

Amisulpride for the Rescue Treatment of Postoperative Nausea or Vomiting in Patients Failing Prophylaxis

A Randomized, Placebo-controlled Phase III Trial

Ashraf S. Habib, M.B., B.Ch., Peter Kranke, M.D., Sergio D. Bergese, M.D., Frances Chung, M.D., Sabry Ayad, M.D., Naveed Siddiqui, M.D., Johann Motsch, M.D., David G. Leiman, M.D., Timothy I. Melson, M.D., Pierre Diemunsch, M.D., Ph.D., Gabriel M. Fox, M.B., B.Chir., Keith A. Candiotti, M.D.

ABSTRACT

Background: Although antiemetics are commonly used to prevent postoperative nausea or vomiting, the failure rate is appreciable and there is currently no generally accepted standard for rescue treatment of postoperative nausea or vomiting after failed prophylaxis. This prospective, randomized, double-blind, parallel-group, placebo-controlled, multicenter study was designed to test the hypothesis that intravenous amisulpride, a dopamine D₂/D₃-antagonist, is superior to placebo at treating established postoperative nausea or vomiting after failed prophylaxis.

Methods: A total of 2,285 adult patients undergoing surgery under general inhalational anesthesia and receiving standard antiemetic prophylaxis were enrolled at 23 sites in Canada, France, Germany, and the United States. Of these, 702 patients experienced postoperative nausea or vomiting in the 24-h period after surgery and were randomized to receive a single dose of 5 or 10 mg intravenous amisulpride or matching placebo. The primary endpoint was complete response, defined as no emesis or rescue antiemetic use for 24 h after study drug administration, excluding emesis in the first 30 min. Secondary endpoints included incidence of emesis and rescue medication use, nausea burden, time to treatment failure, and length of stay in post-anesthesia care unit and hospital.

Results: Complete response occurred in significantly more patients receiving 10 mg amisulpride (96 of 230, 41.7%) than placebo (67 of 235, 28.5%), a 13.2% difference (95% CI, 4.6 to 21.8; odds ratio, 1.80; $P = 0.006$). A 5-mg dose of amisulpride did not show a significant benefit (80 of 237, 33.8%); the difference from placebo was 5.2% (95% CI, 3.1 to 13.6; odds ratio, 1.24; $P = 0.109$). The total number of adverse events recorded and proportion of patients with at least one adverse event were comparable between the placebo and amisulpride groups. No clinically relevant toxicities were observed.

Conclusions: A single 10-mg dose of intravenous amisulpride was safe and more effective than placebo at treating established postoperative nausea or vomiting in patients failing postoperative nausea or vomiting prophylaxis. (**ANESTHESIOLOGY 2018; XXX:00-00**)

THE issue of postoperative nausea or vomiting is important for patients, physicians, and healthcare providers. Vomiting or retching can have adverse medical consequences, such as wound dehiscence, dehydration, electrolyte derangement, and aspiration of gastric contents, and has been reported to be the postsurgical outcome least desired by patients.¹ Postoperative nausea, or vomiting often delays discharge,² is one of the main causes of unanticipated admission after ambulatory surgery,³ and it adds considerably to resource use and costs.⁴

Risk-based postoperative nausea or vomiting prophylaxis is well established in guidelines,⁵ but adherence can be poor⁶ and the failure rate exceeds 30%.⁷ At present, prophylaxis most commonly involves 5HT₃-antagonists, such as ondansetron, often in combination with dexamethasone.⁸ Although a few retrospective and prospective studies have investigated

Editor's Perspective

What We Already Know about This Topic

- Although antiemetics are commonly used to prevent postoperative nausea or vomiting, the failure rate is appreciable and there is little evidence to guide best therapy for rescue treatment after failed prophylaxis

What This Article Tells Us That Is New

- Ten milligrams of intravenous amisulpride, a dopamine D₂/D₃-antagonist, is superior to placebo at treating established postoperative nausea or vomiting after failed prophylaxis, whereas 5 mg was not superior to placebo

antiemetics for the rescue treatment of postoperative nausea or vomiting after failure of prophylaxis,⁹⁻¹⁵ to our knowledge no agent has previously been shown in a prospective trial to

be more effective than placebo for treating postoperative nausea or vomiting in patients who have failed prophylaxis. One survey found that repeat dosing with a 5HT₃-antagonist was common among anesthesiologists,¹⁶ even though trials have repeatedly shown it to be ineffective.^{13–15} Consensus guidelines specifically recommend that an antiemetic used to treat postoperative nausea or vomiting should be from a different pharmacologic class to any drugs given prophylactically.⁵ Commonly used options, such as promethazine, metoclopramide, and dimenhydrinate, are not supported by evidence from randomized, controlled trials. Furthermore, those agents are associated with numerous side effects, including sedation and extrapyramidal side effects, which can result in prolongation of postanesthesia care unit (PACU) stay. There remains, therefore, a significant unmet medical need.

The selective dopamine D₂/D₃-antagonist amisulpride has been used as an oral antipsychotic for more than 30 yr and has been notable for its favorable side effect profile.¹⁷ It has been recently shown to be an effective and safe antiemetic when given intravenously at very low doses.^{18,19} Because dopaminergic antiemetics are rarely used nowadays for postoperative nausea or vomiting prophylaxis, this is potentially an attractive mechanism for a rescue antiemetic.

We conducted this multicenter, randomized, double-blind, placebo-controlled, parallel-group trial to assess the clinical effectiveness and safety of a single intravenous dose of amisulpride as treatment for established postoperative nausea or vomiting in surgical patients who had failed standard prophylaxis involving antiemetics from other pharmacologic classes. We hypothesized that amisulpride would be significantly more effective than placebo as rescue treatment of postoperative nausea or vomiting for the 24-h period after administration.

Materials and Methods

Study Design

This randomized, double-blind, parallel-group study (chief investigator: A.S.H.) was conducted at 23 centers in the United States, Germany, Canada, and France between March

2016 and January 2017. An independent ethics committee approved the study at each center. Written informed consent was obtained from all patients before enrollment. The study was sponsored and fully funded by Acacia Pharma, Ltd. (United Kingdom). Data were collected and analyzed by the sponsor; all authors had access to the data. The study was overseen by a data monitoring committee and was registered on ClinicalTrials.gov (reference NCT02646566) in January 2016.

Patient Population

Patients of either sex could be considered for inclusion if they were at least 18 yr of age, had freely given written informed consent, were scheduled to undergo open or laparoscopic elective surgery under general inhalational anesthesia expected to last at least 1 hr, and were judged by the investigator to have a moderate or high risk of experiencing postoperative nausea or vomiting, based on established postoperative nausea or vomiting risk factors such as those included in the Apfel risk score.²⁰ Women of childbearing potential had to be able and willing to use a highly effective form of contraception. Patients were ineligible if they were scheduled to undergo transplant surgery or any surgery where postoperative emesis would pose a significant danger to them; were planning to receive only a local anesthetic or regional neuraxial (intrathecal or epidural) block; had received amisulpride for any indication in the 2 weeks before screening; were allergic to amisulpride or any of the excipients of the study medication; had significant ongoing vestibular disease or dizziness; had a known prolactin-dependent tumor or pheochromocytoma; had documented or suspected alcohol or substance abuse within the previous 6 months; had direct or indirect evidence of clinically significant hypokalemia, such as serum potassium less than 3.0 mM; had received postoperatively, and before receiving study drug, any medication with a substantial risk of inducing torsades de pointes; had a documented, clinically significant cardiac arrhythmia or congenital long QT syndrome; were pregnant or breastfeeding; had a history of epilepsy or Parkinson's disease or were being treated with levodopa; or had received emetogenic anticancer chemotherapy in the previous 4 weeks.

Procedures, Randomization, and Masking

Patients were screened for enrollment up to 28 days before surgery. With respect to the surgical procedure, institutions followed their standard practice in terms of anesthetic technique and agents and peri-/postoperative management. Although patients should only have been enrolled if inhalational anesthesia was planned, it was permitted to randomize a patient with postoperative nausea or vomiting who had received total intravenous anesthesia.

To be randomized into a treatment arm, enrolled patients had to have received pre- or perioperative nausea or vomiting prophylaxis, involving the investigator's choice of one

Submitted for publication June 11, 2018. Accepted for publication October 5, 2018. From the Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina (A.S.H.); Department of Anaesthesia and Critical Care, University Hospitals of Würzburg, Würzburg, Germany (P.K.); Department of Anesthesiology, Wexner Medical Center at The Ohio State University, Columbus, Ohio (S.D.B.); Department of Anesthesia, University Health Network, University of Toronto, Toronto, Ontario, Canada (F.C.); Cleveland Clinic Lerner College of Medicine at Case Western Reserve University, Anesthesiology Institute, Outcomes Research, Fairview Hospital, Cleveland, Ohio (S.A.); Department of Anesthesia, Mount Sinai Hospital, Toronto, Ontario, Canada (N.S.); Department of Anesthesiology, Universitätsklinikum Heidelberg, Heidelberg, Germany (J.M.); Hermann Drive Surgical Hospital, Houston, Texas (D.G.L.); Helen Keller Hospital, Sheffield, Alabama (T.I.M.); Service d'Anesthésie-Réanimation Chirurgicale, CHU de Haute-pierre, Strasbourg, France (P.D.); Acacia Pharma Ltd, Cambridge, United Kingdom (G.M.F.); Department of Anesthesiology, Critical Care and Perioperative Medicine, University of Miami, Miami, Florida (K.A.C.).

or more antiemetics, as long as no dopamine-antagonist antiemetic was included; and experienced a “qualifying postoperative nausea or vomiting episode,” defined as a first episode of emesis (retching or vomiting) or request or obvious requirement for antiemetic medication to treat nausea, not more than 24 h after wound closure and before hospital discharge, for which they had not already received an antiemetic. A dopamine-antagonist with antiemetic potential was not to be given for any purpose from 24 h before surgery up to the time of the qualifying postoperative nausea or vomiting episode. Antiemetic rescue medication was to be given immediately on patient request or when there were signs of patient distress attributable to nausea or emesis; or, once 30 min had elapsed after treatment with the study drug, when symptoms were not improving. The choice of rescue antiemetic was according to standard practice in each institution.

A master randomization list was generated by a specialist contractor before study start using Prisym software (Prisym ID, Ltd., United Kingdom), to allocate patients on a 1:1:1 basis to receive 5 mg amisulpride, 10 mg amisulpride, or placebo, with a block size of nine and stratification by study center. Study medication was manufactured by the sponsor and provided in individual patient kits, each pre-labeled with a unique patient identification number from the randomization list. Each kit contained a pair of identical 2-ml vials containing a clear, colorless solution. For the 5-mg treatment, both vials contained 2.5 mg amisulpride; for the 10-mg treatment, both contained 5 mg amisulpride; and for the placebo, both contained the same excipients as the active drug but no amisulpride. All study staff and patients were blinded as to the contents of the vials. To randomize an eligible patient, study staff selected the next available kit from their stock held in pharmacy or PACU and drew up 4 ml of study medication from the two vials. Study drug was administered intravenously over approximately 2 min.

To assess clinical effect, all episodes of emesis (vomiting or retching), nausea (scored using a self-reported 11-point verbal scale, where 0 represented no nausea and 10 represented the worst nausea possible), and rescue medication use were recorded during the 24 h after study drug administration. Nausea was further assessed by direct questioning immediately before and at 5, 15, 30, and 120 min after dosing and at any time the patients spontaneously reported nausea afterward. Patients could be discharged as soon as the investigator was satisfied that it was medically acceptable for them to go home, subject to a minimum 2-h stay postdosing if the criteria for failure had not been met. Patients discharged before 24 h, who had not already met the criteria for failure or were withdrawn from the study, were given a diary card to complete at home and were followed up for the data by telephone as soon as possible after 24 h.

Blood samples were taken for hematology and biochemistry analysis before dosing and at 24 h, or within an hour

of discharge if that occurred sooner. Adverse events were recorded for 7 days after treatment, except for nausea and emesis in the first 24 h, which were already captured as part of the efficacy assessment.

Outcomes

The primary efficacy variable was the dichotomous variable success or failure of initial postoperative nausea or vomiting treatment, where success (also termed complete response) was defined as no emetic episodes (vomiting or retching) or administration of antiemetic rescue medication in the 24-h period after dosing, excluding any emesis events in the first 30 min. The purpose of the 30-min exclusion was to allow time for the study medication to work. A sensitivity analysis was prespecified to assess whether the exclusion period had any impact on the results.

Secondary endpoints included the incidence of vomiting, nausea, significant nausea (defined as a nausea score at or above 4 on an 11-point verbal rating scale²¹), and rescue medication use; severity of nausea; evolution of nausea, defined as area under the curve of nausea scores against time after treatment; time to treatment failure; time spent in PACU after dosing; and overall hospital length of stay after dosing.

Statistical Analysis

A sample size of 690 subjects (average 230 per arm) delivered a power of at least 90% at an overall two-sided α of 0.025 of detecting a difference of 0.16 between the success rate in the placebo group, assumed to be 0.30, based on Kovac *et al.*,¹³ and the success rate in either amisulpride dose group, set pragmatically at 0.46 as a realistic and clinically relevant rate, after adjusting for multiplicity from making two pairwise comparisons with placebo, achieving a global two-sided α of 0.05. Because 25 to 30% of enrolled patients were expected to experience postoperative nausea or vomiting, it was planned to enroll about 2,500 patients.

All statistical analyses were specified *a priori* in a Statistical Analysis Plan, signed before study unblinding, and were conducted in SAS version 9.4 (SAS Institute, USA). Baseline characteristic, efficacy, and safety variables were summarized using standard descriptive statistics. The primary efficacy analysis was a comparison, in the modified intent-to-treat population (all subjects who signed the informed consent form and received a dose of amisulpride or placebo study medication), of the incidence of complete response between each amisulpride group and the placebo group using Pearson's χ^2 test, with a 5% significance level, after applying Hommel's method to control the family-wise error rate. This technique adjusts the *P* value to take account of multiple comparisons (two active groups) against the single placebo group. To test the robustness of the primary analysis, a Cochran-Mantel-Haenszel test of complete response, stratified by center, and a logistic regression analysis, with treatment, number of risk factors, type of surgery (open *vs.*

laparoscopic), and center included as factors in the model, were conducted.

Secondary efficacy variables assessed by incidence (e.g., nausea, vomiting, rescue medication use) were compared between the groups using Pearson's χ^2 test. Time-to-event secondary efficacy variables were compared using the log-rank test. Continuous secondary efficacy variables (e.g., nausea evolution) were compared using a Mann-Whitney test. No statistical testing was prespecified for PACU or hospital length of stay or for adverse event rates.

Results

Disposition and Demographics

Between March 21, 2016, and January 11, 2017, 2,285 patients were enrolled, of whom 705 patients had a qualifying event of postoperative nausea or vomiting and were randomized; 702 received study drug (the modified intent-to-treat population; see figure 1). Two randomized patients withdrew consent and one refused medication just before dosing. The study arms were very similar in terms of baseline

characteristics, including prophylactic antiemetics received (table 1).

Clinical Effect

Primary and secondary efficacy endpoints are shown in table 2. Complete response occurred in 67 of 235 patients in the placebo group (28.5%; 95% CI, 22.74 to 34.28%); 96 of 230 in the 10-mg amisulpride group (41.7%; 95% CI, 35.37 to 48.11%; $P = 0.003$; after Hommel's adjustment: $P = 0.006$); and 80 of 237 in the 5-mg amisulpride group (33.8%; 95% CI, 27.73 to 39.78%; $P = 0.219$). The difference between the success rate for 10 mg amisulpride and placebo was 13.2% (95% CI, 4.6 to 21.8), and the odds ratio was 1.80 (95% CI, 1.22 to 2.64). The adjusted odds ratio for occurrence of complete response for 10 mg amisulpride *versus* placebo using the Cochran-Mantel-Haenszel test was 1.81 (95% CI, 1.22 to 2.69), and using Logistic Regression analysis it was 1.85 (95% CI, 1.23 to 2.76).

During the first 30 min after study drug dosing, emesis occurred in 30 patients: 18, 8, and 4 in the placebo,

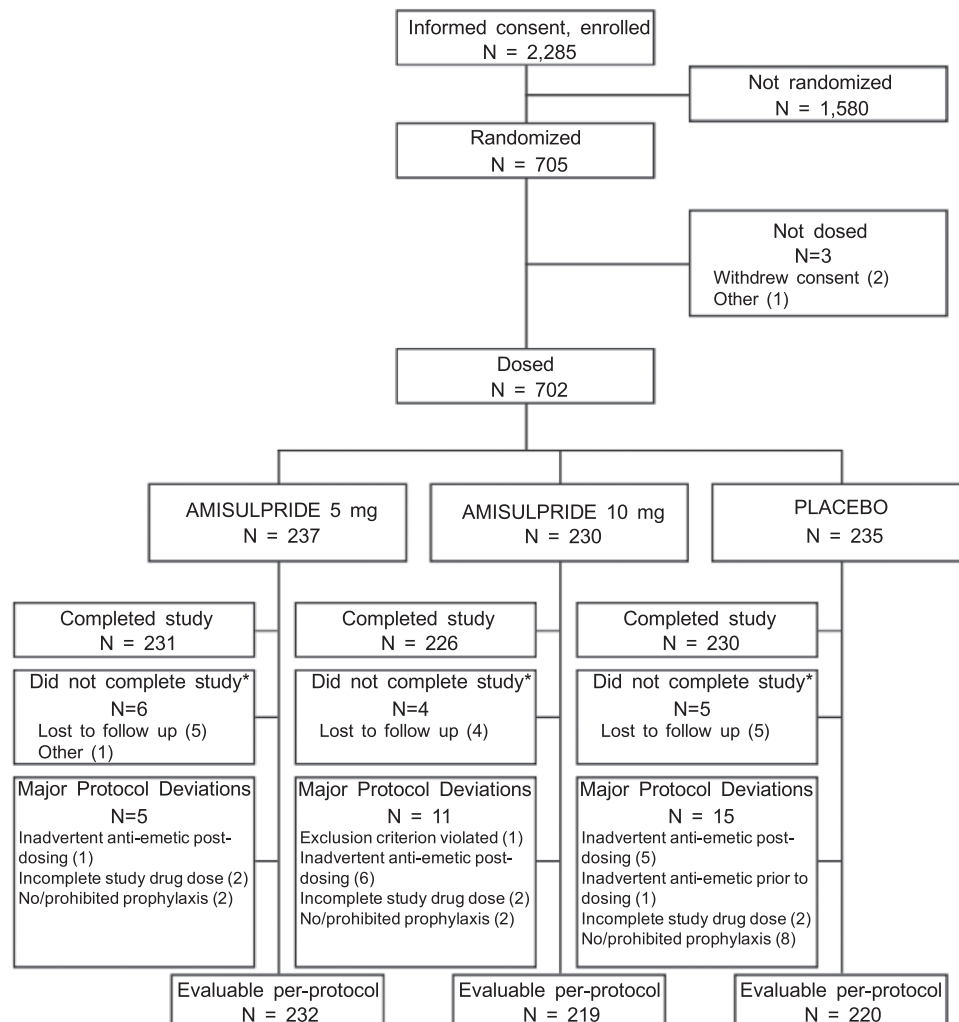


Fig. 1. Disposition of patients. *Day 7 follow up data not collected.

Table 1. Baseline Characteristics

Parameter	Placebo (N = 235)	Amisulpride 5 mg (N = 237)	Amisulpride 10 mg (N = 230)
Age (yr), median (range)	45 (18–81)	46 (18–84)	47 (18–85)
Sex			
Female	212 (90.2)	213 (89.9)	208 (90.4)
Male	23 (9.8)	24 (10.1)	22 (9.6)
Race*			
White	193 (82.1)	196 (82.7)	189 (82.2)
Black	22 (9.4)	19 (8.0)	21 (9.1)
Asian	8 (3.4)	5 (2.1)	6 (2.6)
Other/not reported	12 (5.1)	17 (7.2)	14 (6.1)
Country			
Canada	47 (20.0)	47 (19.8)	48 (20.9)
France	9 (3.8)	9 (3.8)	10 (4.3)
Germany	55 (23.4)	55 (23.2)	48 (20.9)
United States	124 (52.8)	126 (53.2)	124 (53.9)
Baseline PONV risk†			
Previous history of PONV	121 (51.5)	123 (51.9)	110 (47.8)
Previous history of motion sickness	91 (38.7)	83 (35.0)	77 (33.5)
Never smoked	166 (70.6)	183 (77.2)	161 (70.0)
Former smoker	42 (17.9)	32 (13.5)	43 (18.7)
No. of PONV risk factors			
1	2 (0.9)	1 (0.4)	1 (0.4)
2	7 (3.0)	17 (7.2)	10 (4.3)
3	105 (44.7)	90 (38.0)	108 (47.0)
4	121 (51.5)	129 (54.4)	111 (48.3)
Surgical procedure			
Open	121 (51.5)	108 (45.6)	98 (42.6)
Laparoscopic	114 (48.5)	129 (54.4)	132 (57.4)
Duration of surgery (min), mean ± SD	132.7 ± 98.0	117.9 ± 77.8	120.5 ± 83.4
Duration of inhalational anesthesia (min), mean ± SD	162.0 ± 100.6	146.4 ± 80.4	149.0 ± 84.5
Anesthetic agents			
Sevoflurane	138 (58.7)	145 (61.2)	139 (60.4)
Desflurane	91 (38.7)	86 (36.3)	88 (38.3)
Isoflurane	6 (2.6)	5 (2.1)	6 (2.6)
Nitrous oxide	10 (4.3)	6 (2.5)	4 (1.7)
Previous PONV prophylaxis			
Ondansetron	164 (69.8)	170 (71.7)	159 (69.1)
Granisetron	18 (7.7)	26 (11.0)	17 (7.4)
Dexamethasone	145 (61.7)	159 (67.1)	156 (67.8)
Scopolamine	17 (7.2)	21 (8.9)	19 (8.3)
Other agents	4 (1.7)	7 (3.0)	9 (3.9)
1 antiemetic	120 (51.1)	111 (46.8)	121 (52.6)
2 antiemetics	96 (40.9)	104 (43.9)	91 (39.6)
≥3 antiemetics	12 (5.1)	21 (8.9)	18 (7.8)
Qualifying PONV event			
Patients with emesis	57 (24.3)	45 (19.0)	40 (17.4)
Patients with nausea	228 (97.0)	233 (98.3)	228 (99.1)
Mean ± SD nausea score	6.2 ± 2.2	6.2 ± 2.2	6.3 ± 2.3
Occurrence in postanesthesia care unit	172 (73.2)	178 (75.1)	169 (73.5)
Occurrence 0–2 h after surgery	169 (71.9)	181 (76.4)	156 (67.8)

Data are number of patients (%) unless specified otherwise.

*Patients who reported multiple races were counted in each race category. Data on race were not collected in France for legal reasons. †PONV risk factors are as follows: (1) female; (2) nonsmoker; (3) history of PONV or motion sickness; (4) expected use of postoperative opioid analgesia. PONV, postoperative nausea or vomiting.

5-mg, and 10-mg amisulpride groups, respectively. All 30 patients received rescue medication, thus meeting the criteria for treatment failure. Accordingly, the 30-min window

for excluding emesis events had no effect on the complete response rate in any arm. Complete response at each of the prespecified interim time points (2, 4, and 6h) was around

Table 2. Clinical Effect in First 24 h after Treatment

	Placebo (N = 235)	Amisulpride 5 mg (N = 237)	<i>P</i>	Amisulpride 10 mg (N = 230)	<i>P</i>
Complete response	67 (28.5%)	80 (33.8%)	0.219*	96 (41.7%)	0.006*
95% CI	22.7–34.3%	27.7–39.8%		35.4–48.1%	
Complete response at 2 h	116 (49.4%)	134 (56.5%)	0.118	160 (69.6%)	<0.0001
Complete response at 4 h	87 (37.0%)	105 (44.3%)	0.108	136 (59.1%)	<0.0001
Complete response at 6 h	77 (32.8%)	99 (41.8%)	0.043	121 (52.6%)	<0.0001
Emesis†	67 (28.5%)	43 (18.1%)	0.008	36 (15.7%)	0.001
Use of rescue medication	163 (69.4%)	155 (65.4%)	0.359	127 (55.2%)	0.002
Significant nausea‡ (≥4 on 11-point verbal rating scale)	139 (59.1%)	135 (57.0%)	0.632	111 (48.3%)	0.019
Any nausea‡ (≥1 on 11-point verbal rating scale)	181 (77.0%)	183 (77.2%)	1	163 (70.9%)	0.130
Mean nausea area under curve (0–3h)	7,629	6,995	0.516	5,638	<0.0001

Data are number of patients (%) unless specified otherwise; *P* values are for comparison with placebo group.

*After adjustment for multiplicity using Hommel's method. †Excluding nausea/emesis events occurring in first 30 min after treatment.

20% higher with 10 mg amisulpride than placebo. The time to treatment failure was significantly longer for 10 mg amisulpride (median 443 min) than placebo (median 120 min), with a hazard ratio of 0.63 (95% CI, 0.50 to 0.80; *P* < 0.001; fig. 2).

Emesis occurred in significantly fewer patients after either 5 mg or 10 mg amisulpride than placebo. Most other secondary endpoints were significantly improved by 10 mg amisulpride but not 5 mg, including rescue medication use, incidence of significant nausea, maximal nausea severity, and nausea evolution.

The mean length of stay in PACU after study drug dosing was 140.9 min with 10 mg amisulpride (SD, 174.2; median, 96.0 min; range, 0 to 1266) and 175.5 min with placebo (SD, 217.6; median, 116.0; range, 2 to 1353). Overall mean length of hospital stay after dosing was 50.3 h (SD, 79.7; median, 24.4 h; range, 0.7 to 716.3) with 10 mg amisulpride and 56.3 h (SD, 73.4; median, 29.2 h; range, 0.6 to 644.1) with placebo.

Safety

The number of treatment-emergent adverse events and the proportion of patients reporting at least one event were comparable between the placebo and amisulpride groups (table 3). No deaths or withdrawals attributable to toxicity occurred. There were 17 serious adverse events in 14 patients, distributed evenly between the groups. Only nausea and vomiting occurring more than 24 h after dosing, flatulence, constipation, headache, infusion site pain, and pruritus were reported by 5% or more patients in any group. Unexpected or clinically relevant changes in hematology or clinical chemistry parameters were extremely infrequent in all groups.

Discussion

A single 10-mg dose of intravenous amisulpride was significantly more effective than placebo at treating established postoperative nausea or vomiting in patients who had received prior postoperative nausea or vomiting prophylaxis

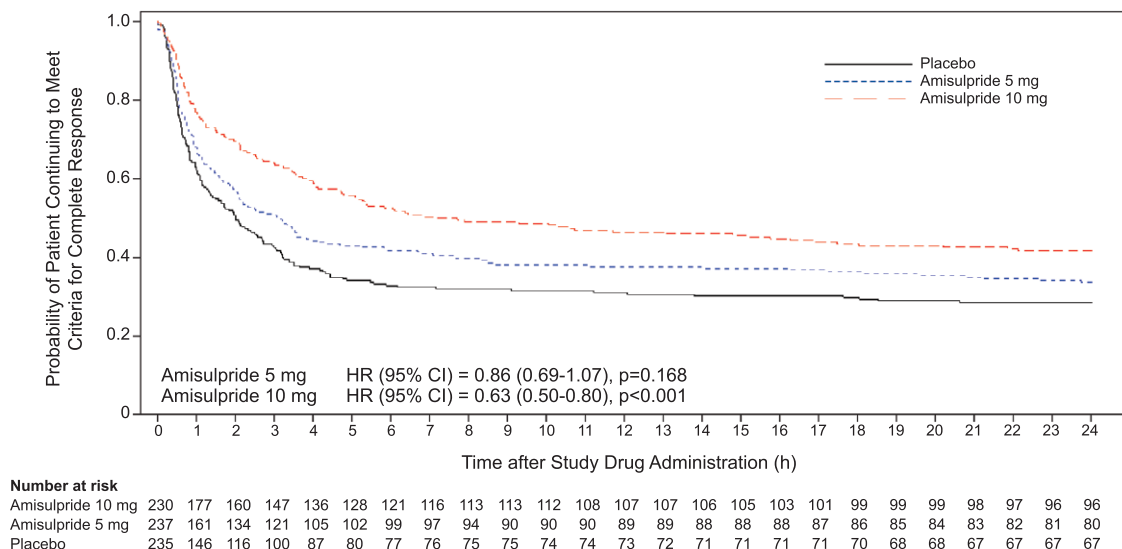


Fig. 2. Kaplan-Meier curves of treatment success over time. HR, hazard ratio.

Table 3. Treatment-Emergent Adverse Events*

	Placebo (N = 235)		Amisulpride 5 mg (N = 237)		Amisulpride 10 mg (N = 230)	
	No. of Patients	No. of Events	No. of Patients	No. of Events	No. of Patients	No. of Events
At least one treatment-emergent adverse event	113 (48.1)	262	100 (42.2)	203	99 (43.0)	198
Any serious adverse event	5 (2.1)	6	6 (2.5)	6	3 (1.3)	5
Any event leading to death	0	0	0	0	0	0
Intensity of event						
Any life-threatening event	0		0		1 (0.4)	
Any severe event	10 (4.3)		5 (2.1)		4 (1.7)	
Any moderate event	38 (16.2)		28 (11.8)		23 (10.0)	
Any mild event	65 (27.7)		67 (28.3)		71 (30.9)	
Relationship to study medication						
Any probably related event	17 (7.2)		10 (4.2)		12 (5.2)	
Any possibly related event	8 (3.4)		9 (3.8)		12 (5.2)	
Events occurring in ≥ 5% of any group						
Nausea	30 (12.8)	32	30 (12.7)	33	27 (11.7)	28
Flatulence	18 (7.7)	18	13 (5.5)	13	13 (5.7)	13
Constipation	17 (7.2)	17	13 (5.5)	13	11 (4.8)	11
Vomiting	13 (5.5)	13	11 (4.6)	14	10 (4.3)	11
Headache	17 (7.2)	17	10 (4.2)	10	10 (4.3)	10
Infusion site pain	10 (4.3)	10	8 (3.4)	8	12 (5.2)	12
Pruritus	13 (5.5)	13	7 (3.0)	7	10 (4.3)	10

Data are number of patients (%). *Excluding any events of nausea or emesis occurring in the first 24 h after study drug administration.

with one or more agents of a different pharmacologic class, and was not associated with any more toxicity than a placebo injection. A 5-mg dose was not significantly superior to placebo. To our knowledge, only three prospective, randomized treatment trials involving patients failing standard prophylaxis have previously been published,^{13–15} none of which demonstrated clinical effectiveness for the agents tested. Because of the current lack of any appropriately safe and effective agent for postoperative nausea or vomiting rescue, we considered a placebo-controlled trial to be a scientifically and ethically justifiable design for this trial.

Amisulpride had a rapid onset of action, shown by the immediate separation of the Kaplan–Meier curves. This is clinically important because rapid resolution of nausea and vomiting can enable earlier patient mobilization and discharge from the highly resource-intensive PACU, offering benefits to both patients and healthcare institutions.¹⁰ The 20% difference between amisulpride and placebo success at time points in the first 6 h may therefore be as relevant as the difference in 24-h success rates. We cannot draw firm conclusions as to whether any differences were associated with genuine reductions in length of PACU or overall hospital stay in this study, as we did not prespecify statistical testing of those outcomes, but this is clearly an area which merits further investigation.

The patient population in this study was highly representative of that typically experiencing postoperative nausea or vomiting in clinical practice. Most patients had three or all four of the major postoperative nausea or vomiting risk factors (female, past history of postoperative nausea or vomiting

or motion sickness, nonsmoker, expected use of postoperative opioid analgesia),²⁰ almost all underwent standard inhalational anesthesia, and almost all had failed prophylaxis with a 5HT₃-antagonist (mostly ondansetron) or dexamethasone. A broad range of operations was included, both open and laparoscopic, with both in-patients and ambulatory cases enrolled. Though useful in terms of validity, the broad population limits the ability to identify whether response to treatment might vary across different surgical groups.

The method used in this trial was very similar to that of the few previously published postoperative nausea or vomiting treatment studies, as was the placebo group success rate, adding weight to the robustness of the findings. In a study of 428 patients who had failed ondansetron prophylaxis, complete response (defined as in this study) at 24 h occurred in 32% of the placebo group and 28% of those redosed with ondansetron,¹³ compared with the 28.5% placebo rate in our study. That ondansetron response rate was corroborated by a subsequent study in the same ondansetron prophylaxis failure setting, which yielded complete response rates of 30% for ondansetron retreatment and 31% for palonosetron.¹⁵ The complete response of 41.7% seen with amisulpride in this study is lower than that reported in a previous study where complete response with promethazine in patients who had failed ondansetron prophylaxis was 68%.¹¹ That study, however, was retrospective and involved a much shorter (2-h) assessment period for complete response, and therefore is not directly comparable with this large prospective study where complete response for the 24-h period after rescue was the primary outcome of the study.

Although clinical data demonstrate the ineffectiveness of redosing ondansetron after its failure for prophylaxis, and consensus guidelines⁵ and the ondansetron label itself advise against it, such redosing remains a common practice,^{11,16} reflecting the dearth of acceptable options. It cannot simply be assumed that an antiemetic will be effective at treating breakthrough postoperative nausea or vomiting just because it works in prevention. Certainly, drugs that are slow to take effect, such as dexamethasone and transdermal scopolamine, are inappropriate for resolving acute postoperative nausea or vomiting. Other agents may lack the potency to resolve active postoperative nausea or vomiting, or may require a different dose from that used in prophylaxis. It is therefore essential to prove treatment efficacy and optimal dosing in prospective, randomized trials. For instance, we tested a 5-mg dose of amisulpride, because that had previously been shown to be effective for postoperative nausea or vomiting prophylaxis^{18,19}; but we also investigated a dose of 10 mg, in case a higher dose might be needed for treatment than for prevention. Assessing the side effect profile in the perioperative setting and thereby evaluating the benefit–risk ratio are no less important. One reason 5HT₃-antagonist redosing remains widespread, despite being ineffective, is that antiemetics from other classes have clinically important side effects, such as cardiac arrhythmias and extrapyramidal toxicity associated with older dopamine-antagonists,^{22,23} tissue damage caused by promethazine extravasation,²⁴ and sedation caused by some antihistamines and dopamine-antagonists, such as promethazine¹¹ and droperidol.²⁵

The benign safety profile of intravenous amisulpride is therefore noteworthy. Even after excluding events of nausea and vomiting in the first 24 h after treatment, the raw number of adverse events reported in the amisulpride groups was lower than that in the placebo group, though it should be stressed that the difference was not tested statistically. This is consistent with previous data in the prophylaxis setting,¹⁸ which suggest that controlling postoperative nausea or vomiting may lead to a general improvement in patient well-being, in line with the strong recommendation for aggressive postoperative nausea or vomiting management in the latest Enhanced Recovery After Surgery consensus statement.²⁶

One potential limitation of the study is that a broad, heterogeneous patient population was enrolled, undergoing a wide range of surgical operations, both open and laparoscopic, including both in-patients and ambulatory cases. Many of the subgroups were too small to permit robust investigation of possible differences in response to treatment, and further studies in subgroups of particular interest may be valuable. On the other hand, the heterogeneity may be useful in terms of external validity. Another limitation is the absence of electrocardiograph data collection. However, data collected in a thorough QT study, which are far more rigorous than any that could be collected in a hospital trial setting, indicate that both a 5- and 10-mg dose of intravenous amisulpride are associated with a QT prolongation of less

than 10 ms and are therefore unlikely to carry a meaningful clinical risk.²⁷

In conclusion, this study demonstrates that a single 10-mg dose of intravenous amisulpride is safe and more effective than placebo as rescue treatment for acute postoperative nausea or vomiting episodes in patients who have failed prior prophylaxis.

Research Support

The study was sponsored and fully funded by Acacia Pharma Ltd, Cambridge, United Kingdom.

Competing Interests

Dr. Fox is an employee of Acacia Pharma Ltd, Cambridge, United Kingdom, and holds company stock. Dr. Kranke has undertaken paid consulting work for Acacia Pharma. The remaining authors declare no competing interests.

Reproducible Science

Full protocol available at: gabrielfox@acaciapharma.com. Raw data available at: gabrielfox@acaciapharma.com.

Correspondence

Address correspondence to A. S. Habib: Department of Anesthesiology, Duke University Medical Center, Box 3094, Durham, North Carolina 27710. ashraf.habib@duke.edu. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

References

- Macario A, Weinger M, Carney S, Kim A: Which clinical anesthesia outcomes are important to avoid? The perspective of patients. *Anesth Analg* 1999; 89:652–8
- Chung F, Mezei G: Factors contributing to a prolonged stay after ambulatory surgery. *Anesth Analg* 1999; 89:1352–9
- Fortier J, Chung F, Su J: Unanticipated admission after ambulatory surgery—a prospective study. *Can J Anaesth* 1998; 45:612–9
- Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed MR, Glass PS, Gan TJ: Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. *ANESTHESIOLOGY* 2000; 92:958–67
- Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR; Society for Ambulatory Anesthesia: Consensus guidelines for the management of postoperative nausea and vomiting. *Anesth Analg* 2014; 118:85–113
- Kooij FO, Klok T, Hollmann MW, Kal JE: Automated reminders increase adherence to guidelines for administration of prophylaxis for postoperative nausea and vomiting. *Eur J Anaesthesiol* 2010; 27:187–91
- White PF, O'Hara JF, Roberson CR, Wender RH, Candiotti KA; POST-OP Study Group: The impact of current antiemetic practices on patient outcomes: a prospective study on high-risk patients. *Anesth Analg* 2008; 107:452–8
- Habib AS, Gan TJ: The use of droperidol before and after the Food and Drug Administration black box warning: A survey

- of the members of the Society of Ambulatory Anesthesia. *J Clin Anesth* 2008; 20:35–9
9. Habib AS, Gan TJ: The effectiveness of rescue antiemetics after failure of prophylaxis with ondansetron or droperidol: A preliminary report. *J Clin Anesth* 2005; 17:62–5
 10. Habib AS, Chen YT, Taguchi A, Hu XH, Gan TJ: Postoperative nausea and vomiting following inpatient surgeries in a teaching hospital: A retrospective database analysis. *Curr Med Res Opin* 2006; 22:1093–9
 11. Habib AS, Reuveni J, Taguchi A, White WD, Gan TJ: A comparison of ondansetron with promethazine for treating postoperative nausea and vomiting in patients who received prophylaxis with ondansetron: A retrospective database analysis. *Anesth Analg* 2007; 104:548–51
 12. Meyer TA, Roberson CR, Rajab MH, Davis J, McLeskey CH: Dolasetron *versus* ondansetron for the treatment of postoperative nausea and vomiting. *Anesth Analg* 2005; 100:373–7
 13. Kovac AL, O'Connor TA, Pearman MH, Kekoler LJ, Edmondson D, Baughman VL, Angel JJ, Campbell C, Jense HG, Mingus M, Shahvari MB, Creed MR: 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
 14. Candiotti KA, Nhuch F, Kamat A, Deepika K, Arheart KL, Birnbach DJ, Lubarsky DA: Granisetron *versus* ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: A pilot study. *Anesth Analg* 2007; 104:1370–3, table of contents
 15. Candiotti KA, Ahmed SR, Cox D, Gan TJ: Palonosetron *versus* ondansetron as rescue medication for postoperative nausea and vomiting: A randomized, multicenter, open-label study. *BMC Pharmacol Toxicol* 2014; 15:45
 16. Macario A, Claybon L, Pergolizzi JV: Anesthesiologists' practice patterns for treatment of postoperative nausea and vomiting in the ambulatory Post Anesthesia Care Unit. *BMC Anesthesiol* 2006; 6:6
 17. Coulouvrat C, Dondey-Nouvel L: Safety of amisulpride (Solian): A review of 11 clinical studies. *Int Clin Psychopharmacol* 1999; 14:209–18
 18. Kranke P, Eberhart L, Motsch J, Chassard D, Wallenborn J, Diemunsch P, Liu N, Keh D, Bouaziz H, Bergis M, Fox G, Gan TJ: I.V. APD421 (amisulpride) prevents postoperative nausea and vomiting: A randomized, double-blind, placebo-controlled, multicentre trial. *Br J Anaesth* 2013; 111:938–45
 19. Gan TJ, Kranke P, Minkowitz HS, Bergese SD, Motsch J, Eberhart L, Leiman DG, Melson TI, Chassard D, Kovac AL, Candiotti KA, Fox G, Diemunsch P: Intravenous amisulpride for the prevention of postoperative nausea and vomiting: Two concurrent, randomized, double-blind, placebo-controlled trials. *ANESTHESIOLOGY* 2017; 126:268–75
 20. Apfel CC, Läärä 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
 21. Boogaerts JG, Vanacker E, Seidel L, Albert A, Bardiau FM: Assessment of postoperative nausea using a visual analogue scale. *Acta Anaesthesiol Scand* 2000; 44:470–4
 22. Drolet B, Zhang S, Deschênes D, Rail J, Nadeau S, Zhou Z, January CT, Turgeon J: Droperidol lengthens cardiac repolarization due to block of the rapid component of the delayed rectifier potassium current. *J Cardiovasc Electrophysiol* 1999; 10:1597–604
 23. Foster PN, Stickle BR, Laurence AS: Akathisia following low-dose droperidol for antiemesis in day-case patients. *Anaesthesia* 1996; 51:491–4
 24. Malesker MA, Malone PM, Cingle CM, Cochran RM 2nd: Extravasation of i.v. promethazine. *Am J Health Syst Pharm* 1999; 56:1742–3
 25. Henzi I, Sonderegger J, Tramèr MR: Efficacy, dose-response, and adverse effects of droperidol for prevention of postoperative nausea and vomiting. *Can J Anaesth* 2000; 47:537–51
 26. Feldheiser A, Aziz O, Baldini G, Cox BP, Fearon KC, Feldman LS, Gan TJ, Kennedy RH, Ljungqvist O, Lobo DN, Miller T, Radtke FF, Ruiz Garces T, Schrickler T, Scott MJ, Thacker JK, Ytrebø LM, Carli F: Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: Consensus statement for anaesthesia practice. *Acta Anaesthesiol Scand* 2016; 60:289–334
 27. Täubel J, Ferber G, Fox G, Fernandes S, Lorch U, Camm AJ: Thorough QT study of the effect of intravenous amisulpride on QTc interval in Caucasian and Japanese healthy subjects. *Br J Clin Pharmacol* 2017; 83:339–48