the infusion is terminated the effects disappear. The antiemetic effects of propofol remain unclear.

The multidrug prophylaxis was very effective and demonstrates clearly that a combination of two or more drugs is the most effective prophylaxis for PONV today, even if all patients are not free from postoperative nausea and vomiting. Multidrug prophylaxis or treatment (135, 137) appears to be much more effective than propofol, and it seems meaningful to recommend this regimen in patient groups with a known high risk for postoperative nausea and vomiting (162).
CONCLUSIONS

The following conclusions could be drawn from the results of these studies.

* Propofol did not abolish apomorphine-induced vomiting and therefore propofol does not have dopamine antagonistic effects.

* Propofol reduced the number of retchings induced by ipecacuanha, which releases serotonin from enterochromaffin cells in the gastrointestinal tract, and it can be concluded that propofol may possess a weak 5-HT₃ antagonistic effect.

* Propofol sedation did not influence gastric emptying of liquids, but it slightly prolonged orocecal transit time.

* Propofol abolished gastric relaxation induced by morphine, but it did not abolish morphine-induced delay of gastric emptying.

* Propofol in a low dose infusion reduced the incidence of postoperative nausea and vomiting in patients undergoing breast and abdominal surgery, but nausea, and especially vomiting, increased significantly after termination of the infusion.
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