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ORIGINAL ARTICLE

Alizapride and ondansetron for the prevention of postoperative nausea and vomiting in patients undergoing laparoscopic gynaecological surgery

A double-blind, randomised, placebo-controlled noninferiority study

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BACKGROUND Postoperative nausea and vomiting (PONV) can be prevented. Alizapride is an established antiemetic that may be effective in this role.

OBJECTIVE Our primary objective was to test the hypothesis that alizapride is noninferior to ondansetron for the prophylaxis of PONV.

DESIGN A randomised, placebo-controlled, double-blinded noninferiority study.

SETTING University hospitals of Leuven, Belgium, from November 2008 to July 2011.

PATIENTS A total of 523 patients undergoing laparoscopic gynaecological surgery were included in the study. Reasons for exclusion were American Society of Anesthesiologists (ASA) greater than 2, hypersensitivity to the study medication, pregnancy, mental disorders, psychiatric illness or consumption of antiemetic drugs within 24 h before initiation of the study.

INTERVENTION Patients received either alizapride 100 mg, ondansetron 4 mg or placebo intravenously 30 min before the end of surgery.

MAIN OUTCOME MEASURES The main outcome measures included the incidences of postoperative nausea (PON) and postoperative vomiting (POV) during the stay in the postanaesthetic care unit (PACU), with noninferiority testing for alizapride versus ondansetron. The region of noninferiority was defined as a relative difference in incidence of 25%. Secondary outcome was the incidence of PONV in the PACU and after 24 h.

RESULTS In the alizapride group, 32% of the patients experienced PON during the PACU stay, compared with 28% in the ondansetron group [relative risk 1.13, 90% confidence interval (CI) 0.87 to 1.46], exceeding the predefined margin of noninferiority. With respect to the incidences of POV during the PACU stay, 12.8% of the patients randomised to receive alizapride experienced POV, compared with 7.7% of who received ondansetron (relative risk 1.67, 90% CI 1.00 to 2.87). The incidences of PON and POV in the placebo group during the PACU stay were 34.2 and 9.8%, respectively. The 24-h incidences of PONV were lower than expected in this high-risk group of patients and were similar at 39.3, 36.8 and 31.5% in the placebo, alizapride and ondansetron groups, respectively (χ^2, $P = 0.36$). Patients treated with ondansetron required significantly less rescue medication than placebo-treated patients ($P = 0.035$). Due to the lower than expected incidences of PONV in this study, the power to conclude any noninferiority of alizapride was reduced to only 41%.

CONCLUSION We found no evidence to support the noninferiority of alizapride 100 mg when compared with ondansetron 4 mg for the intraoperative prophylaxis of PONV. However, the lower than expected incidences of PONV reduced the power of this study to conclude noninferiority or confirm significant beneficial effects for either antiemetic for PON and POV during the PACU stay.

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Introduction

In recent years, postoperative nausea and vomiting (PONV) has gained increasing attention. The overall incidence of PONV is currently estimated to be 20 to 30%.[1] Several classes of drug are used in the management of PONV, but no single class of drug is completely effective in controlling PONV. The D_2-receptor antagonist alizapride is a methoxy-2-benzamide derivative structurally related to metoclopramide.[2,3] In several European and South American countries (Belgium, Italy, France, Germany, Netherlands, Brazil and Colombia), alizapride is an established antiemetic that is widely used in oncology and perioperative medicine.[3,4] Alizapride has a favourable safety profile with only infrequently occurring side effects, which include headache, dizziness, akathisia, dry mouth and extrapyramidal syndromes.[5]

Ondansetron, a 5-HT_3 receptor antagonist, is one of the best studied and most potent antiemetic drugs to prevent PONV.[6–8] Ondansetron has few side effects (e.g. headache, akathisia and QT-elongation), but is still relatively expensive.[9] Although alizapride has been demonstrated to be equally as effective as ondansetron in the treatment of PONV,[10] alizapride and ondansetron have never been compared in an adequately powered, randomised, placebo-controlled trial with respect to their efficacy in preventing PONV. This lack of data on the efficacy of alizapride for the prevention of PONV has been noted in a recent Cochrane report.[11] Therefore, we performed a randomised, double-blind, placebo-controlled noninferiority study to test the hypothesis that alizapride is noninferior to ondansetron for the prophylaxis of PONV in a group of patients known to exhibit a particularly high risk of PONV.

Materials and methods

A total of 523 women scheduled for laparoscopic gynaecological surgery were included in this double-blind, randomised, placebo-controlled noninferiority trial. The study protocol (Ethical Committee No. OG 032) was approved by the ethics committee of the University Hospitals of KU Leuven, Leuven, Belgium (Chairperson Prof J. Vermylen) on 4 September 2008 and approved/registered by the Belgian government (EUDRACT number CT 2008-004789-20). Written informed consent was obtained from all enrolled subjects. Inclusion criteria were American Society of Anesthesiologists' (ASA) physical status 1 or 2 and age more than 18 years. The exclusion criteria were hypersensitivity to any of the study medications, ASA grades 3 to 5, pregnancy, Parkinsonism, mental disorders, psychiatric illness or consumption of antiemetic drugs within 24 h before initiation of the study. Randomisation was performed using a computer-generated randomisation code (Microsoft Excel). The patients were assigned randomly to one of three groups: the ondansetron group (group O, $n = 200$), the alizapride group (group A, $n = 200$) or the placebo group (group, $n = 123$).

Allocation concealment was ensured by enclosing assignments in sealed, opaque, sequentially numbered envelopes that were opened only after arrival of the patient in the operation room. Study drugs (alizapride 100 mg, ondansetron 4 mg or 0.9% saline) were prepared by an independent anaesthetist not involved in the treatment or follow-up of the study patients. All drugs were delivered in identical syringes with a total volume of 4 ml (dilution of ondansetron with 0.9% saline), and administered intravenously (i.v.) approximately 30 min before the end of surgery. Patients, anaesthetists and the study nurse who collected the trial data were blinded to group allocation.

The anaesthesia technique was standardised for all patients. Patients were premedicated with alprazolam (0.5 mg orally) 1 h before surgery. Anaesthesia was induced with propofol ($2\ mg\ kg^{-1}$), sufentanil ($0.2\ \mu g\ kg^{-1}$) and rocuronium ($0.5\ mg\ kg^{-1}$). After tracheal intubation, maintenance of anaesthesia was achieved with sevoflurane (2.0 to 3.0%) in an oxygen/air mixture and additional boluses of sufentanil if deemed necessary by the attending anaesthetist. In addition, paracetamol ($15\ mg\ kg^{-1}$) and ketorolac ($0.5\ mg\ kg^{-1}$) were administered immediately after induction of anaesthesia. For postoperative analgesia during the hospital stay, patients received paracetamol ($15\ mg\ kg^{-1}$ i.v. every 6 h), ketorolac ($0.5\ mg\ kg^{-1}$ i.v. every 8 h) and piritramide boluses [2 mg i.v. in the PACU and $0.25\ mg\ kg^{-1}$ intramuscularly (i.m.) every 6 h] as a rescue therapy. Episodes of PONV were treated with the first-line rescue therapy consisting of 1.25 mg droperidol i.v. and 5 mg dexamethasone i.v. When PONV still persisted after 30 min, ondansetron 4 mg and alizapride 100 mg were administered i.v. as a second rescue therapy.

Postoperative nausea (PON) was defined as the feeling of the urge to vomit and scored by means of a visual analogue scale (VAS), with a VAS score of 0 representing lack of nausea, and a VAS score of 10 being the worst imaginable form of nausea. Treatment was initiated if the VAS score exceeded 2. These VAS scores were used only as a guide to treatment. Postoperative vomiting (POV) was defined as the expulsion of stomach contents through the mouth.

PONV was defined as the presence of nausea and/or vomiting. A complete response to the study medications was defined as no episodes of PONV in 24 h and no need for rescue antiemetics. The incidence and severity of PONV were evaluated using the following three variables: the incidences of PON, of POV and of the combination of nausea and vomiting (PONV). These outcome variables were monitored every hour until

discharge from the PACU or until ambulation (in day-case surgery). Postoperatively, patients were interviewed (either personally or, in day-case surgery, via telephone) at 24 h to report the incidence/severity of nausea and vomiting in the previous 24 h.

Primary outcome

The incidences of PON (VAS score ≥1) and POV in the PACU were considered as primary outcome with noninferiority being tested separately for both. A patient was declared positive for nausea irrespective of the time at which PON occurred and irrespective of the number of PON episodes.

Secondary outcomes

Evaluation of noninferiority of alizapride for PONV in PACU and after 24 h was considered a secondary outcome. Subgroup analyses were performed for patients with two PONV risk factors and for patients with three or four risks factors according to the simplified risk score of Apfel *et al.*[12] In addition, the need for rescue medication was compared among the three groups.

Sample size estimation

According to the risk score of Apfel *et al.*[12] (which allows a risk stratification according to the presence of four PONV risk factors, i.e. female sex, perioperative use of opioids, nonsmoking status and a previous history of PONV) and the prevalence of three risk factors in the majority of our patients, a control event rate in the group P of 60% was expected in our patient population. As the preventive use of ondansetron is known to reduce the incidence of PONV by 25%, a PONV incidence of 45% was expected in the ondansetron group.[13] We hypothesised that alizapride 100 mg would be noninferior to ondansetron 4 mg and defined the margin of noninferiority at an absolute risk difference of 12.5%. With 45% as the expected incidence rate for both antiemetics, the required number of patients per group to find noninferiority with at least 80% power was 196 on the basis of a one-sided test and an α error of 5%. Further, 111 patients were needed in group P to find a significant difference in incidences between both antiemetic groups combined ($n = 392$) of 45% and the expected rate of 60% in the placebo group, using a two-sided χ^2 test and an α error of 5%.

Statistical analysis

Analyses were performed using SAS software, version 9.2 of the SAS System for Windows (SAS Institute Inc., Cary, North Carolina, USA). Exact confidence intervals (CIs) for the difference in proportions and relative risks were obtained with StatXact-9 (Cytel Inc., Cambridge, Massachusetts, USA). The noninferiority of alizapride compared to ondansetron was tested using the exact two-sided 90% CI approach for the difference in proportions and relative risk, which corresponds to the appropriate one-sided *P* value less than 0.05 to conclude noninferiority.[14] Kaplan–Meier survival analysis was used to compare durations of freedom from PONV during the PACU stay.

A logistic regression model stratified by group (ondansetron, alizapride, placebo) was used to predict PONV incidence during the PACU stay from several separate patient characteristics (age, BMI, duration of anaesthesia, duration of surgery, ASA risk classification, smoking behaviour, history of PONV and risk grouping according to the Apfel score). All these characteristics (except risk grouping, as this is already based on smoking behaviour and history of PONV) were combined in an additive multivariable logistic regression model. *P* values less than 0.05 were considered significant.

Posthoc changes to statistical analysis plan

Due to lower than expected incidences of PONV in our study, it was necessary to abandon the predefined margin of noninferiority expressed as an absolute risk difference of 12.5% and to use a relative risk difference of 25%, or a risk ratio of 1.25 instead. This change from an absolute to relative risk approach represented a pragmatic attempt to approximate the original margin of noninferiority due to the lower than expected incidences observed in our study.

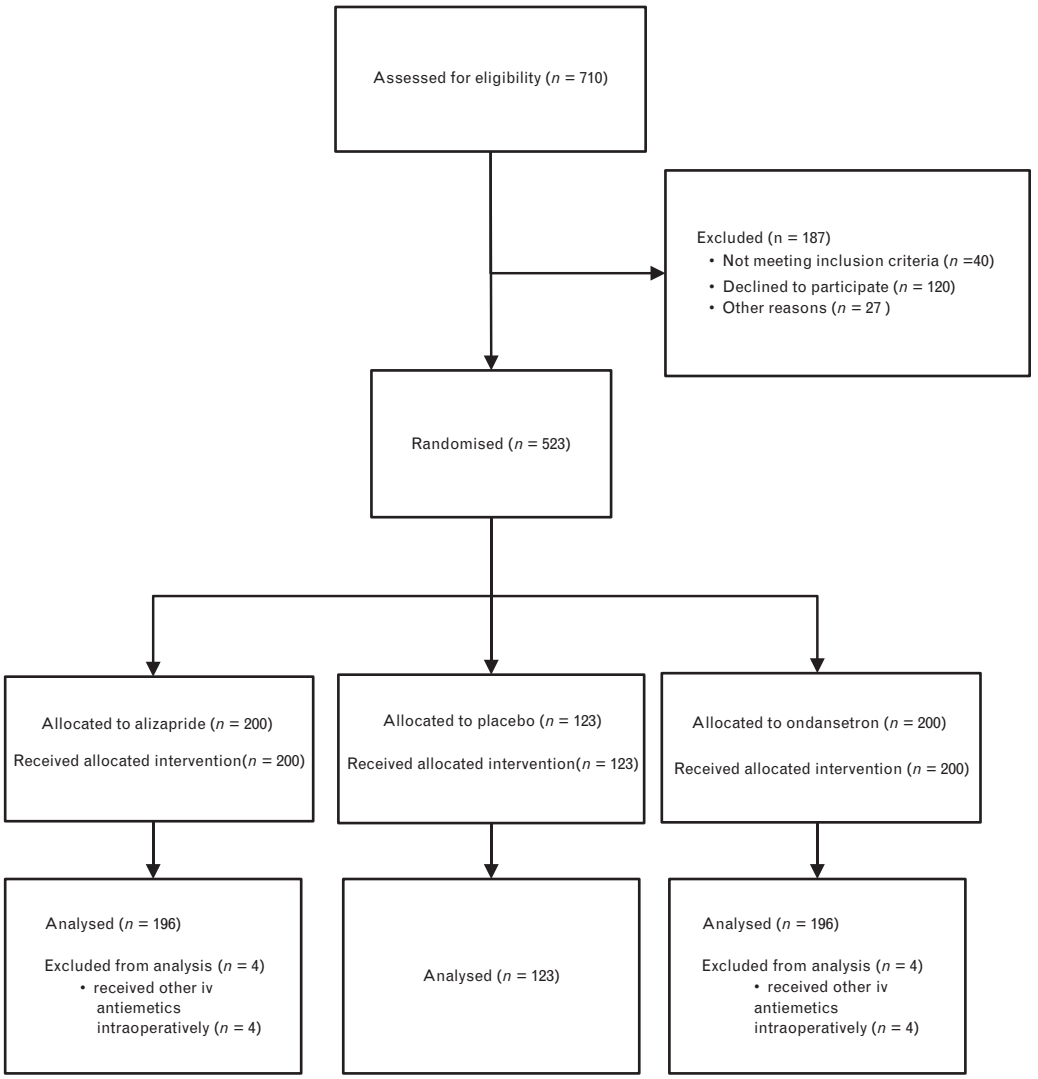
Results

Figure 1 shows a flow chart of the study. Patients did not differ in respect of demographic/biometric data, risk factors for PONV, or durations of anaesthesia and surgery (Table 1). All patients received opioids perioperatively with no difference in opioid doses among the three groups.

Our results failed to demonstrate our primary outcome of noninferiority of alizapride in comparison with ondansetron in respect of the incidence of PON during the PACU stay. In the alizapride group, 31.6% of the patients experienced PON during the PACU stay, compared with 28.1% of patients in the ondansetron group (relative risk 1.13, 90% CI 0.87 to 1.46, exceeding the predefined margin of noninferiority) (Fig. 2, Table 2). In respect of the incidence of POV during the PACU stay, alizapride also failed to show noninferiority in comparison to ondansetron; 12.8% of patients randomised to receive alizapride experienced vomiting during the PACU stay, compared with 7.7% of those who received ondansetron (relative risk 1.67, 90% CI 1.00 to 2.87) (Fig. 2, Table 2). The incidences of PON and POV in the placebo group were 34.2 and 9.8%, respectively.

In respect of our secondary outcome of the incidence of PONV during the PACU stay, alizapride failed to reach noninferiority. We found that 32.1% of patients in the alizapride group experienced PONV, compared with 28.6% in the ondansetron group (relative risk 1.13, 90% CI 0.87 to 1.45). The incidence of PONV in the PACU was 34.2% in the placebo group (Fig. 2, Table 2).

Fig. 1



CONSORT flow chart.

The 24-h incidences of PONV were lower than expected in this high risk group of patients and were similar at 39.3, 36.8 and 31.5% in the placebo, alizapride and ondansetron groups, respectively (χ^2, $P = 0.36$). In respect of the overall incidence of PONV in the first 24 h, alizapride could not be considered noninferior in comparison with ondansetron. The incidence of PONV in the alizapride group was 36.8% compared with 31.5% in the ondansetron group (relative risk 1.17, 90% CI 0.91 to 1.50). The incidence of PONV in the placebo group during the first postoperative 24 h was 39.3% (Fig. 2, Table 2).

For the secondary outcome incidences of PONV within PACU and PONV within 24 h, there was an interaction between the prevalence of risk factors and the incidence of PONV ($P = 0.045$ for PONV in PACU and $P = 0.059$ for PONV within 24 h) (Table 3). In the low-risk group, alizapride was not inferior in respect of PONV in the PACU, but was inferior for PONV within 24 h. In the high-risk group, alizapride could not be considered noninferior.

In the logistic regression analysis, we found age, nonsmoking and a history of PONV to predict the risk of PONV in the PACU independently. Other baseline characteristics (BMI, duration of anaesthesia/surgery and the ASA grade) were not significantly associated with an increased risk of PONV (Table 4).

A prespecified secondary analysis demonstrated that patients who received ondansetron required significantly less rescue medication than patients in group P ($P = 0.035$), whereas the use of rescue medication in the alizapride group showed no statistically significant difference to that in the placebo group.

Table 1 Patient characteristics

	All ($n = 515$)	Ondansetron ($n = 196$)	Alizapride ($n = 196$)	Placebo ($n = 123$)
Age (years)	39 (32 to 50)	38 (32 to 49)	39 (31 to 50)	39 (31 to 51)
Weight (kg)	65 (59 to 74)	66 (59 to 74)	65 (60 to 74)	65 (57 to 73)
Height (cm)	165 (161 to 170)	166 (162 to 170)	165 (161 to 170)	165 (160 to 170)
BMI ($kg\,m^{-2}$)	24 (22 to 27)	24 (21 to 26)	24 (22 to 27)	23 (21 to 26)
ASA physical status	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)	1 (1 to 2)
Smoking (%)	25.1	23.6	24.1	29
PONV history (%)	20	22	18.1	19
PONV risk grouping				
Low risk (%)	20.3	20	19	23.2
High risk (%)	79.7	80.1	81	76.9
Duration of anaesthesia (min)	102 (70 to 155)	108 (70 to 165)	95 (65 to 145)	110 (65 to 180)
Duration of surgery (min)	65 (40 to 120)	65 (44 to 124)	65 (40 to 105)	65 (40 to 120)
Cumulative opioid consumption				
Sufentanil ($\mu g\,kg^{-1}$)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.4)
Piritramide i.v. ($mg\,kg^{-1}$)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)	0.0 (0.0 to 0.1)
Piritramide i.m. ($mg\,kg^{-1}$)	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)	0.0 (0.0 to 0.2)

Continuous data are presented as median (IQR). ASA, American Society of Anesthesiologists.

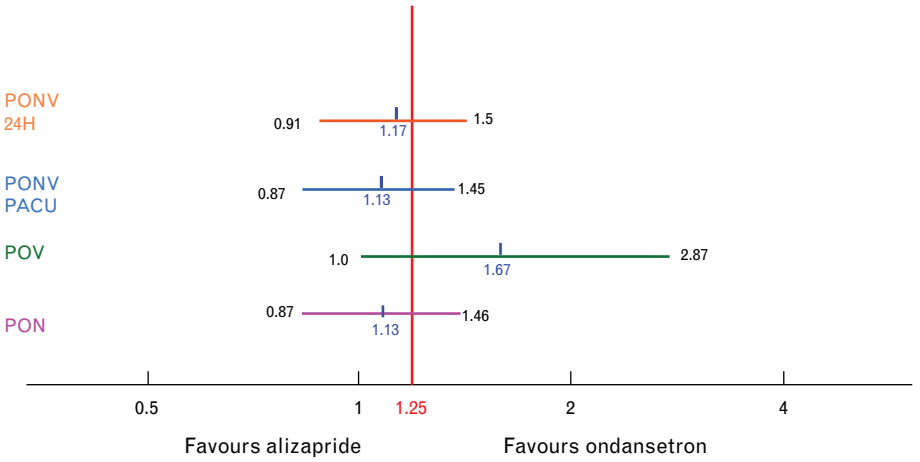
No serious adverse events were documented in any patient.

Discussion

The results of the present study cannot rule out with certainty the noninferiority of alizapride over ondansetron for the prevention of PONV. However, our observations suggest that alizapride should not be considered an equally effective form of PONV prophylaxis.

Although ondansetron is one of the most frequently studied drugs in anaesthesia, only four studies in the literature have systematically investigated alizapride for the prevention of PONV.[2–4,15] This remarkable paucity of data may be, at least in part, attributed to the fact that alizapride is marketed only in a limited number of countries (Belgium, Italy, France, Germany, Netherlands, Brazil and Colombia). These four studies showed that alizapride in doses of 50 to 200 mg exhibits an antiemetic effect during the first 4 to 24 postoperative hours and hence contradict our observations at first sight. However, these studies are difficult to compare with our results due to the inclusion of different patient populations, the investigation of other endpoints and the use of different alizapride dosing regimens. Moreover, the previous studies were published in the 1980s, and since then, anaesthetic techniques and drugs have evolved significantly. Furthermore, these historical investigations included considerably fewer patients than in our study. In addition, none of these studies compared alizapride with ondansetron. Finally, significant methodological weaknesses result in noncompliance with the recently published requirements for standardised PONV studies as suggested by Apfel *et al.*[16]

Fig. 2



Treatment differences expressed as relative risk (alizapride versus ondansetron). Observed treatment differences for the primary and secondary endpoints (according to Piaggio *et al.*[18]). The small vertical lines (blue) within the horizontal lines represent the relative risk of alizapride versus ondansetron for the respective outcome. Horizontal lines represent 2-sided 90% CIs (with the exact values depicted at both margins). The vertical red line (at $x = 1.25$) indicates the noninferiority margin. PACU, postanaesthetic care unit; PON, postoperative nausea; PONV, postoperative nausea or vomiting; POV, postoperative vomiting.

Table 2 Incidences of postoperative nausea, postoperative vomiting and postoperative nausea or vomiting in the three groups and comparison of alizapride with ondansetron

	Incidence (95% CI)						Comparison alizapride with ondansetron	
	Alizapride		Ondansetron		Placebo			
	n/*N*	% (95% CI)	*n*/N	% (95% CI)	*n*/*N*	% (95% CI)	Diff % (90% CI)	RR (90% CI)
PON	62/196	31.6 (25.2 to 38.6)	55/196	28.1 (21.9 to 34.9)	42/123	34.2 (25.8 to 43.2)	3.6 (−4.1 to 11.2)	1.13 (0.87 to 1.46)
POV	25/196	12.8 (8.4 to 18.3)	15/196	7.7 (4.3 to 12.3)	12/123	9.8 (5.1 to 16.4)	5.1 (−0.1 to 10.3)	1.67 (1.00 to 2.87)
PONV PACU	63/196	32.1 (25.7 to 39.2)	56/196	28.6 (22.4 to 35.4)	42/123	34.1 (25.8 to 43.2)	3.6 (−4.2 to 11.3)	1.13 (0.87 to 1.45)
PONV 24h	63/171	36.8 (29.6 to 44.5)	56/178	31.5 (24.7 to 38.8)	42/107	39.3 (30.0 to 49.2)	5.4 (−3.1 to 14.0)	1.17 (0.91 to 1.50)

CI, confidence interval; Diff, absolute risk difference; PACU, postanaesthetic care unit; PONV, postoperative nausea or vomiting; POV, postoperative vomiting; RR, risk ratio, PON, postoperative nausea.

It is well known from several meta-analyses that ondansetron is one of the most effective antiemetic agents available for prevention and treatment of PONV.[6] It is therefore striking that we failed to demonstrate the superiority of ondansetron versus placebo with statistical significance, although our study (and the sample size calculation) addressed a high-risk population with a predicted PONV risk of 40 to 80% (average risk of 60%) according to the risk score of Apfel *et al.*[12] However, the study was not powered for the comparison of ondansetron separately with placebo. Of note, on the background of the incidences observed in our placebo group and assuming a relative risk reduction of 25% by ondansetron,[17] incidences of PON, POV, PONV in the PACU and PONV after 24 h would be expected to be 25.6, 7.3, 25.6 and 29.4%, respectively. In fact, the observed event rates in the ondansetron patients were only slightly different (28.1, 7.7, 28.6 and 31.5%), corresponding with relative risk reductions close to 25% (17.8, 21.6, 16.3 and 19.9%). Moreover, in our study, the efficacy of ondansetron might still be reflected by the fact that significantly less rescue medication was necessary in those patients who had received intraoperative ondansetron prophylaxis, whereas alizapride prophylaxis did not decrease the necessity to administer rescue medication. This observation is in accordance with a recent Cochrane meta-analysis.[11] The use of rescue medication might have masked the true difference in the PONV incidences among the different groups.

Hence, treatment with ondansetron achieved the expected reduction in PONV incidences, but the difference was not significant in our patients. However, alizapride performed even worse. The differences between alizapride and placebo were smaller than the differences between ondansetron and placebo. Moreover, in the direct head-to-head comparison, alizapride decreased the risk of PON and POV to a lesser extent than ondansetron, both during the stay in PACU and during the first 24 postoperative hours. According to a recently published extension of the CONSORT 2010 statement, the position of the CIs for the risk ratios (Fig. 2) indicates that the result is inconclusive 'in that it is still plausible that the true difference between alizapride and ondansetron is less than the predefined margin of noninferiority'.[18] Consequently, our study cannot discard with certainty the noninferiority of alizapride versus ondansetron for the prevention of PONV, although the current results suggest that there is no reason to consider alizapride to be an equally effective prophylaxis against PONV.

Interestingly, a subgroup analysis (Table 3) revealed that alizapride appeared to be noninferior for the prevention of PONV in the PACU in low-risk groups when compared with ondansetron. However, this observation refers only to a subpopulation with very few patients. The reasons for this observation are purely speculative. It is tempting to postulate that different emetic mechanisms prevail in different risk groups, making patients in one group more susceptible to a specific intervention than another. In fact, recent evidence shows that the efficacy of 5-HT_3 antagonists is significantly affected by pharmacogenetics.[19]

We acknowledge that our study has several limitations. First, as mentioned above, the PONV incidence observed in our study was considerably lower than predicted from the well established and validated risk score originally proposed by Apfel *et al.*[12] As the observed incidence of PONV was much lower than that expected when

Table 3 Incidences of postoperative nausea or vomiting in postanaesthetic care unit and in the first 24 h

			Alizapride	Ondansetron	RR (95% CI)	*P*	P_{int}
PONV	Low-risk	*n*/*N* (%)	4/37 (10.8)	10/39 (25.6)	0.422 (0.15 to 1.22)	0.1	0.045
PACU	High-risk	*n*/*N* (%)	58/158 (36.7)	46/157 (29.3)	1.253 (0.91 to 1.72)	0.16	
PONV	Low-risk	*n*/*N* (%)	4/33 (12.1)	10/39 (25.6)	0.473 (0.16 to 1.37)	0.15	0.059
24 h	High-risk	*n*/*N* (%)	58/137 (42.3)	46/139 (33.1)	1.279 (0.94 to 1.74)	0.11	

Subgroup analysis of the incidence of PONV during the PACU stay and the first 24 postoperative hours for the low-risk group (two risk factors: female sex and opioid use) and the high-risk group (three or four risk factors: female sex, opioid use, PONV history and/or nonsmoking). The value of P_{int} relates to comparison between risk groups. The risk factors are in accordance with the simplified risk score of Apfel *et al.*[12] CI, confidence interval; PACU, postanaesthetic care unit; PONV, postoperative nausea or vomiting; RR, relative risk.

Table 4 Risk of experiencing postoperative nausea and vomiting during the postanaesthetic care unit stay as a function of baseline characteristics

	Univariable		Multivariable	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Age (per year)	0.966 (0.951 to 0.981)	<0.0001	0.958 (0.941 to 0.975)	<0.0001
BMI (kg m^{-2})	0.911 (0.951 to 1.033)	0.68	1.000 (0.955 to 1.048)	0.99
Duration of anaesthesia (per 15 min)	1.000 (0.969 to 1.032)	0.75	0.996 (0.988 to 1.005)	0.38
Duration of surgery (per 15 min)	1.014 (0.975 to 1.055)	0.49	1.005 (0.996 to 1.015)	0.28
ASA classification (1 ↔ 2)	1.288 (0.875 to 1.898)	0.42	0.815 (0.515 to 1.291)	0.38
Smoking (Yes ↔ No)	0.508 (0.316 to 0.817)	0.005	0.388 (0.234 to 0.643)	0.0002
PONV history (Yes ↔ No)	2.800 (1.790 to 4.379)	0.0001	2.603 (1.629 to 4.158)	<0.0001
Risk grouping (High ↔ Low)	2.218 (1.305 to 3.768)	0.003		

ASA, American Society of Anesthesiologists' physical status classification system; CI, confidence interval; PACU, postanaesthetic care unit.

estimating the sample size, the power to show noninferiority was therefore markedly reduced to 41% in our study. We acknowledge that a more optimal design of the study would have included a blinded interim analysis, with the sole purpose of verifying the assumed incidence, and a recalculation of the sample size needed in case of a discrepancy. We thus acknowledge that the lower than expected incidences of PONV considerable reduced the power of this study to be able conclude noninferiority. Nevertheless, the observed relative risk of 1.67 for POV suggests that the failure to show noninferiority of alizapride should not be attributed entirely to a mere lack of power.

The appropriateness of the original definition of the margin of noninferiority as an absolute difference of 12.5% is also questionable. In hindsight, this definition seems too liberal because it is not much lower than the absolute risk difference of 15% expected between placebo and ondansetron. Furthermore, we are unable to explain the low incidence of PONV that was observed in our study, although we strictly adhered to the PONV risk factors during inclusion of the patients. Moreover, we were able to confirm the validity of these risk factors in our population and used a conventional anaesthetic regimen based on volatile anaesthetics. Of note, the Apfel risk score was developed 14 years ago,[12] and it may be argued that, given the development of anaesthetic and surgical techniques since then, the predicted PONV incidences might have changed. In high risk groups, previously reported incidences of PONV that were lower than predicted, and comparable to the findings in our study, have been reported.[20] Alternatively, the observed differences in PONV incidences might be attributable to the use of sufentanil in our study, although this is speculative; the majority of PONV studies from which the PONV incidences were derived were performed with fentanyl or remifentanil.[17] Although controversial, sufentanil has been claimed to trigger less PONV than fentanyl.[21] Future studies should specifically address the question of whether incidences of PONV may be dependent upon the type of opioid used.

Next, we opted to use the incidences of POV and PON during the PACU stay as primary outcome parameters. This choice was made on the basis of practical considerations; nearly half of our patient population (47%) underwent surgery on an ambulatory basis, and absence of PONV is one of the main discharge criteria. The incidence of PONV after 24 h was one of our secondary outcome parameters. Interestingly, we could not identify a single patient suffering from PONV in the first 24 h who had not already exhibited PON or POV during the PACU stay. Moreover, the use of rescue medication was not standardised in our trial, although this does not affect the primary outcome parameters. Although this was a noninferiority trial, we decided to include a placebo group. It has been suggested that only the presence of a placebo group allows a true estimate of the relative efficacy and harm of antiemetic interventions in the perioperative setting.[1,16]

Finally, although we specifically studied the efficacy of alizapride for the prevention of PONV, the design of our study did not allow testing of the efficacy of alizapride for the treatment of PONV.

In conclusion, we found no evidence to support the noninferiority of alizapride 100 mg when compared with ondansetron 4 mg for intraoperative prophylaxis of PONV. However, the lower than expected incidences of PONV reduced the power of this study to conclude noninferiority or confirm significant beneficial effects of either antiemetic for PON and POV during the PACU stay.

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References

1 Tramèr 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.

2 Kauste A, Tuominen M, Heikkinen H, *et al.* Droperidol, alizapride and metoclopramide in the prevention and treatment of postoperative emetic sequelae. *Eur J Anaesthesiol* 1986; **3**:1–9.
3 Booij LH, Rachmat S, Bulder ER. Alizapride in prevention of postoperative nausea and vomiting. *Neth J Surg* 1988; **40**:6–9.
4 Dejonckheere M, Deloof T, Dustin N, Ewalenko P. Alizapride in the prevention of postthyroidectomy emetic sequelae. *Eur J Anaesthesiol* 1990; **7**:421–427.
5 Seng KT, Tiong CE, Hiang TC. Antiemetic effect of high-dose metoclopramide vs alizapride: a randomised crossover study. *Br J Clin Pharmacol* 1994; **38**:282–284.
6 Tramèr MR, Reynolds DJ, Moore RA, McQuay HJ. Efficacy, dose-response, and safety of ondansetron in prevention of postoperative nausea and vomiting: a quantitative systematic review of randomized placebo-controlled trials. *Anesthesiology* 1997; **87**:1277–1289.
7 Dershwitz M, Conant JA, Chang Y, *et al.* A randomized, double-blind, dose-response study of ondansetron in the prevention of postoperative nausea and vomiting. *J Clin Anesth* 1998; **10**:314–320.
8 Tang DH, Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 h for postoperative nausea and vomiting prophylaxis. *Clin Ther* 2012; **34**:282–294.
9 Cholwill JM, Wright W, Hobbs GJ, Curran J. Comparison of ondansetron and cyclizine for prevention of nausea and vomiting after day-case gynaecological laparoscopy. *Br J Anaesth* 1999; **83**:611–614.
10 Stienstra R, Samhan YM, el-Mofty M, *et al.* Double-blind comparison of alizapride, droperidol and ondansetron in the treatment of postoperative nausea. *Eur J Anaesthesiol* 1997; **14**:290–294.
11 Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2006;CD004125.
12 Apfel CC, Läärä E, Koivuranta M, *et al.* A simplified risk score for predicting postoperative nausea and vomiting: conclusions from cross-validations between two centers. *Anesthesiology* 1999; **91**:693–700.
13 Ormel G, Romundstad L, Lambert-Jensen P, Stubhaug A. Dexamethasone has additive effect when combined with ondansetron and droperidol for treatment of established PONV. *Acta Anaesthesiol Scand* 2011; **55**:1196–1205.
14 Agresti A, Min Y. On small-sample confidence intervals for parameters in discrete distributions. *Biometrics* 2001; **57**:963–971.
15 Vanacker B, Van Aken H. Alizapride in the prevention of postoperative vomiting. A double-blind comparison. *Acta Anaesthesiol Belg* 1988; **39**:247–250.
16 Apfel CC, Roewer N, Korttila K. How to study postoperative nausea and vomiting. *Acta Anaesthesiol Scand* 2002; **46**:921–928.
17 Apfel CC, Korttila K, Abdalla M, *et al.* A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. *N Engl J Med* 2004; **350**:2441–2451.
18 Piaggio G, Elbourne DR, Pocock SJ, *et al.*, CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012; **308**:2594–2604.
19 Kovac AL. Update on the management of postoperative nausea and vomiting. *Drugs* 2013; **73**:1525–1547.
20 Rüsch D, Eberhart LHJ, Wallenborn J, Kranke P. Nausea and vomiting after surgery under general anesthesia: an evidence-based review concerning risk assessment, prevention, and treatment. *Dtsch Arztebl Int* 2010; **107**:733–741.
21 Phitayakorn P, Melnick BM, Vicinie AF. Comparison of continuous sufentanil and fentanyl infusions for outpatient anaesthesia. *Can J Anaesth* 1987; **34**:242–245.