British Journal of Anaesthesia 1996;77:463–467

Antiemetic effect of subhypnotic doses of propofol after thyroidectomy†

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Summary

Postoperative nausea and vomiting (PONV) are unpleasant, often underestimated side effects of anaesthesia and surgery, not devoid of medical complications. Prevention with antiemetics is only partially effective. Propofol has been shown recently to possess antiemetic properties in several situations. In this prospective, randomized, controlled trial, we have compared the antiemetic efficacy of subhypnotic doses of propofol, with Intralipid as placebo, after thyroidectomy. We studied 64 patients of both sexes, aged 22–71 yr, ASA I or II, undergoing thyroidectomy. After premedication with a benzodiazepine, balanced anaesthesia was produced with isoflurane and nitrous oxide in oxygen, and supplementary analgesia with fentanyl i.v. as required. Postoperative analgesia was provided with non-opioids, and piritramide 0.25 mg kg^{-1} i.m. on demand. Patients were allocated randomly and blindly to receive a 20-h infusion of either propofol or 10% Intralipid 0.1 ml kg^{-1} h^{-1}. Intralipid, the excipient of propofol, was chosen as placebo as it is devoid of antiemetic effects. Sedation scores, respiratory and cardiovascular variables, and incidence of PONV were assessed every 4 h for 24 h. Pulse oximetry and ECG were monitored continuously. Both groups were comparable in characteristics, surgical and anaesthesia procedures, amount of opioids given during and after operation, and total amount of the study drug infused after operation. Occurrence of PONV was similar before the start (propofol 41%, Intralipid 50%) and after completion (propofol 0.64%, Intralipid 1.6%) of infusion and decreased with time in both groups during the infusion. However, symptoms were reduced to nil with propofol but persisted and were more severe with Intralipid during infusion ($P \leq 0.01$). The overall incidence of PONV during infusion was 10% (three of 32 patients) in the propofol group and 65% (21 of 32 patients) in the Intralipid group. Cardiovascular and respiratory variables, and Sp_{O_2} were unaltered, and sedation decreased similarly with time in both groups. We conclude that propofol, given at subhypnotic doses, effectively reduced the incidence of PONV without untoward sedative or cardiovascular effects. (*Br. J. Anaesth*. 1996;**77**:463–467)

Key words

Vomiting, nausea. Vomiting, nausea, anaesthetic factors. Anaesthetics i.v., propofol. Surgery, thyroidectomy.

Postoperative nausea and vomiting (PONV) are common, often neglected side effects of surgery. Their incidence has been estimated, in multicentre studies, to be as high as 40–60%[1]. Apart from the distressing inconvenience, the muscular efforts accompanying these symptoms may contribute to medical complications such as aspiration pneumonia, wound dehiscence, bleeding and even wound infection[2]. Thyroidectomy is associated with a high rate of PONV and prevention with antiemetics such as metoclopramide or alizapride reduces their frequency from 60% to only approximately 40%[3].

Propofol has been associated with a reduced rate of PONV when used as a continuous infusion to provide anaesthesia[4–9]. This advantage is limited to the early postoperative period, up to 6 h after completion of surgery[8]. In contrast, propofol has been used successfully at subhypnotic doses (0.5–1 mg kg^{-1} h^{-1}) for the prevention and treatment of chemotherapy-induced emesis[10 11] and after surgery[12 13].

We have evaluated, in a randomized, prospective study, the antiemetic properties of propofol infused continuously at subhypnotic doses compared with a placebo, in thyroidectomized patients. Intralipid 10% was chosen as placebo as, being the excipient of propofol, it is indistinguishable from the drug and has proved to be devoid of antiemetic and emetogenic effects[14].

Patients and methods

After obtaining institutional approval from the Ethics Committee, we studied 66 patients of both sexes, ASA I–II, aged 22–71 yr, undergoing thyroidectomy. Patients with allergy or intolerance to any of the products to be used during or after operation, or those receiving neuroleptics, were excluded. All patients gave informed consent before participation and were allocated randomly to receive either propofol or placebo after operation.

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†Presented in part at the European Society of Anaesthesiologists Annual Congress, CNIT Paris, France, 29 April–3 May, 1995 (*British Journal of Anaesthesia* 1995; **74** (Suppl. 1); A279.

The anaesthetic procedure was the same for all patients. Premedication comprised midazolam i.m., 30 min before induction of anaesthesia. Oral diazepam, 60 min before induction, was given to a few patients reluctant to have an injection. In the operating theatre, patients received an i.v. balanced electrolytic solution (Plasmalyte, Travenol, Baxter) via a peripheral vein and standard monitoring was commenced (ECG lead II, heart rate, automatic arterial pressure, pulse oximetry). Anaesthesia was induced with fentanyl 2 $\mu g\ kg^{-1}$ i.v. and thiopentone 3–5 $mg\ kg^{-1}$ i.v. A single dose of atracurium 0.4–0.5 $mg\ kg^{-1}$ was used to facilitate tracheal intubation and neuromuscular block was not used thereafter. After tracheal intubation with a cuffed armoured tube, anaesthesia was maintained with 0.5–2% isoflurane and 60–70% nitrous oxide in oxygen administered via a respirator. Ventilatory variables and respiratory gases were monitored conventionally. Supplementary analgesia during surgery was provided with boluses of fentanyl 50–100 μg i.v.

At the end of operation, after tracheal extubation, patients were transferred to the surgical intensive care unit for 24 h. Postoperative monitoring was standard and comprised ECG, pulse oximetry and regular assessment of conscious status, arterial pressure, ventilatory frequency and fluid balance. Analgesia consisted of intra-rectal administration of indomethacin 100 mg twice daily or propacetamol 1 g i.v. every 4 h, or both. If inadequate, additional doses of piritramide (Dipidolor, Janssen Pharmaceutica) 0.1–0.25 $mg\ kg^{-1}$ i.m. were given at the request of the patient at a maximum frequency of every 4 h.

When patients were considered sufficiently oriented by the nursing staff, an infusion of propofol or 10% Intralipid, prepared and provided according to the randomization schedule, was started at a rate of 0.1 $ml\ kg^{-1}\ h^{-1}$ via a syringe pump.

Factors contributing to PONV, such as clinical status (euthyroidism, hyperthyroidism treated or not), previous history of PONV, date of last menses for women, duration of anaesthetic and surgical procedure, occurrence of hypotension during anaesthesia (defined as a decrease in systolic arterial pressure of more than 20% from baseline), difficulty of tracheal intubation (graded as easy, moderately difficult, difficult) and administration of opioid analgesia were recorded in order to assess the comparability of the two groups.

During the whole infusion period, the incidence and severity of PONV and eventual side effects were assessed as follows: every 4 h, patients were questioned and asked if they had experienced nausea and vomiting during the preceding period; in addition, any episode occurring outside the observation time and not self-reported was taken into account and noted. As the observation lasted at least 24 h, the assessment could not be made by only one investigator, but was made by trained nurses and controlled subsequently by the chief nurse (C. W.) and another investigator, preferentially always the same (S. J.). Nausea and vomiting were assessed using the score of Bellville[15]: 0 = no symptoms; 1 = nausea (subjective unpleasant sensation with awareness of urge to vomit); 2 = retching (spasmodic contractions of abdominal wall and diaphragmatic muscles without expulsion of gastric content); 3 = vomiting (same as (2) but with forceful expulsion of gastric contents). Whenever symptoms occurred, metoclopramide 10 mg i.v. was given as rescue drug, every 4 h if necessary.

Sedation was evaluated simultaneously using a four-point rating scale[10]. A score of 1 (patient fully awake) or 2 (patient sleepy, but rousable by verbal stimulation) was considered adequate. If the sedation score reached 3 (sleepy, not responding to verbal, but well to painful stimulation), the infusion rate of the study drug was reduced by half and stopped if the score was 4 (not rousable, not responding to painful stimulation).

Pain and satisfaction scores were also assessed after 10 and 20 h of infusion of the study drug, using a visual analogue scale (VAS) from 0 (no pain) to 10 (worst conceivable pain). During the night, if the patient was found quietly asleep, he/she was not awakened and only monitoring signs were noted. At the end of the infusion period, patients were observed for an extra 4-h period to assess evolution of PONV.

STATISTICAL ANALYSIS

Parametric data were submitted to analysis of variance. When the F ratio reached statistical significance, a t test (two-sided unpaired Student's test or two-tailed Fisher's exact test) was applied. Non-parametric data were analysed where applicable by the chi-square or Wilcoxon rank sum test. $P \leq 0.05$ was considered statistically significant.

Results

There were 32 patients in each group. Sex distribution, age, weight, height and ASA status were comparable. There was no difference in clinical status or other preoperative factors predisposing to PONV. Duration of anaesthesia and surgery, intubation difficulty, hypotensive episodes, and peroperative use of fentanyl were similar in both groups (table 1).

Patients received the same amount of propofol or Intralipid at the same rate and during the same period. Infusion of the study drug was started at the same time in both groups (with a median time of 30

Table 1 Patient data and predisposing factors (mean (SEM or range) or number. No significant differences between groups

	Propofol group ($n = 32$)	Intralipid group ($n = 32$)
Age (yr)	44 (22–60)	44 (23–71)
Sex (F/M)	26/6	31/1
Weight (kg)	67 (13)	67 (11)
Height (cm)	167 (9)	164 (7)
ASA status I/II	17/15	17/15
History of PONV (no/yes)	19/8	18/10
Hypotensive episodes (no/yes)	26/3	29/2
Difficult intubation (easy/moderate/difficult)	25/3/2	27/4/0
Preoperative fentanyl total dose (μg)	418 (18)	436 (26)
Anaesthesia duration (min)	162 (5)	165 (8)
Surgery duration (min)	122 (5)	123 (8)

Table 2 Trial drug infusion data (mean (SEM), median (range) or number). No significant differences between groups

	Propofol group	Intralipid group
Time from extubation until start of infusion (min)	30 (5–270)	35 (10–180)
Infusion rate (ml kg^{-1} h^{-1})	6.8 (0.2)	6.7 (0.2)
Total amount infused (ml)	130 (4.5)	125 (4.5)
Rate change (*n*) (no/half/stopped)	30/2/0	27/5/0

min in the propofol group and 35 min in the Intralipid group) after the end of operation. The infusion rate was reduced by the nurses twice in the propofol group and five times in the Intralipid group (ns) because of a sedation score of 2 after 8 h of perfusion

Table 3 Incidence of symptoms during observation period (number of patients (%))

	Propofol group	Intralipid group	*P*
Before infusion			
No symptoms	19 (59)	16 (50)	
Nausea	3	6	ns
Retching	1	2	
Vomiting	9	8	
0–4 h			
No symptoms	30 (94)	22 (73)	
Nausea	0	3	0.0134
Retching	0	0	
Vomiting	2	7	
4–8 h			
No symptoms	31 (97)	19 (59)	
Nausea	1	3	0.0004
Retching	0	0	
Vomiting	0	9	
8–12 h			
No symptoms	32 (100)	25 (78)	
Nausea	0	0	0.0099
Retching	0	3	
Vomiting	0	3	
12–20 h			
No symptoms	32 (100)	28 (88)	
Nausea	0	2	0.037
Retching	0	0	
Vomiting	0	2	
After infusion			
No symptoms	29 (90)	25 (78)	
Nausea	1	3	ns
Retching	0	0	
Vomiting	1	2	
No. of emetic episodes during observation period (pre-, per- and post-infusion)			
1	10	10	
2	4	13	
3	0	1	
4	0	2	
5	0	1	
Total number of patients with PONV			
Global	14 (44)	27 (84)	< 0.05
Pre-infusion	13 (41)	16 (50)	ns
During infusion	3 (10)	21 (65)	< 0.01
After infusion	2 (6)	5 (15)	ns

Table 4 Concomitant medication (metoclopramide and piritramide) (number of patients)

	Propofol group	Intralipid group	*P*
Metoclopramide			
None	21	10	< 0.01
1 dose	8 (7 pre-infusion)	12 (7 pre-infusion)	ns
2 doses	1	8	< 0.05
3 doses	0	1	—
Piritramide			
None	22	17	ns
1 dose	8	9	ns
2 doses	0	2	ns
3 doses	0	1	ns

(although this was considered acceptable in the study design) (table 2).

Before the start of infusion of the study drug, PONV had occurred in 45% of patients: 13 of 32 (41%) patients in the propofol group and 16 of 32 (50%) patients in the Intralipid group (ns). During the first period, two patients were still symptomatic (one nauseous, one vomiting) in the propofol group compared with 10 (three nauseous, seven vomiting) in the Intralipid group. One patient was slightly nauseous during the second period, and then the incidence decreased to nil in the propofol group during the rest of the infusion. PONV decreased with time in the Intralipid group but persisted during the whole infusion period. Repeated symptoms were more frequent in the Intralipid group. The differences were statistically significant throughout infusion. After cessation of infusion, PONV was observed in two (6%) patients (one relapse, one nausea "de novo") in the propofol group, compared with five (15%) in the Intralipid group (ns). The overall number of patients with PONV during the whole observation period in the propofol group was 14 (44%) and 27 (84%) in the Intralipid group ($P<0.05$). When only the infusion period was considered, there was a total of three (10%) symptomatic patients in the propofol group P compared with 21 (65%) in the Intralipid group ($P<0.01$) (table 3).

Slight sedation (sedation score of 2) was observed equally in both groups, particularly during the immediate postoperative period and decreased with time in a similar manner. There was no statistically significant difference either in the amount of opioid received (table 4) or the degree of sedation (table 5) at any time. After 10 h of infusion, the median VAS pain score was 0 (range 0–3) in the propofol group and 2 (range 0–6) in the Intralipid group; at 20 h the values were 0 (0–3) and 1 (0–6), respectively. These

Table 5 Sedation score (SS) during infusion (number of patients). No significant differences between groups

	Propofol		Intralipid	
	SS = 1	SS = 2	SS = 1	SS = 2
0–4 h	17	15	18	14
4–8 h	23	9	27	3
8–12 h	26	6	27	4
12–20 h	27	5	26	4

slight differences were not significant. There were no differences between groups in cardiovascular variables and Sp_{O_2} which remained within the normal range throughout the 24 h of observation.

Discussion

We have found that in thyroidectomized patients, PONV was very common, and that propofol, at subhypnotic doses, was effective in comparison with placebo in controlling the incidence, without unwanted sedative, respiratory or cardiovascular side effects.

Different pre- and peroperative factors may contribute to PONV and, if not correctly taken into account, introduce bias in the interpretation of results[1 16]. We found no difference in the preoperative state of patients or in their per- and postoperative courses. In particular, the amount of opioids used before and after operation did not differ between the two groups. As our patients represented a very homogeneous population, any difference in the occurrence of emetic symptoms may reasonably be attributed to the study drug.

We showed previously, in a controlled, randomized study, that thyroidectomy was a surgical procedure associated with a high incidence of PONV (up to 60%) when every mild symptom was taken as positive. This high incidence is probably related to the age range and sex of the patients (mostly middle-aged women) and intense peroperative vagal stimulation (surgical handling of the neck structures). In that study, prophylaxis with alizapride, a conventional antiemetic agent, reduced the incidence to only 40% compared with placebo[3]. In this study, 45% of patients (29 of 64) had PONV before the start of infusion of the study drug. Of the 13 (41%) symptomatic patients in the propofol group before infusion, only two were still vomiting during the first observation period. Only one patient was still slightly nauseous during the second observation period and then she became totally asymptomatic; however, she relapsed after the end of infusion. Otherwise, rapid and complete control of PONV was obtained with infusion of propofol at a rate of 1 mg kg^{-1} h^{-1}. In the control group, the overall incidence of PONV was 84% (51% before infusion and the remainder during infusion). This confirms the high incidence of PONV after thyroidectomy when no prophylaxis is used. In this group, PONV persisted throughout the infusion period, although there was a decrease in the frequency and severity of symptoms with time. As the two groups were comparable for all factors contributing to PONV, it may reasonably be concluded that the relief of symptoms was related to the antiemetic properties of propofol.

It is usually recommended that an antiemetic be given prophylactically before surgery or chemotherapy to improve the efficacy of the drug. As we wanted the effect of the drug to be dissociated completely from residual sedation caused by narcosis and no interference, the drug was given only when patients were sufficiently awake (sedation score of 1 or 2). Even with this less favourable regimen, complete response was obtained within less than 2 h in 94% of patients (30 of 32) and reached 100% success rate subsequently.

The mechanisms by which propofol acts as an antiemetic are unclear. The mechanisms of vomiting are complex and have been reviewed elsewhere[1]. Propofol is not thought to have vagolytic properties[12]. Borgeat and colleagues suggested that propofol may have failed as an antiemetic in patients who had undergone laparoscopic gynaecological procedures because of uninhibited vagal stimulation[12]. In our study, propofol was completely successful in the treatment of emetic symptoms after thyroidectomy, a procedure also accompanied by intense surgical stimulation of vagal afferents. However, the location and nature of this stimulation are not comparable with laparoscopy and do not involve irritation or distension of gastrointestinal structures that may convey chemoception or nociception via other afferents than parasympathetic. This suggests that the failure of propofol in the study of Borgeat and colleagues may not have been related wholly to absence of vagal inhibition. Other mechanisms for the non-hypnotic actions of action of propofol, including its antiemetic properties, have been reviewed recently[17 18]. A sedative effect of propofol, as sometimes suggested[17], can be ruled out in our patients as first, the degree of sedation was the same in both groups and second, sedation decreased with time in all patients whereas the efficacy of propofol increased. None of our patients had a sedation score higher than 2. Low doses of propofol may induce anxiolysis[19] sufficient to modify cortical afferents to the vomiting centre. Although we did not specifically test the anxiety status of our patients, clinical data describe no behavioural difference and indirectly indicate that an anxiolytic effect, if present, is not important enough to be the principal factor. A dopamine D2 receptor antagonist effect has also been suggested[20], but not proved. Propofol has also been shown to possess weak anti-serotonin ($5HT_3$) properties[21], suggesting a possible effect on the CTZ, but not enough to fully explain the efficacy of the drug in emetic syndromes refractory to 5-HT_3 antagonist therapy[11]. The exact mechanisms by which propofol acts remain subject to speculation and await further studies.

The exact concentration at which propofol exerts its antiemetic properties is not well documented[22]. A blood concentration of 197 ng ml^{-1} has been reported in one patient after 48 h of propofol infused at a rate of 1 mg kg^{-1} h^{-1} for the treatment of refractory PONV[13]. An i.v. bolus of 10 mg (sometimes repeated once) is usually effective for approximately 30 min in the treatment of chemotherapy-induced emesis[12]. From the pharmacokinetic models available, it is suggested that the effective concentration range is very low, certainly less than 0.5 μg ml^{-1} [23]. These values are lower than those recommended for sedation[24]. As already mentioned, in this study, the efficacy of propofol increased while sedation decreased with time. This provides another argument against an association between the sedative and antiemetic properties of propofol.

Can infusions of propofol of prolonged duration interact with lipid metabolism because of the emulsion (10% Intralipid) formulation of the drug? After several days of sedation with propofol in intensive care units, at a dose range of 1–3 mg kg^{-1} h^{-1}, no subsequent modifications in triglycerides or fatty accumulation were reported[25]. Hence, no changes would be expected in our patients, as propofol was infused at lower doses for a shorter period of time.

The lowest rate necessary to achieve an antiemetic effect and the corresponding plasma concentration of propofol need to be defined more precisely if propofol is to be considered an acceptable regimen for the prevention and treatment of PONV in patients at risk of such symptoms. We did not study the financial impact (benefits *vs* costs) of this therapy and this should be done, including not only the cost of the drug and the material used but all other relevant factors[11 26 27]: efficacy, psychological satisfaction, decreased strain on the nursing staff, postoperative surgical course (haematoma, healing) and duration of hospital stay. At present, considering the efficacy and high degree of acceptance and satisfaction of the treatment, we believe that propofol may be proposed prophylactically as an antiemetic agent in patients identified at high risk of PONV or as rescue drug in case of failure of conventional antiemetic therapy. It should be noted that 5-HT_3 antagonists have also been used successfully in this situation, although the success rate did not reach 100%[28]. To our knowledge, no controlled study has directly compared the respective efficacy and costs of propofol and 5-HT_3 antagonists.

Acknowledgements

We thank Zeneca and especially G. Byttebier and D. D'Hulster for their assistance and help in the statistical analysis, and Kabi-Pharmacia for their gracious supply of 10% Intralipid.

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