Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design

C. C. Apfel[1*], P. Kranke[1], M. H. Katz[2], C. Goepfert[1], T. Papenfuss[1], S. Rauch[1], R. Heineck[1], C.-A. Greim[1] and N. Roewer[1]

[1]Department of Anaesthesiology, Julius-Maximilians-University of Wuerzburg, Josef-Schneider Strasse 2, D-97080 Wuerzburg, Germany and [2]Director of Health, 101 Grove Street, Room 308, San Francisco, CA 94102-4593, USA

**Corresponding author*

Background. Despite intensive research, the main causes of postoperative nausea and vomiting (PONV) remain unclear. We sought to quantify the relative importance of operative, anaesthetic and patient-specific risk factors to the development of PONV.

Methods. We conducted a randomized controlled trial of 1180 children and adults at high risk for PONV scheduled for elective surgery. Using a five-way factorial design, we randomly assigned subjects by gender who were undergoing specific operative procedures, to receive various combinations of anaesthetics, opioids, and prophylactic antiemetics.

Results. Of the 1180 patients, 355 (30.1% 95% CI (27.5–32.7%)) had at least one episode of postoperative vomiting (PV) within 24 h post-anaesthesia. In the early postoperative period (0–2 h), the leading risk factor for vomiting was the use of volatile anaesthetics, with similar odds ratios (OR (95% CI)) being found for isoflurane (19.8 (7.7–51.2)), enflurane (16.1 (6.2–41.8)) and sevoflurane (14.5 (5.6–37.4)). A dose–response relationship was present for the use of volatile anaesthetics. In contrast, no dose response existed for propofol anaesthesia. In the delayed postoperative period (2–24 h), the main predictors were being a child (5.7 (3.0–10.9)), PONV in the early period (3.4 (2.4–4.7)) and the use of postoperative opioids (2.5 (1.7–3.7)). The influence of the antiemetics was considerably smaller and did not interact with anaesthetic or surgical variables.

Conclusion. Volatile anaesthetics were the leading cause of early postoperative vomiting. The pro-emetic effect was larger than other risk factors. In patients at high risk for PONV, it would therefore make better sense to avoid inhalational anaesthesia rather than simply to add an antiemetic, which may still be needed to prevent or treat delayed vomiting.

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Despite impressive advances in the field of anaesthesia, 25–30% of patients continue to experience postoperative nausea and vomiting (PONV) within the first 24 h.[1] PONV can result in significant morbidity (e.g. suture dehiscence, oesophageal rupture), and may also lead to life-threatening aspiration.[2] In addition, PONV generates considerable costs (e.g. drugs, nursing care, longer stay in the postanaesthetic care unit, unanticipated re-admission).[3] With approximately 250 million operations performed annually throughout the world, such costs amount to several billion Euros yr^{-1}.

Accordingly, there has been much interest in the question of whether it is more cost effective to employ prophylactic antiemetics, or to wait until the patient vomits and then give an antiemetic.[4] However, this solution to the problem ignores the reality that patients consider postoperative nausea, along with pain, to be the most troublesome minor complication of anaesthesia.[5] In an attempt to minimize PONV, more than 4000 randomized controlled trials with antiemetics have been performed in the past 40 yr with controversial results.[6]

Unfortunately, few studies have attempted to identify the causes of PONV from large-scale cohort studies.[7 8] In contrast to radiation- or chemotherapy-induced vomiting, no animal model has yet been developed to reliably trigger PONV. In addition, there are considerable individual differences among patients in their response to PONV, complicating the performance of experimental studies in humans. Most anaesthetists consider the genesis of PONV as 'multifactorial', involving operative, anaesthetic, and patient-specific risk factors.[2] Prior observational studies evaluating the cause of PONV have been unable to evaluate the individual impact of these factors because they were related to one another (e.g. patients with certain types of surgery were more likely to receive certain types of anaesthetics). To overcome this problem, we performed a randomized controlled study using a five-way factorial design to quantify the impact of patient gender, type of surgery, specific anaesthetics for maintenance, use of opioids, and use of prophylactic antiemetics on PONV.

Patients and methods

Study protocol

After obtaining the approval of the local ethics committee and written informed consent, 1180 patients (587 adults and 593 children) scheduled for elective otolaryngeal or strabismus surgery were enrolled in a double-blind, randomized controlled trial. The patients were aged between 4 and 65 yr, and had to have a predicted risk of more than 20% for postoperative vomiting (PV). For adults, a risk score for predicting the probability of PV after inhalational anaesthesia was employed,[9] while in children it is known that the incidence of PV is more than 20% above the age of 4 yr.[1] Exclusion criteria were known allergies or previous adverse reactions to any of the study drugs, as well as antiemetic treatment within 24 h before the operation.

To enable a detailed investigation of the relative impact of the factors and their possible two-factor interactions, a list was created with all permutations of: (i) gender (2 classes); (ii) type of surgery—categorized as strabismus surgery, adenotomies/tonsillectomies, tympanoplasties, sinus surgery and diagnostic procedures (5 classes); (iii) use of opioids: fentanyl, alfentanil, sufentanil or none (4 classes); (iv) maintenance anaesthetic: isoflurane, enflurane, sevoflurane or propofol (4 classes); and (v) use of prophylactic antiemetics: tropisetron, dimenhydrinate, droperidol, metoclopramide or placebo (5 classes).

Since the use of propofol without an opioid was considered to be inappropriate for these operations (propofol has no intrinsic analgesic properties), this permutation was not applied. This factorial design resulted in a total of 750 possible combinations (600 of which involved inhalational maintenance ($2\times5\times4\times3\times5=600$) and 150 which used propofol maintenance ($2\times5\times3\times1\times5=150$)).

As premedication, adult patients (children) received midazolam 7.5 mg (0.5 mg kg^{-1}) orally (rectally) about 30 min before the operation. Depending on the randomization number, adults (children) received either fentanyl 100 μg (2 μg kg^{-1}), alfentanil 1 mg (0.02 mg kg^{-1}), sufentanil 10 μg (0.2 μg kg^{-1}) or no opioids. After induction of anaesthesia with propofol 2–3 mg kg^{-1} and appropriate face mask ventilation, a dose of succinylcholine 1–1.5 mg kg^{-1} was administered to facilitate intubation. Anaesthesia was maintained with isoflurane, enflurane, sevoflurane or propofol in nitrous oxide and oxygen 2:1. Volatile anaesthetics were started at approximately 1 MAC end-expiratory concentration and propofol with 10 mg kg^{-1} h^{-1} for children and 7.5 mg kg^{-1} h^{-1} for adults. Further dosage was dictated by clinical needs. All patients received volume controlled normo-ventilation (end expiratory P_{CO_2} between 34 and 36 mm Hg). Antiemetics were given according to the randomization. Reversal of muscle relaxation was not necessary, since non-depolarizing muscle relaxants were not used. Antiemetic rescue treatment was only given if more than three emetic episodes were observed or if the patient requested it. Postoperative pain management was supported by the prophylactic and therapeutic application of acetaminophen. In the case of a pain score of >4 on the verbal rating scale (VRS) ranging between 0 and 10, tramadol (1.5 mg kg^{-1}, max. 5 mg kg^{-1}) or piritramide (0.05 mg kg^{-1}, max. 0.5 mg kg^{-1}) was given in small boluses in the postanaesthetic care unit or *via* a 100 ml isotonic electrolyte infusion within 5 to 10 min on the ward.

Patients were monitored by a specially trained investigator and interviewed using a standardized questionnaire in the postanaesthetic care unit (PACU) 60 and 120 min after extubation. After transfer to the ward, interviews were repeated after 6 h and 24 h after the end of anaesthesia. Either vomiting or retching was classed as postoperative vomiting and the respective time-points were recorded. Postoperative nausea (PN) and pain were assessed separately on an 11 VRS (ranging from 0 to 10).

To ensure comparability between children and adults, the incidence of PV (i.e. number of patients suffering from PV) were taken as the primary endpoint. For adults, secondary endpoints were the occurrence of PN and PONV. The incidence of PN was determined by the number of patients experiencing an episode of nausea during the 24 h study period. The incidence of PONV was determined by the number of patients with PN and/or PV during the 24 h study period.

Primary and secondary endpoints were analysed for the time intervals 0–2 h, 2–6 h, 6–24 h and 0–24 h. Since the influence of the risk factors in the 2–6 h interval was virtually identical with that in the 6–24 h interval, these two intervals were, for the sake of simplicity, lumped together as the 2–24 h interval. The 0–2 h and 2–24 h intervals were also called early and delayed postoperative periods, respectively.

Statistical analysis

A type I error of 0.05, a type II error of 0.2 and a 50% reduction in the examined endpoint was considered to be appropriate and clinically relevant. Only high-risk patients were included in the trial so that a mean incidence of 40% PV was expected. A mean reduction by half (i.e. to 20%) required a sample size of 91 patients per group. Confirmatory testing of the main factors leads to 1+4+3+3+4=15 comparisons, so that a type I error adjustment to 0.05/15=0.0033 (Bonferroni correction) may be considered. To protect against the chance of a type I error we set $P<0.001$. This required a group size of 160 patients, that is a total of 800 patients for 5-class factors (e.g. prophylactic antiemetic).

Although the primary intention of the factorial design was not interaction analyses, we sought exploratory testing of *two*-factor interactions to generate future hypotheses. Since the smallest subgroups occur when the interaction between the antiemetics (5 classes) and the type of operations (5 classes) is tested, this was used to calculate the minimum sample size. This interaction is of particular clinical significance, since it enables us to determine whether a certain antiemetic is particularly effective for a particular operation. We defined that this would be the case if a reduction from 40% to 10% could be achieved. For this, 38 patients per group would be needed, making an overall total of 950 patients.

Since there are no formulae available for sample size estimations with a five-way factorial design undergoing multiple logistic regression analysis, we have applied the generally accepted rule suggested by the textbook on multivariable analysis (i.e. that for multiple logistic regression analysis at least 10 outcomes for each independent (binary) variable should be in the model).[10] Thus, we considered 10 (for gender) +40 (for operations, since there are 4 additional classes) +30 (for opioids) +30 (for maintenance anaesthetics) +40 (for antiemetics) resulting in 150 outcomes. Since most patients were likely to receive antiemetics, they may be expected to have had an incidence of vomiting of about 20%. Therefore, five times more patients (i.e. a total of 750 patients) was needed.

Thus, depending on the question to be analysed, all sample size estimations resulted in fewer than 1000 patients. However, since a total of 750 combinations were possible, the randomization list had to be a multiple of 750 and it was decided to aim at 1500 patients. The study was planned to stop with 1500 patients or after the 2 yr (when at least 1000 patients were reached), whichever occurred first.

For analyses of all patients, odds ratios (OR) and their 95% confidence intervals (CI) were calculated for the potential impact on PV of each anaesthetic, surgical and individual risk/preventive factor separately using contingency tables (*un*adjusted OR). OR adjusted for all factors were calculated by multiple linear logistic regression

Table 1 Patient characteristics, anaesthetic and surgical data. Values are number of patients (%) or means with 95% confidence intervals (95% CI). BMI=body mass index

	Placebo	**Tropisetron**	**Dimenhydrinate**	**Droperidol**	**Metoclopramide**	**Sum or average**
No. of patients						
Children, *n* (%)	110 (46.4)	114 (49.6)	130 (53.9)	110 (46.8)	129 (54.4)	593 (49.7)
Adults, *n* (%)	127 (53.6)	116 (50.4)	111 (46.1)	125 (53.2)	108 (45.6)	587 (50.3)
Age (years)						
Children, mean (95% CI)	8.2 (7.4; 8.9)	8.1 (7.4; 8.8)	8.3 (7.6; 8.9)	7.6 (6.9; 8.4)	8.3 (7.6; 9.0)	8.1 (7.8; 8.4)
Adults, mean (95% CI)	37.2 (35.0; 39.3)	36.0 (33.8; 38.3)	33.7 (31.6; 35.7)	35.5 (33.3; 37.6)	35.2 (33.1; 37.3)	35.6 (34.6; 36.5)
BMI (kg m^{-2})						
Children, mean (95% CI)	17.3 (16.7; 18.0)	16.8 (16.3; 17.3)	17.2 (16.7; 17.8)	16.7 (16.2; 17.3)	17.2 (16.6; 17.7)	17.1 (16.8; 17.3)
Adults, mean (95% CI)	24.8 (23.9; 25.7)	24.3 (23.5; 25.1)	23.7 (23.0; 24.4)	24.6 (23.8; 25.4)	25.2 (24.2; 26.1)	24.5 (24.1; 24.9)
Gender						
Male, *n* (%)	103 (43.5)	99 (43.0)	104 (43.2)	102 (43.4)	103 (43.5)	511 (43.3)
Female, *n* (%)	134 (56.5)	131 (57.0)	137 (56.8)	133 (56.6)	134 (56.5)	669 (56.7)
Maintenance						
Propofol, *n* (%)	48 (20.3)	47 (20.4)	48 (19.9)	45 (19.1)	46 (19.4)	234 (19.8)
Isoflurane, *n* (%)	64 (27.0)	63 (27.4)	65 (27.0)	59 (25.1)	63 (26.6)	314 (26.6)
Enflurane, *n* (%)	61 (25.7)	60 (26.1)	61 (25.3)	66 (28.1)	63 (26.6)	311 (26.4)
Sevoflurane, *n* (%)	64 (27.0)	60 (26.1)	67 (27.8)	65 (27.7)	65 (27.4)	321 (27.2)
Opioids						
None, *n* (%)	49 (20.7)	50 (21.7)	45 (18.7)	49 (20.9)	46 (19.4)	239 (20.3)
Fentanyl, *n* (%)	62 (26.2)	60 (26.1)	68 (28.2)	58 (24.7)	60 (25.3)	308 (26.1)
Alfentanil, *n* (%)	67 (28.3)	60 (26.1)	62 (25.7)	60 (25.5)	67 (28.3)	316 (26.8)
Sufentanil, *n* (%)	59 (24.9)	60 (26.1)	66 (27.4)	68 (28.9)	64 (27.0)	317 (26.9)
Duration (min), mean (95% CI)	84.8 (78.9; 90.8)	89.0 (82.0; 96.0)	86.8 (80.7; 93.0)	91.7 (85.3; 98.2)	87.3 (81.0; 93.5)	87.9 (85.1; 90.8)
Operation						
Diagnostic procedures, *n* (%)	49 (20.7)	47 (20.4)	48 (19.9)	47 (20.0)	48 (20.3)	239 (20.3)
Adenotomies, *n* (%)	38 (16.0)	36 (15.7)	38 (15.8)	35 (14.9)	37 (15.6)	184 (15.6)
Sinus-operations, *n* (%)	42 (17.7)	40 (17.4)	43 (17.8)	42 (17.9)	43 (18.1)	210 (17.8)
Tympanoplasties, *n* (%)	48 (20.3)	49 (21.3)	52 (21.6)	51 (21.7)	49 (20.7)	249 (21.1)
Strabismus-op., *n* (%)	60 (25.3)	58 (25.2)	60 (24.9)	60 (25.5)	60 (25.3)	298 (25.3)
Postoperative opioids, *n* (%)	51 (21.5)	56 (24.3)	51 (21.2)	40 (17.0)	47 (19.8)	245 (20.8)

Table 2 Frequencies and odds ratio of PV within the overall period (0–24 h). *Reference group; †adjusted using logistic regression analysis for all other variables in the table; ‡history of PONV refers to a positive history of PONV and/or motion sickness

	n	Incidence *n* (%)	Unadjusted		Adjusted†		*P*
			Relative odds	95% confidence interval	Relative odds	95% confidence interval	
Antiemetics							
Tropisetron	230	73 (31.7)	0.82	(0.56; 1.20)	0.75	(0.50; 1.13)	
Dimenhydrinate	241	60 (24.9)	0.58	(0.39; 0.86)	0.54	(0.35; 0.81)	
Droperidol	235	59 (25.1)	0.59	(0.40; 0.88)	0.54	(0.35; 0.82)	
Metoclopramide	237	77 (32.5)	0.84	(0.58; 1.23)	0.80	(0.54; 1.21)	
Placebo*	237	86 (36.3)	1.00	(ref)	1.00	(ref)	0.010
Maintenance of anaesthesia							
Isoflurane	314	107 (34.1)	2.43	(1.61; 3.67)	3.41	(2.18; 5.37)	
Enflurane	311	102 (32.8)	2.30	(1.52; 3.47)	3.11	(1.98; 4.88)	
Sevoflurane	321	105 (32.7)	2.29	(1.52; 3.45)	2.78	(1.79; 4.31)	
Propofol*	234	41 (17.5)	1.00	(ref)	1.00	(ref)	<0.001
Opioids							
Alfentanil	316	104 (32.9)	1.26	(0.87; 1.82)	1.54	(1.03; 2.30)	
Fentanyl	308	96 (31.2)	1.16	(0.80; 1.69)	1.64	(1.11; 2.45)	
Sufentanil	317	88 (27.8)	0.99	(0.68; 1.43)	1.24	(0.83; 1.86)	
None*	239	67 (28.0)	1.00	(ref)	1.00	(ref)	0.126
Duration							
≤90 min	452	155 (34.3)	1.38	(1.07; 1.78)	1.77	(1.27; 2.49)	
<90 min*	728	200 (27.5)	1.00	(ref)	1.00	(ref)	<0.001
Operation							
Strabismus surgery	298	98 (32.9)	1.37	(0.94; 1.99)	1.78	(1.12; 2.84)	
Adenotomies	184	50 (27.2)	1.04	(0.68; 1.61)	1.17	(0.70; 1.96)	
Sinus operations	210	60 (28.6)	1.12	(0.74; 1.69)	1.22	(0.78; 1.92)	
Tympanoplasties	249	84 (33.7)	1.42	(0.96; 2.10)	1.04	(0.69; 1.59)	
Other operations*	239	63 (26.4)	1.00	(ref)	1.00	(ref)	0.015
Age category							
Children	593	206 (34.7)	1.56	(1.22; 2.01)	2.02	(1.45; 2.81)	
Adults*	587	149 (25.4)	1.00	(ref)	1.00	(ref)	<0.001
Gender							
Females	669	217 (32.4)	1.30	(1.01; 1.67)	1.48	(1.12; 1.97)	
Males*	511	138 (27.0)	1.00	(ref)	1.00	(ref)	0.006
History of PONV‡							
Yes	483	176 (36.4)	1.66	(1.29; 2.13)	2.02	(1.52; 2.69)	
No*	697	179 (25.7)	1.00	(ref)	1.00	(ref)	<0.001
Non-smoking							
Yes	964	316 (32.8)	2.21	(1.53; 3.21)	2.29	(1.51; 3.50)	
No*	216	39 (18.1)	1.00	(ref)	1.00	(ref)	0.001
Postoperative opioids							
Yes	245	90 (36.7)	1.47	(1.09; 1.97)	2.32	(1.62; 3.31)	
No*	935	265 (28.3)	1.00	(ref)		(ref)	<0.001

analysis (adjusted OR). Adjusted OR were also calculated separately for the early (0–2 h) and delayed (2–24 h) periods.

All possible two-factor interactions were tested by logistic regression analysis with a forward selection procedure for the early, delayed and overall postoperative periods. In view of this large number of tests, and to exclude over-interpretation of a chance event, an error probability of $P<0.001$ was taken for inclusion.

Assessment of significance was mainly described with the upper and lower limits of 95% CI or with *P*-values where appropriate. Calculations were carried out with SPSS for Windows (version 8.01) or a program for Confidence Interval Analysis developed by Gardner and colleagues.[11]

Since the results of the above-mentioned analyses indicated that the analysed period played a major role, and that the inhalational anaesthetics had the strongest impact on PV, Kaplan–Meier curves were drawn for patients receiving isoflurane, enflurane, sevoflurane and propofol anaesthesia. In agreement with the results of the multivariate analyses, these curves showed the influence of each of the inhalational anaesthetics to be so similar that they were analysed together in a single group (see below).

To illustrate the interaction between the degree of exposure in terms of 'applied concentration×duration' of volatile anaesthetics (standardized to MAC h) and the incidence of vomiting in the first 2 h after surgery, the patients were divided into five percentile groups, corresponding to the duration of the anaesthesia. The same procedure was applied to propofol, so that the effect of the exposure on vomiting for both types of anaesthesia could be compared directly. In order to ensure absolute sample

equality between inhalation and propofol anaesthesia in this sub-analysis too, only those patients receiving opioids intraoperatively were taken into account.

Study blinding

Syringes (10 ml) containing tropisetron 2.5 mg, dimenhydrinate 62.5 mg, droperidol 2.5 mg, metoclopramide 50 mg or 0.9% NaCl were prepared at the university pharmacy. Tropisetron and droperidol were diluted up to obtain the same volume of 10 ml with 0.9% NaCl. This was the standard dosage for adults. Children received 0.2 ml kg^{-1} (max. 10 ml) comprising tropisetron 50 μg kg^{-1} (max. 2.5 mg), dimenhydrinate 1.25 mg kg^{-1} (max. 62.5 mg), droperidol 50 μg kg^{-1} (max. 2.5 mg), metoclopramide 1 mg kg^{-1} (max. 50 mg), or placebo. The syringes were labelled with code numbers to ensure blinding.

Six medical students were instructed on how to perform postoperative assessments in a standardized fashion, and were blinded to the anaesthetics/antiemetics given to the patient, thus ensuring double-blind assessment. Of the 1180 patients, 85 showed an interest in the type of anaesthesia and the drugs they were to receive. The addresses of these patients were recorded, and details were mailed to them after the study was over and the analysis completed.

The data were entered into a database (Access 97) in different tables for randomization, preoperative assessments, intraoperative assessments and postoperative assessments. The randomization table was isolated from the database and was inaccessible to the investigators throughout the entire study period. Decisions on how to proceed with protocol violations were made, after completion of the entire study, by investigators blinded to the randomization and outcome.

At the end of the study, when the table containing the randomization code was reintegrated into the database, the analysis was carried out in a non-blinded fashion.

Results

Within the 2-yr study period, informed consent was obtained from 1217 patients. Of these, 14 patients were not operated on and received no anaesthesia, five patients had to be ventilated postoperatively following unforeseeably extensive operations, four patients erroneously received the wrong syringe, 14 patients accidentally received

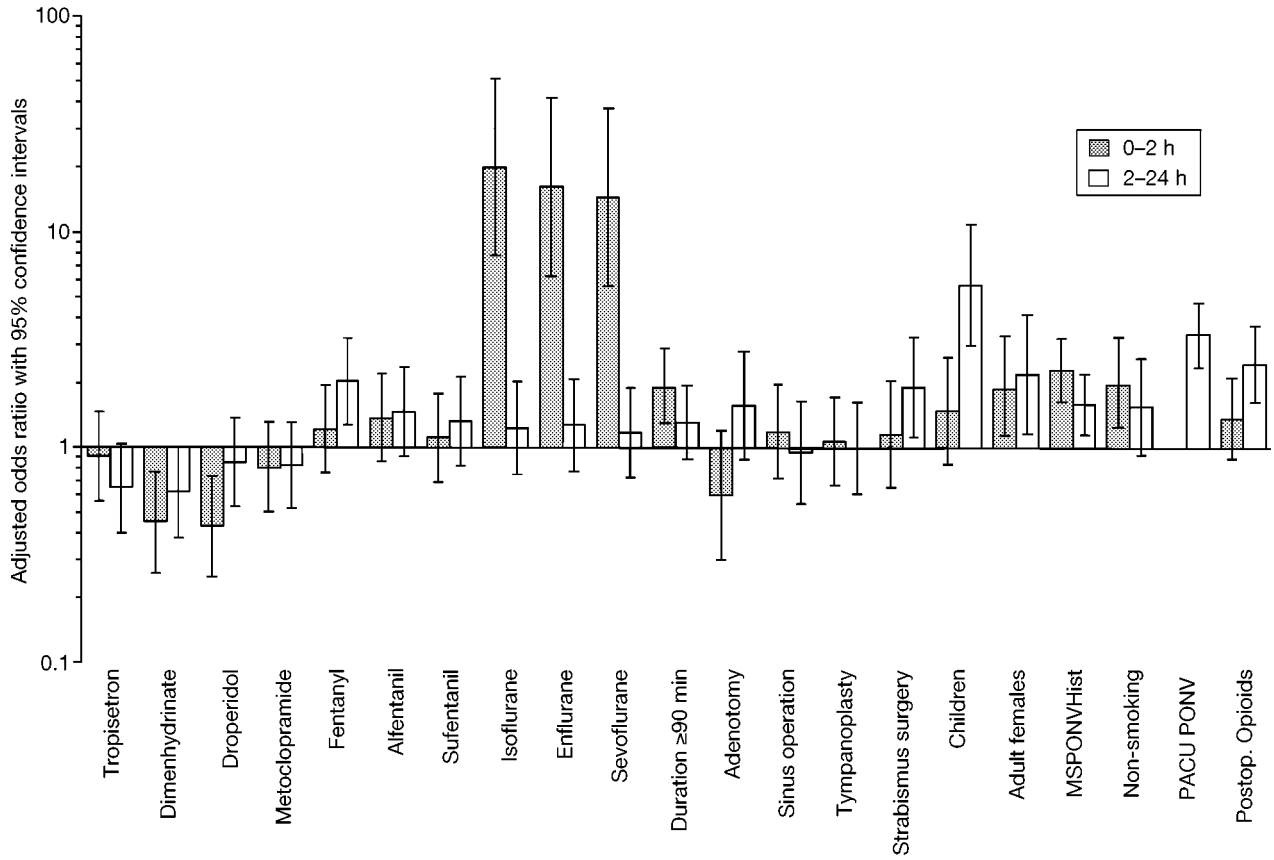

Fig 1 Adjusted odds ratio for PV with 95% confidence intervals (n=1180). Note that the log-scale displays the relative impact of anti- and pro-emetogenic effects in proportion (e.g. the emetogenic effects of volatile anaesthetics in the first 2 h are considerably stronger than the antiemetics). MSPONVHist=history of motion sickness and/or PONV; PACU PONV=postoperative nausea and/or vomiting in the postanaesthetic care unit.

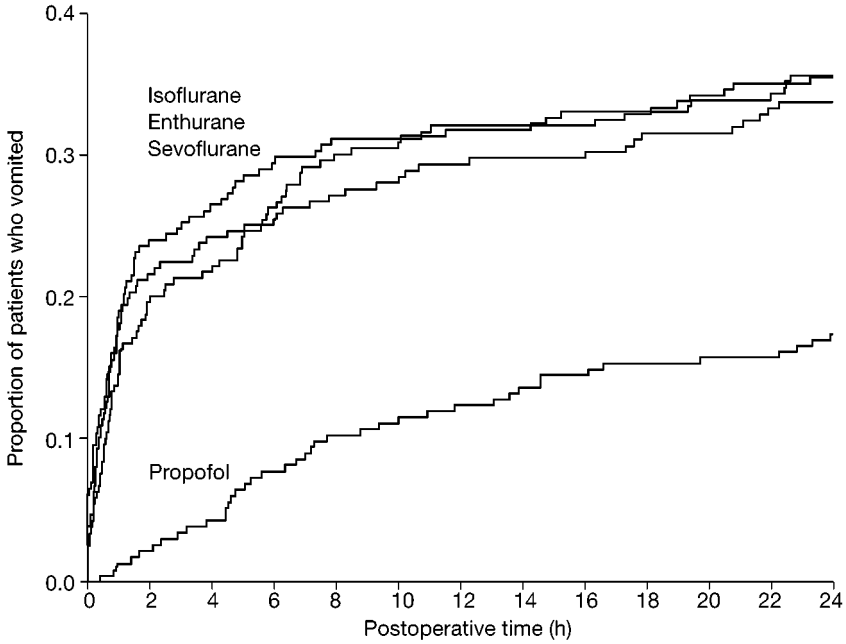

Fig 2 Kaplan–Meier curves representing the proportion of patients who vomited over time broken down by the type of maintenance anaesthetics (n=941). In order to ensure the comparability with propofol, patients receiving volatile anaesthetics but no intra-operative opioids (n=239) were excluded. Note that the difference between propofol and volatile anaesthetics is related only to the early postoperative period.

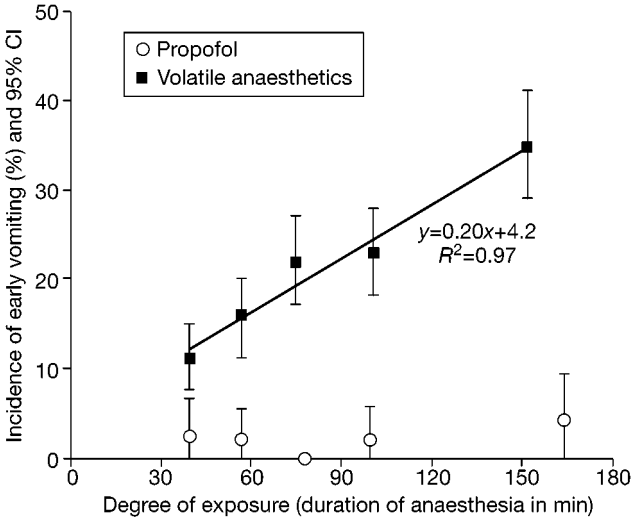

Fig 3 Correlation between the degree of exposure to anaesthesia and early postoperative vomiting in the first 2 h. In order to be able to compare inhalational and propofol anaesthesia, five percentile groups were formed for each, as a function of the anaesthesia duration. Note that the incidence of early vomiting correlates positively with the degree of exposure to inhalational anaesthesia but not to propofol anaesthesia.

an infusion containing tramadol 300 mg, droperidol 2.5 mg and metamizol 2.5 g. These cases were all withdrawn from the study and were not analysed, resulting in a final sample size of 1180 patients.

Of the 1180 patients, 355 (30.1%, 95% CI (27.5–32.7%)) had at least one episode of PV within 24 h post-anaesthesia. Owing to the factorial design of the study, there were no differences in groups and subgroups between the antiemetics, maintenance of anaesthesia with volatile anaesthetics or propofol, intraoperative opioids and operations (Table 1). Nor were there any significant differences between groups and subgroups of anaesthetic procedures in terms of patient-related risk factors.

The strongest risk factor for PV was the use of volatile anaesthetics compared with propofol (Table 2). The OR for isoflurane, enflurane and sevoflurane were 2.4 (1.6–3.7), 2.3 (1.5–3.5) and 2.3 (1.5–3.5), respectively, and were even higher when adjusted for the other factors by multiple logistic regression (i.e. 3.4 (2.2–5.4), 3.1 (2.0–4.9) and 2.8 (1.8–4.3)), respectively. Of the four antiemetics, only dimenhydrinate and droperidol were associated with a significant reduction in PV with unadjusted OR (CI) of 0.58 (0.39–0.86) and 0.59 (0.40–0.88), respectively. The other factors with an adjusted OR>2.0 were childhood, non-smoking, a history of motion sickness or PONV and the use of postoperative opioids.

Analysis of the early postoperative period (0–2 h) identified volatile anaesthetics as the main risk factor, with adjusted OR of 19.8 (7.7–51.2), 16.1 (6.2–41.8) and 14.5 (5.6–37.4) for isoflurane, enflurane and sevoflurane, respectively (Fig. 1).

The other factors with OR>2.0 or <0.5 were a history of motion sickness or PONV, non-smoking, dimenhydrinate and droperidol. In the delayed postoperative period (2–24 h), childhood proved to be the leading risk factor, with an adjusted OR of 5.7 (3.0–10.9). In addition, when PONV

Table 3 Frequencies of PV, PN and PONV with upper and lower limits of the 95% confidence intervals (CI) depending on the maintenance and on prophylactic antiemetics in adults

Maintenance	Outcome	Early (0–2 h)		Delayed (2–24 h)		Overall (0–24 h)	
		%	(95% CI)	%	(95% CI)	%	(95% CI)
Volatile anaesthetics	PV	23.8	(19.9; 27.7)	14.5	(11.3; 17.7)	28.8	(24.7; 32.9)
n=462	PN	35.3	(30.9; 39.6)	24.7	(20.7; 28.6)	43.3	(38.8; 47.8)
	PONV	40.3	(35.8; 44.7)	28.8	(24.7; 32.9)	47.6	(43.1; 52.2)
Propofol	PV	4.0	(1.3; 9.1)	11.2	(5.7; 16.7)	12.8	(6.9; 18.7)
n=125	PN	10.4	(5.0; 15.8)	20.8	(13.7; 27.9)	27.2	(19.4; 35.0)
	PONV	10.4	(5.0; 15.8)	23.2	(15.8; 30.6)	28.8	(20.9; 36.7)
All adults	PV	19.6	(16.4; 22.8)	13.8	(11.0; 16.6)	25.4	(21.9; 28.9)
n=587	PN	30.0	(26.3; 33.7)	23.9	(20.4; 27.3)	39.9	(35.9; 43.8)
	PONV	33.9	(30.1; 37.7)	27.6	(24.0; 31.2)	43.6	(39.6; 47.6)

Table 4 Odds ratio of all significant risk factors for PV and PONV in adults within the overall period (0–24 h). The variables were selected by forward stepwise logistic regression analysis. Note, that volatile anaesthetics per hour were the first selected risk factor for both outcomes

Odds ratio of influencing factors	Odds ratio	95% confidence interval
Influencing factors for PV		
1. Volatile anaesthetics per hour	1.87	(1.53; 2.30)
2. Previous history of motion sickness or PONV	2.44	(1.58; 3.75)
3. Postoperative opioids	2.51	(1.60; 3.97)
4. Female gender	2.44	(1.48; 4.02)
5. Antiemetic		
Tropisetron	0.81	(0.45; 1.47)
Dimenhydrinate	0.31	(0.16; 0.62)
Droperidol	0.41	(0.21; 0.77)
Metoclopramide	0.83	(0.45; 1.52)
6. Non-smoking status	1.88	(1.18; 3.02)
Influencing factors for PONV		
1. Volatile anaesthetics per hour	1.86	(1.52; 2.28)
2. Antiemetic		
Tropisetron	0.57	(0.33; 1.00)
Dimenhydrinate	0.22	(0.13; 0.42)
Droperidol	0.40	(0.23; 0.70)
Metoclopramide	0.47	(0.27; 0.84)
3. Operation		
Adenotomies	0.79	(0.34; 1.83)
Sinus operations	1.97	(1.21; 3.23)
Tympanoplasties	1.41	(0.83; 2.39)
Strabismus surgery	3.73	(1.97; 7.04)
4. Previous history of motion sickness or PONV	1.91	(1.31; 2.79)
5. Postoperative opioids	2.26	(1.47; 3.46)
6. Female gender	1.69	(1.13; 2.54)
7. Non-smoking status	1.58	(1.06; 2.36)

occurred already in the first 2 h postoperatively, or when postoperative opioids were necessary, the OR for PONV in the delayed period were 3.4 (2.4–4.7) and 2.5 (1.7–3.7), respectively.

To better understand the impact of anaesthetic type on early PONV, we compared the time to the development of PONV across the four groups. The Kaplan–Meier curves showed that isoflurane, enflurane, and sevoflurane had similar curves (Fig. 2, $P>0.05$ for all comparisons), while propofol was associated with significantly lower PONV. Because of the similarities in the curves of the three volatile anaesthetics, these were combined.

A strong dose–response relationship existed between duration and use of volatile anaesthetics (Fig. 3). This relationship did not exist with propofol.

Of 587 adults, 107 experienced nausea without vomiting, 127 both nausea and vomiting and 22 vomiting with no nausea at any time, to give incidences of PV, PN and PONV of 25.4% (149/587), 39.9% (234/587) and 43.6% (256/587), respectively. Since only 14.8% (22/149) of patients who vomited had no nausea, the numbers for PN and PONV were similar (Table 3) and the results of PN are not given separately. The results of the logistic regression analyses with a stepwise forward selection procedure which considered all influencing factors and all possible two-factor interactions for PV and PONV are presented in Table 4. The interaction of duration with volatile anaesthetics was the strongest influencing factor primarily selected by the algorithm for both outcomes. No other interaction between the investigated variables were selected by the algorithm. All other influencing factors had a similar impact, with the exception of the type of operation, which was only significant when PN or PONV was considered.

Discussion

According to our data, the use of volatile anaesthetics was the strongest risk factor for the development of PV. Detailed analyses have shown that this effect (i) was restricted to the early postoperative period (0–2 h); (ii) depended on the degree of exposure as quantified by duration of anaesthesia; (iii) was irrespective of whether isoflurane, enflurane or sevoflurane was used; and (iv) was stronger by several orders of magnitude than all other factors (including antiemetics) in the early postoperative period. The pro-emetogenic effect of volatile anaesthetics must therefore be considered to be a main cause of PONV in the *early* postoperative period. Although the lower incidence of PONV found to be associated with i.v. anaesthesia is ascribed to the antiemetic property of propofol, this presumed mechanism would appear unlikely to be of great importance, since no relationship has been found between

early postoperative vomiting and the degree of exposure to propofol. The strongest predictor for delayed vomiting (2–24 h) was childhood. To our surprise, there were no statistically significant interactions of antiemetics with anaesthetic or surgical variables.

The unique advantage of this factorial design is that a relatively large number of conditions can be compared, as they are balanced in terms of distribution of a number of confounding factors. To our knowledge, this is the first controlled study of factorial design to assess the relative impacts of anaesthetic, surgical and patient-related risk factors.

Isoflurane, enflurane and sevoflurane were each associated with a similar incidence of PV. This is in accord with the large controlled multi-centre study by Forrest and colleagues[12] involving 16 000 patients, which provided substantial evidence that there are no differences in the incidence of PV between halothane, enflurane and isoflurane. We therefore conclude that there are no clinically relevant differences in PONV between the volatile anaesthetics investigated, and that sevoflurane is not associated with a lower incidence in comparison with the other inhalational anaesthetics. However, the question arises whether the difference between inhalational and propofol anaesthesia is caused by intrinsic antiemetic properties of propofol or by emetogenic properties of volatile anaesthetics.

In 1992, Borgeat and colleagues[13] demonstrated that PONV could be treated with a single dose of propofol 10 mg. In children, however, despite sedative side effects, such a dose was of no benefit.[14] Owing to the high incidence of relapse, Scuderi and colleagues[15] studied, in addition to a bolus of propofol 0.1 mg kg^{-1}, a continuous infusion of 1 mg kg^{-1} h^{-1} to prevent PONV. However, there was no significant antiemetic effect. This appears to contradict the results reported by Gan and colleagues[16] suggesting that subhypnotic plasma concentrations of 343 ng ml^{-1} may reduce nausea in 50% of cases. A study by Hvarfner and colleagues[17] in healthy volunteers, revealed that both propofol and midazolam showed antiemetic properties only in doses producing identical levels of clinically relevant sedation and it was postulated that the antiemetic properties of propofol may be an unspecific side effect of sedation. Regardless of potential effects at subhypnotic doses, meta-analyses have shown that propofol is associated with a lower incidence of PONV than inhalational anaesthesia.[18] This fact may be one reason why propofol is widely believed to possess significant antiemetic properties. However, basing an antiemetic effect on the observation of lower incidences may not be correct when the drug or method is just less emetogenic than the comparator. Halothane, for example, was previously assumed to be an antiemetic based on a study reporting a lower incidence of PONV with halothane than with previously used anaesthetics.[19] However, no recent clinical data have confirmed this finding.[20]

The Kaplan–Meier curve revealed that the main difference between propofol and inhalational anaesthesia occurs within the first 2 h, when pharmacological kinetic effects are most likely to account for differences (Fig. 2). Thereafter, there is a parallel rise suggesting that this difference is not caused by the chosen anaesthetics. This is supported by the multivariate analyses of the delayed period.

In a subsequent analysis, we investigated the question whether this difference is caused mainly by the antiemetic effect of propofol, or by an emetogenic effect of volatile anaesthetics. We were able to show that, in the early postoperative period, there is a close relationship between vomiting and the degree of exposure to inhalational anaesthetics. We were not able to find any dose-dependent relationship between vomiting and the amount of propofol applied during i.v. anaesthesia. Since all anaesthetics were supplemented with nitrous oxide, it might now be suggested that this difference is due to the emetogenic effect of the nitrous oxide which is virtually eliminated by propofol anaesthesia. Although an emetogenic effect continues to be ascribed to nitrous oxide,[21] meta-analyses show that the influence, with its relative risk of approximately 1.4, is relatively low,[22] so that such an explanation would appear improbable. We therefore have to conclude that the difference between propofol and volatile anaesthesia is caused mainly by the emetogenic effects of the volatile anaesthetics and not—as is generally believed—by antiemetic properties of propofol.

The effect of the antiemetics led, at best, to a halving of the vomiting incidence. Tropisetron failed to reach statistical significance. Although a dose-finding study identified 2 mg as an optimal dose,[23] a more recent study found tropisetron 5 mg to be more effective than 2 mg.[24] Thus, it is not clear whether, at a higher dose, the results might have been better. In contrast, the 'older' and 'cheaper' antiemetics, namely dimenhydrinate and droperidol, appear to have acceptable antiemetic properties consistent with reports in the literature.[2] Interestingly, however, this does not appear to apply to metoclopramide. Rowbotham[6] has pointed out that studies on the efficacy of metoclopramide are conflicting and that 0.25 mg kg^{-1} metoclopramide has been reported to be equally as effective as droperidol, while 0.15 mg kg^{-1} was less effective in children after strabismus surgery.[6] In accordance with recent meta-analyses, we therefore assumed that most negative results might have been caused by a simple underdosage of metoclopramide.[25] Thus, taking into account the fact that more than 10 mg kg^{-1} metoclopramide was given daily to avoid chemotherapy-induced vomiting before the availability of 5-HT_3 antagonists, we decided to use only 1 mg kg^{-1} (max. 50 mg), to our knowledge the highest dose used so far to prevent PONV. Despite this high dose, our results suggest that metoclopramide does not lead to a clinically relevant decrease in PONV. Since restlessness or extrapyramidal symptoms occurred in 14 out of 235 patients ($P<0.05$), the

use of prophylactic metoclopramide to reduce the incidence of PONV would not appear justified.

Even the administration of effective antiemetics in the early postoperative period had an inadequate effect in comparison with the pro-emetogenic effect of volatile anaesthetics. In patients at a high risk for PONV therefore, the usual practice of administration of volatile anaesthetics with a single prophylactic antiemetic would appear to be questionable. However, the prophylactic administration of antiemetics to prevent PONV might well make good sense in the delayed period, irrespective of the anaesthetic procedure employed.

The overall impact of intraoperative opioids was small, possibly due to the low doses used. To our surprise, the somewhat higher incidence of emetic sequelae became apparent in the delayed postoperative period. It might be speculated that the dopaminergic effect of opioids in the chemoreceptor trigger zone lasts much longer than the elimination half-time in the plasma. Forrest and colleagues[12] have compared fentanyl/nitrous oxide-anaesthesia with volatile anaesthetics/nitrous oxide-anaesthesia and found higher incidences of PONV after fentanyl/nitrous oxide. In contrast to our own results, Langevin and coworkers[26] reported less emesis after alfentanil, as compared with fentanyl anaesthesia. Higher dosages of intraoperative opioids may have led to less PONV in the first 2 h after surgery (by reducing the dose of volatile anaesthetics needed). However, if these opioids lead to more PONV in the delayed period, this effect might predominate.

Type of operation is widely regarded as a major risk factor for PONV.[1 2 27] By stratifying this study for five types of operations we intended to investigate whether some antiemetics would be more effective than others for specific operations. As an example, we assumed that adenotomies, tonsillectomies or sinus operations would exert their main emetogenic impact by swallowed blood in the stomach acting on vagal innervation,[28] and we hoped that this might be prevented by tropisetron. We also assumed that the main emetogenic impact in tympanoplasties stems from vestibular irritation and thought that this might be more effectively prevented by antihistamics such as dimenhydrinate. However, we were unable to find any significant interactions between the types of operation investigated, and the antiemetics. In addition, adenotomies and tonsillectomies, sinus operations and tympanoplasties were not associated with a higher risk of PV than diagnostic procedures when the other risk factors were corrected for by logistic regression analysis. Strabismus surgery appeared to have an increased risk for the delayed, but not the early, postoperative period.

We recognize that our study can make no pronouncements about operations other than those investigated, although there is increasing evidence from other studies that the impact of abdominal, gynaecological or other types of operations may be limited.[7 9 29] It is interesting to note that, in adults, the risk factors for nausea and vomiting were very similar—except for the type of operation which appeared to have some impact on nausea, but not vomiting, in the delayed and overall postoperative period. Since there is no doubt that certain operations are associated with a higher incidence of PONV, further systematic investigations using multivariate analyses are needed to distinguish between simple correlations and causal relationships.

However, even if it should be found that some operations have an influence on nausea and vomiting, the data obtained so far appear to show that this influence is appreciably smaller than that of the volatile anaesthetics. It might therefore be postulated that the term *postoperative* nausea and vomiting erroneously prompted numerous *surgery-related* explanations, with the result that the true, namely *anaesthesia-related* causes of nausea and vomiting attracted less attention.

Although PONV is a multi-factorial event, our data suggest that the use of volatile anaesthetics must be considered as a main cause of this complication for early PONV (0–2 h). However, volatile anaesthetics had no impact on delayed PONV (2–24 h) for which childhood, early PONV, and the use of postoperative opioids were the main predictors. Accordingly, in patients at high risk for PONV,[7–9] it would make better sense to avoid volatile anaesthetics rather than simply add a single antiemetic, which may still be needed to prevent or treat delayed vomiting. Future, large-scale multicentre trials are needed to quantify the benefits of combining antiemetic strategies in a multimodal approach.[30]

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