General Anesthesia

A risk adapted approach reduces the overall institutional incidence of postoperative nausea and vomiting

[Une approche préventive adaptée aux risques réduit l'incidence générale de nausées et de vomissements postopératoires en milieu hospitalier]

Andreas Biedler MD,* Julius Wermelt MD,† Oliver Kunitz MD,‡ Andrea Müller MD,‡ Wolfram Wilhelm MD,* Jürgen Dethling MD,§ Christian C. Apfel MD†¶

Purpose: Routine prophylactic antiemetic treatment of surgical patients appears justified only in case of an increased risk of postoperative nausea and vomiting (PONV). The objective of this investigation was to assess the feasibility and efficacy of a dichotomized risk score adapted management of PONV based on ondansetron prophylaxis and treatment with respect to the overall institutional rate of PONV.

Methods: After estimating the individual PONV risk by a simplified score, 162 adult patients scheduled for elective surgery received either 4 mg ondansetron intravenously (two to four risk factors = high-risk) or no prophylaxis (zero to one risk factor = low-risk). For antiemetic treatment ondansetron was given intravenously and orally. Incidence of PONV was recorded during the first 24 hr after recovery.

Results: Data from 159 subjects were analyzed with 44 patients classified as low-risk and 115 patients classified as high-risk. Nine low-risk and 58 high-risk patients experienced PONV. The expected institutional PONV incidence of 47% was reduced to 36%. Treatment with ondansetron was necessary in seven low-risk and 37 high-risk patients with a complete response rate of 71% (low-risk) and 43% (high-risk).

Conclusion: Providing antiemetic prophylaxis with ondansetron to high-risk patients strictly based on a simplified risk score can reduce the overall institutional rate of PONV. However, classifying patients into two groups while using ondansetron as the single antiemetic in the high-risk group appears to be of limited efficacy as the incidence of PONV in high-risk patients is still double that of low-risk patients.

Objectif : *Le traitement antiémétique préventif courant des opérés semble justifié seulement en cas de risque accru de nausées et de vomissements postopératoires (NVPO). Nous voulions évaluer la faisabilité et l'efficacité d'un traitement, adapté aux scores de risque dichotomique de NVPO, fondé sur une action préventive et thérapeutique avec l'ondansétron en regard du taux global de NVPO à l'hôpital.*

Méthode : *Après avoir estimé le potentiel individuel de NVPO par un score simplifié, 162 adultes devant subir une intervention chirurgicale réglée ont reçu soit 4 mg d'ondansétron par voie intraveineuse (de deux à quatre facteurs de risque = haut risque) ou aucune prophylaxie (zéro ou un facteur de risque = faible risque). Comme antiémétique, l'ondansétron a été administré par voie intraveineuse et orale. L'incidence des NVPO a été notée pendant les 24 premières heures après la récupération.*

Résultats : *Les données de 159 sujets ont été analysées dont celles de 44 patients à faible risque et 115 à haut risque. Neuf patients à faible risque et 58 à haut risque ont eu des NVPO. L'incidence attendue de NVPO de 47 % a été réduite à 36 %. Le traitement avec l'ondansétron a été nécessaire chez sept patients à faible risque et 37 à haut risque pour un taux de réponse complet de 71 % (faible risque) et 43 % (haut risque).*

Conclusion : *L'administration préventive d'antiémétique avec ondansétron aux patients à haut risque, fondée strictement sur un score de risque simplifié, peut réduire le taux global de NVPO à l'hôpital. Mais la répartition des patients en deux groupes et l'utilisation d'ondansétron antiémétique chez les patients à haut risque seulement*

From the Klinik für Anaesthesiologie und Intensivmedizin, Universitätskliniken des Saarlandes, Homburg/Saar,* the Klinik für Anaesthesiologie, Julius-Maximilians-Universität, Würzburg,† the Klinik für Anaesthesiologie der Medizinischen Fakultät der RWTH, Aachen,‡ and GlaxoSmithKline, München,§ Germany; and Department of Anesthesiology and the Outcomes Reseach Institute, University of Louisville, Louisville, Kentucky,¶ U.S.A.

Address correspondence to: Dr. Andreas Biedler, Klinik für Anaesthesiologie und Intensivmedizin, Universitätskliniken des Saarlandes, 66421 Homburg/Saar, Germany. Phone: +49-6841-1622443; Fax: +49-6826-530304; E-mail: anabie@med-rz.uni-sb.de

This study was supported by GlaxoSmithKline, Germany.

Accepted for publication April 9, 2003.

nous semble d'efficacité limitée, étant donné que l'incidence de NVPO chez ces patients demeure deux fois plus élevée que chez les patients à faible risque.

DESPITE new advances in anesthesia and the introduction of a new class of antiemetics, postoperative nausea and vomiting (PONV) is still one of the most common postoperative patient complaints.[1] About 30% of patients receiving a general anesthetic are affected and the incidence is known to rise up to 80% or more in high-risk patient groups.[2,3] Numerous studies have investigated the administration of different antiemetics to reduce the incidence of PONV but, still, there is controversy on the optimal approach.[4] Quantitative systematic reviews show that, for prophylactic antiemetics, the relative reduction rate of PONV is in the range of 30 to 40%.[5] Moreover, prophylactic compared with therapeutic antiemetic treatment improves the satisfaction of patients at increased risk for PONV but not the satisfaction of low-risk patients.[6] Considering this limited efficacy, routine antiemetic prophylaxis in unselected patients is questionable. Therefore, it appears more reasonable to manage PONV according to the individual risk of each patient. This means limiting prophylaxis to patients with a high risk of PONV and providing only postoperative treatment with, for example, ondansetron intravenously or orally to patients with a low risk. With such rational use of resources it should be possible not only to improve patient satisfaction and to reduce the overall "institutional" rate of PONV but also to improve cost effectiveness.

The primary objective of the present investigation was to assess prospectively the efficacy of managing PONV strictly based on a dichotomized classification of the individual risk by either giving prophylactic ondansetron (when the estimated risk for PONV is high) or limiting therapy to rescue treatment with ondansetron only (when the estimated risk for PONV is low). The secondary objective was to investigate the efficacy and safety of treating established PONV with *iv* and oral ondansetron.

Patients and methods

The study was approved by the Ethics Committees of the three participating investigational sites (Universitätskliniken des Saarlandes, Homburg/Saar; Julius-Maximilians-Universität, Würzburg; Rheinisch Westfälische Technische Hochschule, Aachen). After written informed consent had been obtained, male and female patients aged between 18 and 70 yr, ASA physical status I to III and scheduled for elective surgery under general anesthesia were enrolled. Patients were excluded in case of participation in another clinical trial within the last 30 days, a known hypersensitivity to ondansetron, pregnancy and breastfeeding, phenylketonuria, malfunction of the gastrointestinal motility, diabetes, severe internal or neurological disease, acute life-threatening conditions, nausea or vomiting or antiemetic treatment within 24 hr prior to surgery and a history of alcohol or drug abuse.

Anesthesia

Each patient was prepared for anesthesia following standard institutional practice. On the morning of surgery, an oral benzodiazepine (at the anesthesiologist's discretion) was administered for premedication. Anesthesia was induced intravenously using either thiopentone or propofol. Tracheal intubation was facilitated with neuromuscular blocking agents which were repeated according to clinical needs. For maintenance, all patients received a balanced anesthetic technique with a volatile anesthetic and opioids. Nitrous oxide was used at the anesthesiologist's discretion. Postoperative analgesia was obtained with opioids and non-opioids, as required clinically.

PONV

Prior to anesthesia, patients were classified according to the expected risk for PONV using the simplified risk score of Apfel *et al.*[2] The four risk factors considered in this score are: 1) female gender; 2) history of PONV or motion sickness; 3) non-smoking status; and 4) the use of postoperative opioids. When zero or one risk factor was present the patients were classified "low-risk;" patients with two or more risk factors were classified "high-risk." High-risk patients received 4 mg ondansetron *iv* 30 min before the expected termination of anesthesia; patients at low-risk received no antiemetic prophylaxis. Patients who experienced PONV in the postanesthesia care unit (PACU) received an *iv* injection of ondansetron 4 mg (open-label) which could be repeated once if the therapeutic effect was unsatisfactory after 30 min or in case of recurrence of nausea, vomiting or retching. After transfer from the PACU to the ward, patients suffering from PONV received an orally disintegrating tablet (ODT) of ondansetron 4 mg (bio-availabilty 60%). This treatment could be repeated once if the therapeutic effect was unsatisfactory after 30 min or in case of recurrence of nausea, vomiting or retching.

TABLE 1 Patient characteristics

Patient characteristics	*"Low-risk" (n = 44)*	*"High-risk" (n = 115)*
Age (yr)	41.1 (37.8 – 44.4)	44.0 (41.4 – 46.6)
Female patients	15.9%, *n* = 7	73.0%, *n* = 84
Non-smoker	15.9%, *n* = 7	60.0%, *n* = 69
History of PONV or motion sickness	2.3%, *n* = 1	54.8%, *n* = 63
Postoperative opioids	45.4%, *n* = 20	88.7%, *n* = 102
Type of surgery		
major gynecological surgery	6.8%, *n* = 3	23.5%, *n* = 27
major orthopedic surgery	65.9%, *n* = 29	53.9%, *n* = 62
major abdominal surgery	2.3%, *n* = 1	6.1%, *n* = 7
other surgery	25.0%, *n* = 11	16.5%, *n* = 19
Duration of anesthesia (hr)	2.4 (2.1–2.8)	2.3 (2.1–2.5)
Patients with		
- 0 risk factors (risk = 10%)	5	-
- 1 risk factor (risk = 21%)	39	-
- 2 risk factors (risk = 39%)	-	42
- 3 risk factors (risk = 61%)	-	45
- 4 risk factors (risk = 79%)	-	28
Estimated risk of PONV	20.5%	57.4%
Number of patients expected to experience PONV	*n* = 9	*n* = 66

Values given are means (lower – upper 95% confidence intervals) for continuous data or relative and absolute frequencies (*n*) for count data, respectively. PONV = postoperative nausea and vomiting.

After the maximum dose of ondansetron, if symptoms of PONV persisted, antiemetics could be administered at the discretion of the investigator.

Data collection

Demographic data obtained were gender, weight, age, history of PONV, motion sickness and smoking status. Duration of anesthesia (defined as the time period from induction of anesthesia to the discontinuation of the anesthetics) and time to recovery (defined as the first reaction to a spoken command) were recorded. A patient was considered to have PONV if any degree of nausea and/or any emetic episode occurred within the first 24 hr after recovery. An emetic episode was defined as vomiting or retching (unproductive emesis).[7] The number of emetic episodes, the incidence of nausea and the need for antiemetic treatment with ondansetron or rescue antiemetics were recorded during early (≤ two hours) and late recovery (> two hours). Patients' and nurses' satisfaction with the antiemetic management were assessed before transfer from the PACU (or at two hours if the patient was not transferred) and 24 hr after recovery on a four-point verbal rating scale (very satisfied, satisfied, neither satisfied/nor unsatisfied, unsatisfied).

Statistics

The study was planned to describe the incidence of PONV within the first 24 postoperative hours in (i) low risk, (ii) high risk, and in (iii) all patients and to compare these incidences with the average expected risk of a previously validated simplified risk score. Sample size estimation was calculated based on the anticipated risk for PONV of 35% and a ratio of 2:1 for "high-risk" to "low-risk" patients. A number of 160 patients was calculated to be sufficient to achieve a 95% confidence interval of ± 10% for an overall PONV incidences of 35%. The observed incidence of PONV was compared with the expected incidence according to the simplified risk score. The efficacy of the postoperative administration of ondansetron was compared between patients with and without prior prophylaxis with ondansetron. Patient demographic data were tested for imbalance between groups. Data are presented as means (lower – upper 95% confidence intervals) for continuous data or relative (lower – upper 95% confidence intervals) and absolute frequencies (*n*) for count data, respectively. For statistical analysis Fisher's exact test was used. A significant difference was defined if $P < 0.05$ or the comparing values were beyond the 95% confidence intervals.

Results

In total, 162 patients were enrolled into the study. Three patients were randomized but did not receive general anesthesia and were excluded from the analysis giving 159 patients for intention-to-treat analysis. Patient characteristics including the PONV risk factor analysis are shown in Table I. Forty-four patients presented with no ($n = 5$) or one ($n = 39$) risk factor according to the simplified risk score and were classified as "low-risk" with an expected risk for PONV of 20.5 (11.2–34.5%). One hundred and fifteen patients had two ($n = 42$), three ($n = 45$) or four ($n = 28$) risk factors and were classified as "high-risk" with an expected risk for PONV of 57.4 (48.3–66.0%). There were no significant differences between both risk groups with regard to perioperative variables such as type of benzodiazepine used for premedication, type of anesthetics used for induction or maintenance, surgical procedures, duration of surgery and recovery, time to discharge to the PACU and the length of stay in the PACU.

The incidences of nausea and vomiting are detailed in Tables II and III. Overall, during the 24-hr study period, nine patients [(20.5 (9.8–35.3%)] classified as "low-risk" experienced PONV. In the group of patients classified as "high-risk" 49 patients [42.6 (33.5–52.2%)] experienced PONV ($P < 0.05$ *vs* low-

TABLE II Incidences of nausea and vomiting according to the patient risk group and in total

Observation interval	*Patients with*	*"Low-risk" (n = 44)*	*"High-risk" (n = 115)*	*All patients (n = 159)*
0 – 2 hr	Nausea	13.6%, *n* = 6	26.1%, *n* = 30	22.6%, *n* = 36
(≤ 2 hr)	Vomiting	2.3%, *n* = 1	9.6%, *n* = 11	7.5%, *n* = 12
	PONV	13.6%, *n* = 6	26.1%, *n* = 30	22.6%, *n* = 36
3 – 24 hr	Nausea	11.4%, *n* = 5	28.9%, *n* = 33	24.2%, *n* = 38
(> 2 hr)	Vomiting	4.5%, *n* = 2	14.9%, *n* = 17	12.0%, *n* = 19
	PONV	11.4%, *n* = 5	28.9%, *n* = 33	24.2%, *n* = 38
0 – 24 hr	Nausea	20.5%, *n* = 9	42.6%, *n* = 4	36.5%, *n* = 58
	Vomiting	6.8%, *n* = 3	20.9%, *n* = 24	17.0%, *n* = 27
	PONV	20.5%, *n* = 9	42.6%, *n* = 49	36.5%, *n* = 58

Values are incidences given in % with number of patients (*n*). PONV = postoperative nausea andvomiting.

TABLE III Incidences of nausea and vomiting according to the number of risk factors

Observation interval	*Patients with*	*0 risk factor (n = 5)*	*1 risk factor (n = 39)*	*2 risk factors (n = 42)*	*3 risk factors (n = 45)*	*4 risk factors (n = 28)*
0 – 2 hr	Nausea	0%, *n* = 0	15.4%, *n* = 6	11.9%, *n* = 5	26.7%, *n* = 12	46.4%, *n* = 13
(≤ 2 hr)	Vomiting	0%, *n* = 0	2.6%, *n* = 1	2.4%, *n* = 1	8.9%, *n* = 4	21.4%, *n* = 6
	PONV	0%, *n* = 0	15.4%, *n* = 6	11.9%, *n* = 5	26.7%, *n* = 12	46.4%, *n* = 13
3 – 24 hr	Nausea	20.0%, *n* = 1	10.0%, *n* = 4	23.8%, *n* = 10	24.4%, *n* = 11	42.9%, *n* = 12
(> 2 hr)	Vomiting	20.0%, *n* = 1	2.6%, *n* = 1	9.5%, *n* = 4	11.1%, *n* = 5	28.6%, *n* = 8
	PONV	20.0%, *n* = 1	10.0%, *n* = 4	23.8%, *n* = 10	24.4%, *n* = 11	42.9%, *n* = 12
0 – 24 hr	Nausea	20.0%, *n* = 1	20.5%, *n* = 8	33.3%, *n* = 14	42.2%, *n* = 19	57.1%, *n* = 16
	Vomiting	20.0%, *n* = 1	5.1%, *n* = 2	11.9%, *n* = 5	20.0%, *n* = 9	35.7%, *n* = 10
	PONV	20.0%, *n* = 1	20.5%, *n* = 8	33.3%, *n* = 14	42.2%, *n* = 19	57.1%, *n* = 16

Values are incidences given in % with number of patients (*n*). PONV = postoperative nausea and vomiting.

risk). This number was significantly lower than the expected number of 66 patients [57.4 (48.3–66.0%)] if no antiemetic prophylaxis had been given ($P < 0.05$). The overall institutional incidence of PONV was 36.5 (29.0–44.5%), which was significantly lower than the expected incidence of PONV of 47.2% ($P < 0.05$).

The efficacy of antiemetic treatment with ondansetron is detailed in Table IV. Overall, during the 24-hr study period, treatment was necessary in seven low-risk and 37 high-risk patients and resulted in a complete response rate (no further antiemetic treatment required, no nausea or vomiting) of 71.4% (low-risk) and 43.2% (high-risk), respectively ($P < 0.05$). No patient in the low-risk group and eight patients of the high-risk group required further antiemetic treatment.

Patient and nursing staff satisfaction with the antiemetic management showed no significant differences between the low-risk and high-risk groups. More than 85% of the patients and more than 80% of the nursing staff in the PACU and on the ward were satisfied or very satisfied with the antiemetic management.

Side effects assessed by the investigators as being potentially related to the study medication (based on the known side effects of 5-HT_3-antagonist) were headache ($n = 2$), abdominal disorder ($n = 1$) and drowsiness ($n = 2$). None of the reported side effects were classified as severe and all events resolved without treatment/spontaneously.

Discussion

This study prospectively investigated the risk-adapted management of PONV prophylaxis and treatment with a 5-HT_3-antagonist (ondansetron) in patients receiving general anesthesia for surgery. By limiting prophylaxis to patients classified as "high-risk" - which demonstrated a lower incidence of PONV than expected - the overall institutional incidence of PONV was 11% lower than expected without prophylaxis. However, the incidence of PONV in high-risk patients of approximately twice the incidence of low-risk patients questions the utility of dichotoming patients into two groups and/or to give only a single antiemetic to high-risk patients. The repeated administration of ondansetron for the

TABLE IV Efficacy of treating established PONV with ondansetron in the PACU and on the ward

	"Low-risk" (n = 44)	*"High-risk" (n = 115)*	*All patients (n = 159)*
Patients receiving *iv* ondansetron 4 mg for established PONV in the PACU (0–2 hr)	11.4%, *n* = 5	19.1%, n = 22	17.0%, *n* = 27
Success rate regarding			
- PONV (= no further PONV)	80.0%, *n* = 4	40.9%, *n* = 9	48.1%, *n* = 13
- Rescue treatment (= no further treatment)	100.0%, *n* = 5	81.8%, *n* = 18	85.2%, *n* = 23
Patients receiving oral ondansetron ODT 4 mg for established PONV on the ward (3–24 hr)	9.1%, *n* = 4	21.7% *n* = 25	18.2%, *n* = 29
Success rate regarding			
- PONV (= no further PONV)	75.0%, *n* = 3	52.0%, *n* = 13	56.0%, *n* = 14
- Rescue treatment (= no further treatment)	100.0%, *n* = 4	56.0%, *n* = 14	55.2%, *n* = 16
Patients receiving oral or *iv* ondansetron for established PONV during the 24 hr study period	15.9% *n* = 7	32.2% *n* = 37	27.7%, *n* = 44
Success rate regarding			
- PONV (= no further PONV)	71.4%, n = 5	43.2%, n = 16	47.7%, n = 21
- Rescue treatment (= no further treatment)	100.0%, *n* = 7	67.6%, *n* = 25	72.7%, *n* = 32

Values are incidences given in % with number of patients (*n*). PONV = postoperative nausea and vomiting; PACU = postanesthesia care unit.

treatment of PONV was less effective in high-risk patients compared to patients who did not receive prophylaxis (43% *vs* 71% complete response).

Prophylaxis or treatment of PONV?

There is an ongoing debate regarding the most cost effective strategy for the management of PONV.[8] The use of routine prophylaxis is questioned, in particular the use of the newer and more expensive 5-HT_3 receptor antagonists. No major benefit for routine antiemetic prophylaxis has been shown when drugs are administered non-selectively.[6] Such results are not without contradiction and Sadhasivam *et al.*[9,10] reported that routine prophylaxis with ondansetron not only decreased the incidence and frequency of PONV but also led to greater patient satisfaction. The main reason for these inconsistencies may be related to differences in the underlying patient risk for PONV. A clinically significant improvement in patient satisfaction with prophylaxis seems to occur mainly in subgroups of patients at a high risk for PONV.[6,11] Therefore, a cost-effective approach to the management of PONV would be to provide prophylactic antiemetic therapy in situations with a high-risk of emesis and to give treatment for established PONV in situations where the risk is lower. In order to make such decisions for PONV management, it is mandatory to know the incidence of PONV in the local setting (e.g., by using an established risk score to assess the risk for PONV).

Assessing the risk of PONV

A recent comparison of risk scores demonstrated favourable results both in terms of ease of use and predictive properties for the simplified risk scores.[12] For risk assessment in our patients we decided to use the simplified risk score described by Apfel *et al.*[2] since it is simpler than the risk score described by Koivuranta *et al.*[13] and, apparently, equally reliable.[12] In addition, this score showed favourable predictive properties in a French validation study.[14] To make it even simpler, we classified the patients either as "high-risk" for PONV (two or more risk factors with an expected risk for PONV of approximately 40%) or "low-risk" (less than two risk factors and an expected risk for PONV of approximately 20%).

Efficacy of antiemetic prophylaxis

Providing antiemetic prophylaxis with ondansetron to "high-risk" patients led to an incidence of 42% which was lower than the incidence of 57% expected by the simplified risk score. In the patients classified as "low-risk," the incidence of PONV without ondansetron prophylaxis was 20%, exactly the same as expected from the simplified score. Overall, with an incidence of 36%, management according to risk led to a significantly lower incidence than the expected institutional incidence of 47% of PONV during the 24 hr. Of note, although prophylaxis was limited to high-risk patients, there was no significant difference in the patients' and nurses' satisfaction ratings. Nonetheless, comparing our results with the current literature questions the

benefits of our strategy. Several reasons might contribute to the observed limited efficacy in the reduction of PONV. The expected risk of PONV when two risk factors are present would be approximately 40%, with three risk factors 60% and with four risk factors 80%. It can be assumed that for a better efficacy of prophylaxis in higher-risk patients the combination of two or even more antiemetics may increase the efficacy of prophylaxis and reduce the number of patients with PONV.[8] Omitting volatile anesthetics as a major risk factor for early PONV[15] and using propofol for maintenance instead could decrease the incidence in patients with three or four risk factors. Thus, a multimodal approach[16] may be warranted in high-risk patients.

Efficacy of antiemetic treatment

The efficacy of ondansetron treatment for established PONV differed between "low-risk" and "high-risk" patients. Whereas complete response (no further symptoms of nausea and/or vomiting, no need for further antiemetic medication) after ondansetron 4 mg intravenously was found to be 71% in the low-risk (ondansetron-naïve) group, it was only 43% in the high-risk group. This finding was previously reported by Kovac *et al.*[17] and suggests that established PONV should be treated with a rescue antiemetic acting via a different mechanism. Of note is the comparable complete response rate between patients receiving ondansetron 4 mg intravenously in the first two hours after recovery and patients receiving ondansetron ODT 4 mg that is known to have a bio-availabilty of only 60% later on the ward. This is in accordance with the results of a meta-analysis suggesting that even 1 mg of ondansetron *iv* is effective for the treatment of established PONV.[18]

In conclusion, the use of a prophylactic strategy based on a simplified risk score reduces the overall institutional rate of PONV by reducing the incidence of PONV in the high-risk group. However, when classifying patients into "low-risk" and "high-risk" groups for the management of PONV the number of high-risk patients experiencing PONV remains unacceptably high when ondansetron is used as the single antiemetic. Repeated administration of ondansetron for the therapy of established PONV after prior prophylaxis with ondansetron was well tolerated but of limited benefit.

References

1 *Kovac AL.* Prevention and treatment of postoperative nausea and vomiting. Drugs 2000; 59: 213–43.

2 *Apfel CC, Laara E, Koivuranta M, Greim CA, Roewer N.* A simplified risk score for predicting postoperative nausea and vomiting. Conclusions from cross-validations between two centers. Anesthesiology 1999; 91: 693–700.

3 *Biedler A, Wilhelm W.* Postoperative nausea and vomiting (German). Anaesthesist 1998; 47: 145–58.

4 *Gan TJ.* Postoperative nausea and vomiting–can it be eliminated? JAMA 2002; 287: 1233–6.

5 *Tramer MR.* A rational approach to the control of postoperative nausea and vomiting: evidence from systematic reviews. Part I. Efficacy and harm of antiemetic interventions, and methodological issues. Acta Anaesthesiol Scand 2001; 45: 4–13.

6 *Scuderi PE, James RL, Harris L, Mims GR III.* Antiemetic prophylaxis does not improve outcomes after outpatient surgery when compared to symptomatic treatment. Anesthesiology 1999; 90: 360–71.

7 *Apfel CC, Roewer N, Korttila K.* How to study postoperative nausea and vomiting. Acta Anaesthesiol Scand 2002; 46: 921–8.

8 *Watcha MF.* The cost-effective management of postoperative nausea and vomiting (Editorial). Anesthesiology 2000; 92: 931–3.

9 *Sennaraj B, Shende D, Sadhasivam S, Ilavajady S, Jagan D.* Management of post-strabismus nausea and vomiting in children using ondansetron: a value-based comparison of outcomes. Br J Anaesth 2002; 89: 473–8.

10 *Sadhasivam S, Saxena A, Kathirvel S, Kannan TR, Trikha A, Mohan V.* The safety and efficacy of prophylactic ondansetron in patients undergoing modified radical mastectomy. Anesth Analg 1999; 89: 1340–5.

11 *Eberhart LH, Mauch M, Morin AM, Wulf H, Geldner G.* Impact of a multimodal anti-emetic prophylaxis on patient satisfaction in high-risk patients for postoperative nausea and vomiting. Anesthesia 2002; 57: 1022–7.

12 *Apfel CC, Kranke P, Eberhart LH, Roos A, Roewer N.* Comparison of predictive models for postoperative nausea and vomiting. Br J Anaesth 2002; 88: 234–40.

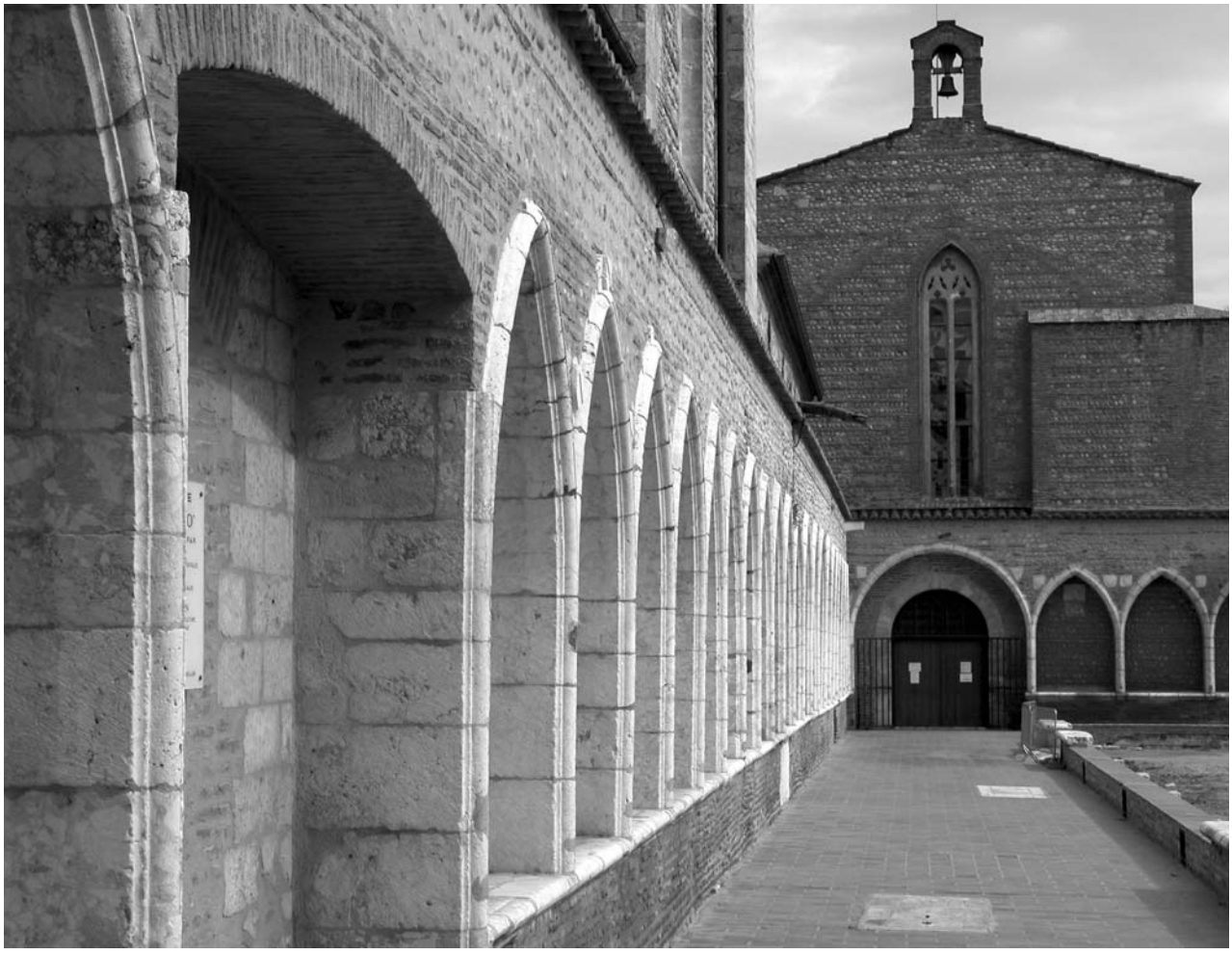
13 *Koivuranta M, Laara E, Snare L, Alahuhta S.* A survey of postoperative nausea and vomiting. Anesthesia 1997; 52: 443–9.

14 *Pierre S, Benais H, Pouymayou J.* Apfel's simplified score may favourably predict the risk of postoperative nausea and vomiting. Can J Anesth 2002; 49: 237–42.

15 *Apfel CC, Kranke P, Katz MH, et al.* Volatile anaesthetics may be the main cause of early but not delayed postoperative vomiting: a randomized controlled trial of factorial design. Br J Anaesth 2002; 88: 659–68.

16 *Scuderi PE, James RL, Harris L, Mims GR III.* Multimodal antiemetic management prevents early postoperative vomiting after outpatient laparoscopy.

Anesth Analg 2000; 91: 1408–14.
17 *Kovac AL, O'Connor TA, Pearman MH, et al.* Efficacy of repeat intravenous dosing of ondansetron in controlling postoperative nausea and vomiting: a randomized, double-blind, placebo- controlled multicenter trial. J Clin Anesth 1999; 11: 453–9.
18 *Tramer MR, Moore RA, Reynolds DJ, McQuay HJ.* A quantitative systematic review of ondansetron in treatment of established postoperative nausea and vomiting. BMJ 1997; 314: 1088–92.



Campo Santo Perpignon