Amisulpride Prevents Postoperative Nausea and Vomiting in Patients at High Risk

A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT

Background: Postoperative nausea and vomiting causes distress for patients and can prolong care requirements. Consensus guidelines recommend use of multiple antiemetics from different mechanistic classes as prophylaxis in patients at high risk of postoperative nausea and vomiting. The prophylactic efficacy of the dopamine D_2/D_3 antagonist amisulpride in combination with other antiemetics was investigated.

Methods: This double-blind, randomized, placebo-controlled, international, multicenter trial was conducted in 1,147 adult surgical patients having three or four postoperative nausea and vomiting risk factors. Patients were randomized to receive either intravenous amisulpride (5 mg) or matching placebo at induction of general anesthesia, in addition to one standard, nondopaminergic antiemetic, most commonly ondansetron or dexamethasone. Vomiting/retching, nausea, and use of rescue medication were recorded for 24 h after wound closure. The primary endpoint was complete response, defined as no emesis or rescue medication use in the 24-h postoperative period.

Results: Complete response occurred in 330 of 572 (57.7%) of the amisulpride group and 268 of 575 (46.6%) of the control group (difference 11.1 percentage points; 95% CI, 5.3 to 16.8; $P < 0.001$). The incidences of emesis (13.8% *vs.* 20.0%, $P = 0.003$), any nausea (50.0% *vs.* 58.3%, $P = 0.002$), significant nausea (37.1% *vs.* 47.7%, $P < 0.001$), and rescue medication use (40.9% *vs.* 49.4%, $P = 0.002$) were significantly lower in the amisulpride group. Adverse events and laboratory and electrocardiogram abnormalities occurred no more frequently with amisulpride than with placebo.

Conclusions: Intravenous amisulpride was safe and effective as prophylaxis of postoperative nausea and vomiting when given in combination with an antiemetic from another class to adult patients at high risk for suffering postoperative nausea and vomiting undergoing elective surgery under inhalational general anesthesia.

Visual Abstract: An online visual overview is available for this article at http://links.lww.com/ALN/B727. (**ANESTHESIOLOGY** 2018; 128:1099-106)

WITHOUT effective prophylaxis, nausea and/or vomiting in the 24 h after surgical operations under volatile anesthesia may occur in 60 to 80% of patients with at least three of the recognized risk factors for postoperative nausea and vomiting: female sex, prior history of postoperative nausea and vomiting or motion sickness, nonsmoker, and expected use of postoperative opioid analgesia.[1]

Agents blocking a variety of neurotransmitter pathways, including serotonin 5-HT$_3$, dopamine D$_2$, and histamine H$_1$, have been shown to prevent postoperative nausea and vomiting in a proportion of patients, as have corticosteroids, the mechanism of action of which is unclear.[2–4] Because it cannot be predicted which pathway(s) will be active in a patient, consensus guidelines recommend that patients at high risk of suffering postoperative nausea and vomiting should be given prophylaxis with a combination of antiemetics with different mechanisms of action.[5] Evidence from a large trial of factorial design suggests that antiemetics of different classes provide

What We Already Know about This Topic

- The incidence of nausea or vomiting within 24 h of operations under volatile anesthesia is 60 to 80% in patients with at least three of four risk factors for postoperative nausea and vomiting
- Consensus guidelines recommend patients at high risk of postoperative nausea and vomiting be provided prophylaxis with a combination of antiemetics with different mechanisms of action

What This Article Tells Us That Is New

- In a double-blind, randomized, placebo-controlled trial, the hypothesis that amisulpride, a potent dopamine D$_2$ and D$_3$ receptor antagonist, is superior to placebo in the prevention of postoperative nausea and vomiting when used with another antiemetic (primarily ondansetron or dexamethasone) was tested in 1,147 patients with three or four risk factors for postoperative nausea and vomiting
- Complete response, defined as no emesis or rescue medication use in the 24-h postoperative period, occurred in 57.7% of the amisulpride group and 46.6% of the control group

This article is featured in "This Month in Anesthesiology," page 1A. This article has an audio podcast.

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additive benefit, each reducing the relative risk of postoperative nausea and vomiting by about 25%.[6]

Corticosteroids and 5-HT$_3$ antagonists are widely used as postoperative nausea and vomiting prophylaxis, but drugs from the other classes are much less popular, generally due to concerns over safety, efficacy, or both. In particular, D$_2$ antagonists, formerly the mainstay of therapy, have now fallen into disuse due to concerns over QT prolongation and extrapyramidal toxicity.[7] Indeed, droperidol would have been a consensus panel's "overwhelming first choice for postoperative nausea and vomiting prophylaxis" but for the Food and Drug Administration boxed warning of torsadogenic risk that it carries.[8]

The potent dopamine D$_2$ and D$_3$ receptor antagonist amisulpride[9] has been used orally for the past 30 yr in Europe and elsewhere, but not the United States, at doses between 50 and 1,200 mg/day for the management of psychoses, and an extensive literature indicates that it has a benign safety profile even with chronic usage.[10–12] In particular, its effect on the QT interval and consequent torsadogenic risk appear to be minimal other than at enormous overdoses,[13] and at doses up to 300 mg/day, extrapyramidal side effects occur no more frequently than with placebo.[10] Recently, a single 5-mg IV dose of amisulpride was shown to be effective at preventing postoperative nausea and vomiting, with no more toxicity than placebo[14] and with no clinically relevant prolongation of the QT interval.[15] We conducted this study to test the hypothesis that amisulpride is superior to placebo when used in combination with another antiemetic in the prevention of postoperative nausea and vomiting in high-risk patients.

Materials and Methods

Study Design
We conducted a double-blind, randomized, placebo-controlled trial at 29 sites in France, Germany, and the United States between February and September 2015. The trial was registered on ClinicalTrials.gov before initiation (NCT02337062). The primary objective was to assess the efficacy of 5 mg of IV amisulpride in combination with a standard antiemetic in prevention of postoperative nausea and vomiting in adult surgical patients at high risk of postoperative nausea and vomiting. The study was designed by the sponsor (Acacia Pharma Ltd., United Kingdom) and the authors. The data were collected and analyzed by the sponsor; all authors had access to the data. The protocol and

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written materials provided to patients were approved for each center by an authorized ethical review committee. The study was conducted in accordance with international standards of good clinical practice and the principles of the Declaration of Helsinki. All patients freely gave written informed consent before any study procedures being carried out.

Patient Population
Patients were recruited by direct approach by study staff, usually at the preoperative clinic visit. Eligible patients were at least 18 yr of age; were due to undergo elective surgery, open or laparoscopic, under volatile general anesthesia expected to last at least an hour; and were at high risk of developing postoperative nausea and vomiting, defined as having three or all four of the Apfel risk factors for postoperative nausea and vomiting: female sex, previous history of postoperative nausea and vomiting or motion sickness, being a nonsmoker, and expected use of postoperative opioids for analgesia.[1] Patients had to have adequate cardiac, hepatic and renal function and serum potassium of at least 3.0 mmol·l⁻¹ and were excluded if they were due to undergo transplant surgery; were expected to remain ventilated for a significant time or require a naso/orogastric tube after surgery; had a known prolactin-dependent tumor, phaeochromocytoma, alcohol use disorder, epilepsy, or Parkinson's disease; or had received any emetogenic anticancer therapy in the previous 4 weeks or amisulpride for any indication in the previous 2 weeks. Concomitant treatment with any regular antiemetic therapy or medications that could induce torsade de pointes was not permitted. Drugs that could incidentally exert an antiemetic effect were to be avoided during the study.

Study Treatments
Admission to hospital, surgical techniques, premedication, and anesthetic technique and agents were according to the usual practice of each investigator, except that propofol use for total intravenous anesthesia or maintenance of anesthesia was not permitted, although a single dose of propofol was permitted for induction. No specific recommendations were given for the treatment of hemodynamic abnormalities or for the use of neuromuscular blocking agents, nitrous oxide, or analgesics for postoperative pain relief.

One standard antiemetic, most commonly ondansetron or dexamethasone, was given intravenously to each patient before or during surgery, according to its approved label and/or usual institutional practice. In general, the same standard antiemetic was given to all patients at a particular site.

The investigational drug amisulpride, which is not approved for any use in the United States, was supplied by the sponsor in 2-ml vials containing 5 mg of drug in solution), along with identical vials of matching placebo, identically constituted but without amisulpride. Vials were prelabeled with individual subject identification numbers. Site staff obtained, *via* a web-based randomization system, the next available subject number from the master randomization list and matched it to the appropriate vial. At the induction of anesthesia, the vial contents were

administered to the patient by intravenous push over 1 min. The randomization list was generated by an independent statistician and assigned patients on a 1:1 basis to amisulpride or placebo, with stratification according to study center and number of postoperative nausea and vomiting risk factors (three *vs.* four). Patients and all personnel involved in the trial conduct were blinded to the treatment assignment. Rescue antiemetic medication was to be given postoperatively to any patient with nausea, from which they requested relief, or emesis, with the choice of agent(s) being at the investigator's discretion.

Evaluations

During the 24 h after wound closure, episodes of emesis (vomiting/retching), nausea, and rescue medication use were recorded by site staff or by the patient in a diary card if after discharge. Nausea was also assessed by direct questioning at 1, 2, 6, and 24 h after wound closure. Severity of nausea was evaluated on an 11-point verbal rating scale, with 0 representing no nausea and 10 the worst nausea imaginable; "significant nausea" was defined as any score of 4 and over. Any drug given in the 24-h postoperative period that would be expected, by virtue of its pharmacology, dosage, and route, to exert a clinically meaningful antiemetic effect was scored as rescue medication, even if not given for that purpose, *e.g.*, diphenhydramine given for itching or intravenous metoclopramide as ileus prophylaxis.

All adverse events were recorded, from administration of study drug through to a follow-up telephone call at day 7. Severity and relationship to study drug were assessed by the investigator for each event. Vital signs, clinical laboratory evaluations, and electrocardiograms were done at the screening visit and postoperatively, between 12 and 26 h after surgery or in the hour before discharge, whichever was the earlier.

Statistics

The modified intention-to-treat analysis population, defined as all patients who were randomized and received a dose of either amisulpride or placebo, was the primary population for efficacy analyses. A per-protocol analysis population (modified intention-to-treat–evaluable patients with no major protocol deviations, such as inadvertent antiemetic use) and an opioid analysis population (per-protocol evaluable patients who received at least one dose of postoperative opioid analgesia before any episode of postoperative nausea and vomiting) were also prespecified. Exclusions from analysis populations were confirmed and documented before database lock.

The primary analysis was the difference between the amisulpride and placebo groups in complete response (equivalent to absence of postoperative nausea and vomiting), defined as no episodes of emesis and no use of rescue medication in the 24-h period after wound closure. Pearson's chi-square test was used to assess the difference between the treatment groups. A sample size of 550 patients per group was estimated to provide a power of 90.6% to detect a difference of 10 percentage points in complete response rate between the control group, assumed to be 50%, and the amisulpride group, assumed to be 60%.

Secondary efficacy analyses included the incidence of emesis, nausea, significant nausea, and use of rescue medication; measures of "total response" (no emesis, use of rescue medication or nausea; and no emesis, use of rescue medication or significant nausea); maximum severity of nausea; time to postoperative nausea and vomiting; and analysis of the key efficacy variables according to the combination antiemetic used. Differences in time-to-event variables were analyzed from Kaplan–Meier curves, and statistical significance was calculated using log-rank tests. Severity of nausea was analyzed using a Mann–Whitney test with significance determined from Hodges–Lehmann estimate of median difference. Where appropriate, hypothesis testing was one-tailed with significance interpreted as $P < 0.025$. SAS software (SAS Institute, USA), version 9.4, was used for all analyses.

Results

Disposition and Demographics

In total, 1,147 patients were randomized into the study, dosed with study drug and evaluable on an intent-to-treat basis, 572 receiving amisulpride and 575 placebo (fig. 1). Baseline characteristics were well balanced between the groups (table 1). More than 95% of the patients were female. Approximately half the patients received ondansetron as the standard antiemetic and half dexamethasone.

Efficacy

Complete response occurred in 57.7% (95% CI, 53.6 to 61.7%) of the amisulpride plus standard antiemetic group and 46.6% (95% CI, 42.5 to 50.7%) of the placebo plus standard antiemetic group (difference 11.1 percentage points; 95% CI, 5.3 to 16.8; $P < 0.001$) (table 2). The Kaplan–Meier plot of time to emergence of postoperative nausea and vomiting (fig. 2) showed almost immediate separation of the curves for amisulpride and placebo, sustained throughout the 24 h. For amisulpride *versus* placebo, the hazard ratio for emesis or use of rescue medication was 0.70 (95% CI, 0.59 to 0.83), with a significant increase in the time to first event ($P < 0.001$).

A benefit of amisulpride over placebo was seen in both three– and four–risk factor patients and when combined with either a corticosteroid or ondansetron (table 2). In the per-protocol population, the incidence of complete response was 59.5% in the amisulpride group and 48.2% in the placebo group ($P < 0.001$), while in the opioid population, it was 54.4% in the amisulpride group and 41.8% in the placebo group ($P < 0.001$).

Individual parameters of emesis, nausea, significant nausea, and use of rescue medication mirrored the pattern seen for complete response (table 3). The maximum severity of nausea was significantly reduced from a mean (SD) of 3.6 (3.6) in the placebo group to 2.8 (3.4) in the amisulpride group ($P < 0.001$).

Safety

The adverse event profile was generally very similar between the amisulpride and placebo groups (table 4). Serious adverse
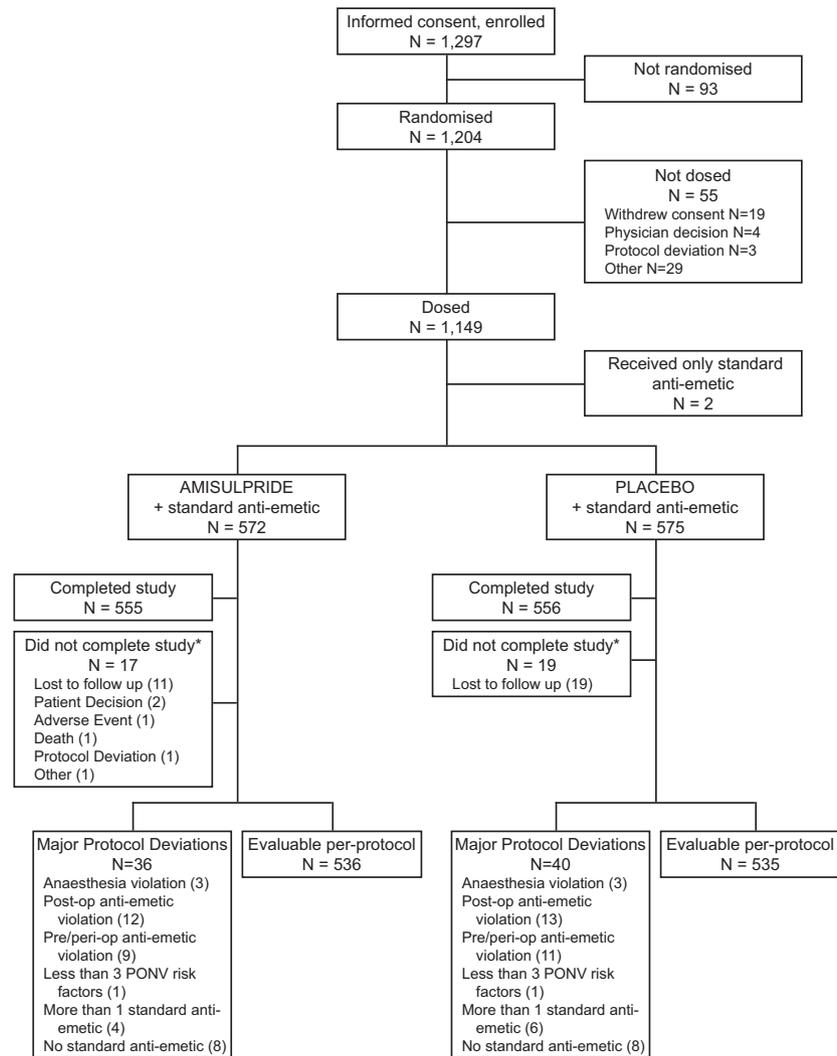
Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of subject disposition. *Day 7 follow-up data not collected. PONV = postoperative nausea and vomiting.

events, adverse events of severe or life-threatening intensity, and adverse events considered possibly or probably related to the study drug were very infrequent and occurred in similar proportions of the two treatment groups. The sole death in the study was judged unrelated to the study drug.

Vital signs and hematology and clinical chemistry parameters showed no material differences between the two groups. Electrocardiogram data also showed no clinically relevant changes. In particular, the change from baseline in QTc interval was similar, with a mean (SD) postoperative prolongation of 4.3 (32.3) ms for the amisulpride group and 6.1 (36.2) ms for the placebo group. No extrapyramidal side effects or sedation were reported in either study group.

Discussion

This study demonstrated that amisulpride given at induction of anesthesia in combination with a standard antiemetic significantly reduced the incidence of postoperative nausea and vomiting in a population of patients at high risk of postoperative nausea and vomiting undergoing a broad range of surgical operations under general anesthesia using volatile agents. The benefit of amisulpride was consistent across the individual efficacy parameters, nausea, emesis, and use of rescue medication and across all time points. Amisulpride in combination with a standard antiemetic was well tolerated and similar to placebo in respect of overall safety profile.

New antiemetics with mechanisms of action that differ from those currently used are needed because the risk of postoperative nausea and vomiting remains high in the substantial population of surgical patients with three or four risk factors.[16,17] This study corroborates previous findings that each risk factor adds around 20 percentage points to the baseline postoperative nausea and vomiting incidence, and each prophylactic antiemetic used reduces the incidence by 20 to 25%. In the control group, which received a single prophylactic antiemetic, the incidence of postoperative nausea and vomiting was 45.7% in those with three risk factors

and 63.3% in those with four. Compared to the predicted postoperative nausea and vomiting incidence in the absence of prophylaxis of 60% and 80% in a three– and four–risk factor population, respectively,[1] both results represent a relative risk reduction in the range 20 to 25%. The addition of amisulpride delivered a further relative risk reduction in a similar range: 19% in those with three risk factors and 22% in those with four.

The absolute difference in breakthrough postoperative nausea and vomiting incidence between amisulpride and placebo was somewhat higher when combined with the dexamethasone subgroup than with ondansetron. There is no

obvious mechanistic basis for a difference, nor any literature to suggest synergism between a dopamine antagonist and a steroid or conversely a reduced effect of a dopamine antagonist combined with a 5-HT_3 antagonist. On the contrary, data from the IMPACT study in more than 5,000 patients given zero, one, two, or three antiemetics strongly suggested a simple, additive relationship between 5-HT_3 antagonist, dopamine antagonist, and corticosteroid antiemetics,[6] a finding corroborated in numerous combination prophylaxis studies.[18–20] The difference seen in this study may therefore be a matter of random variation, especially given that there was considerable overlap between the 95% CIs around each difference. Alternatively, or in addition, the finding may be somewhat artefactual, relating to the composite primary endpoint. This endpoint, which incorporates emesis (vomiting/retching) and use of rescue medication, but not nausea, has been used as the standard in postoperative nausea and vomiting trials for more than 20 yr and is preferred by the Food and Drug Administration for evaluation of antiemetics. However, 5-HT_3 antagonists, such as ondansetron, have generally been found to be considerably better at preventing emesis than nausea,[3] whereas dopamine antagonists, such as droperidol, have been shown to be as good or better against nausea than emesis.[21,22] In the ondansetron subgroup of the present study, the incidence of emesis was low and very similar between amisulpride and placebo, suggesting that ondansetron was indeed effectively preventing the bulk of tractable emesis. However, in terms of significant nausea, there was a significant benefit of 10 percentage points for amisulpride plus ondansetron over placebo plus ondansetron ($P = 0.008$), which was not fully reflected in the composite primary endpoint.

One obvious limitation is that almost all patients in the study were female, and the results may therefore not be generalizable to male patients, although this is of limited significance because men are much less frequently at high risk of postoperative nausea and vomiting. Another is that this study looked only at amisulpride in combination with one other antiemetic and therefore does not provide direct evidence of any benefit when added to two or more antiemetics or indeed when used with antiemetics of classes other than 5-HT_3 antagonists and steroids. However, the IMPACT study[6] provided compelling evidence that antiemetics with different mechanisms of action exert an additive benefit, a finding corroborated in at least one trial directly comparing three antiemetics over two in the setting

Table 1. Demographic Characteristics, Risk Factors for Postoperative Nausea and Vomiting, Combination Antiemetic Administered, and Surgical Technique Used

	Amisulpride + Standard Antiemetic (N = 572)	Placebo + Standard Antiemetic (N = 575)
Age, yr, mean (SD)	49 (14)	48 (14)
Race		
White	438 (76.6%)	425 (73.9%)
Black	48 (8.4%)	58 (10.1%)
Other	7 (1.2%)	7 (1.2%)
Not reported	79 (13.8%)	85 (14.8%)
BMI, kg/m², mean (SD)	30.6 (8.8)	30.0 (8.3)
Sex, female	552 (96.5%)	557 (96.9%)
History of postoperative nausea and vomiting	227 (39.7%)	225 (39.1%)
History of motion sickness	202 (35.3%)	199 (34.6%)
Nonsmoker	516 (90.2%)	514 (89.4%)
Expected postoperative opioid use	567 (99.1%)	573 (99.7%)
Risk factors		
2	1 (0.2%)	1 (0.2%)
3	321 (56.1%)	326 (56.7%)
4	250 (43.7%)	248 (43.1%)
Standard antiemetic		
Ondansetron	285 (49.8%)	294 (51.1%)
Dexamethasone	266 (46.5%)	252 (43.8%)
Betamethasone	12 (2.1%)	21 (3.7%)
Promethazine	1 (0.2%)	0
None given	8 (1.4%)	8 (1.4%)
Surgical technique		
Laparoscopic	302 (52.5%)	291 (50.9%)
Open	273 (47.5%)	281 (49.1%)

Data are n (%) unless otherwise indicated.

Table 2. Complete Response Rates

	Amisulpride + Standard Antiemetic	Placebo + Standard Antiemetic	P Value
All patients	330/572 (57.7%) (95% CI, 53.6–61.7%)	268/575 (46.6%) (95% CI, 42.5–50.7%)	< 0.001
Ondansetron subset	147/285 (51.6%) (95% CI, 45.8–57.4%)	131/294 (44.6%) (95% CI, 38.9–50.2%)	0.045
Corticosteroid subset	180/278 (64.7%) (95% CI, 59.1–70.4%)	134/273 (49.1%) (95% CI, 41.1–53.4%)	< 0.001
Three risk factors	202/321 (62.9%) (95% CI, 57.6–68.2%)	177/326 (54.3%) (95% CI, 48.9–59.7%)	0.013
Four risk factors	127/250 (50.8%) (95% CI, 44.6–57.0%)	91/248 (36.7%) (95% CI, 30.7–42.7%)	< 0.001
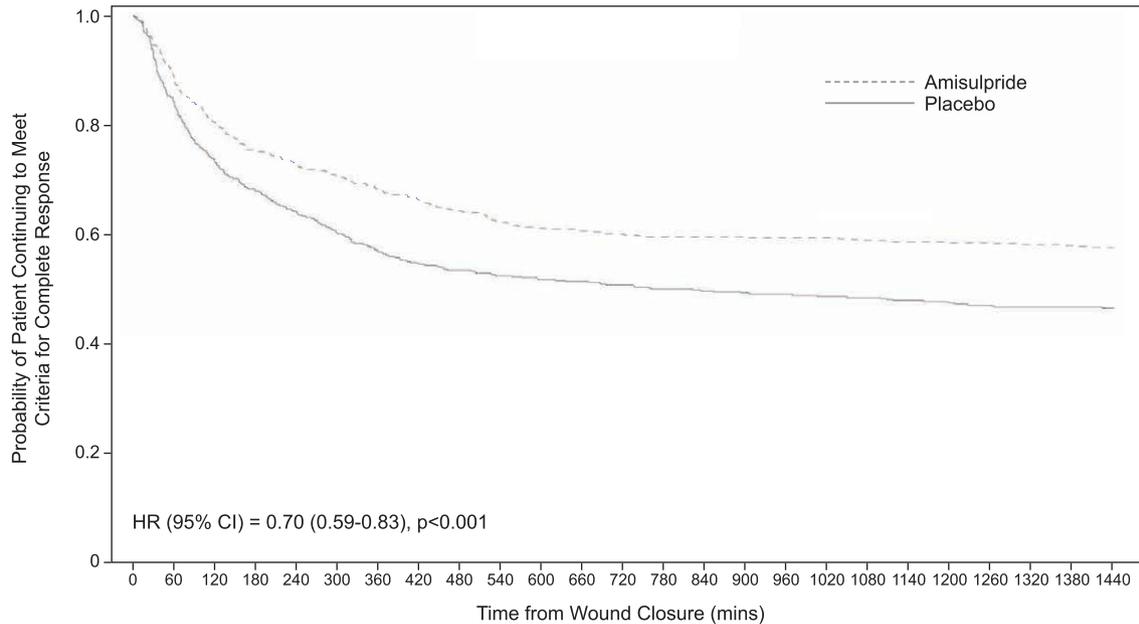
Fig. 2. Kaplan–Meier curves of complete response over time. HR = hazard ratio.

Table 3. Incidence of Secondary Efficacy Variables in 24-h Postoperative Period

	Amisulpride + Standard Antiemetic (N = 572)	Placebo + Standard Antiemetic (N = 575)	P Value
No emesis, use of rescue medication or nausea*	270 (47.2%) (95% CI, 43.1–51.3%)	217 (37.7%) (95% CI, 33.8–41.7%)	< 0.001
No emesis, use of rescue medication or significant nausea†	315 (55.1%) (95% CI, 51.0–59.2%)	246 (42.8%) (95% CI, 38.7–46.8%)	< 0.001
Emesis	79 (13.8%) (95% CI, 11.0–16.6%)	115 (20.0%) (95% CI, 16.7–23.3%)	0.003
Any nausea	286 (50.0%) (95% CI, 45.9–54.1%)	335 (58.3%) (95% CI, 54.2–62.3%)	0.002
Significant nausea	212 (37.1%) (95% CI, 33.1–41.0%)	274 (47.7%) (95% CI, 43.6–51.7%)	< 0.001
Rescue medication	234 (40.9%) (95% CI, 36.9–44.9%)	284 (49.4%) (95% CI, 45.3–53.5%)	0.002

*No nausea score of at least 1. †No nausea score of at least 4.

of postoperative nausea and vomiting.[23] Accordingly, international consensus guidelines recommend use of three antiemetics of different classes as an appropriate strategy for preventing postoperative nausea and vomiting in patients at the highest risk.[5]

Such combination pharmacotherapy ideally requires antiemetics with favorable safety profiles, and it is therefore of interest that the incidence of adverse events and laboratory and electrocardiogram abnormalities seen with IV amisulpride did not significantly differ from placebo and that no toxicities of note were observed. Of note, amisulpride was not worse than placebo in terms of QT prolongation, nor were any extrapyramidal side effects observed, allaying two of the major concerns associated with older dopamine-antagonist drugs. The number of patients experiencing at least one adverse event was lower in the amisulpride-treated group than in those receiving placebo, even with events of postoperative nausea and vomiting excluded. This suggests that a reduction

in postoperative nausea and vomiting may be associated with generally improved well-being among patients, a finding that may attest to the importance of good control of postoperative nausea and vomiting in surgical centers.

In conclusion, this large, double-blind, randomized study showed that a single 5-mg intravenous dose of amisulpride is safe and efficacious as prophylaxis of postoperative nausea and vomiting when given in combination with an antiemetic from another class to adult, surgical patients at high risk of suffering postoperative nausea and vomiting.

Research Support

Competing Interests

Dr. Fox is an employee of Acacia Pharma Ltd. (Cambridge, United Kingdom). Dr. Kranke has received consulting fees

Table 4. Treatment-emergent Adverse Events

	Amisulpride + Standard Antiemetic (N = 572)	Placebo + Standard Antiemetic (N = 575)
Number of TEAE	617	688
Number of TEAE considered related	89	109
Number of serious adverse events	29	29
Patients with:		
At least one TEAE	257 (44.9%)	303 (52.7%)
At least one TEAE considered related	61 (10.7%)	81 (14.1%)
At least one serious adverse event	20 (3.5%)	18 (3.1%)
Withdrawal due to TEAEs	1 (0.2%)	0
Death associated with TEAE	1 (0.2%)	0
At least one life-threatening TEAE	2 (0.3%)	3 (0.5%)
At least one severe TEAE	15 (2.6%)	19 (3.3%)
At least one moderate TEAE	162 (28.3%)	167 (29.0%)
At least one mild TEAE	78 (13.6%)	114 (19.8%)
TEAE occurring in >3% of patients in either group:		
Nausea*	62 (10.8%)	70 (12.2%)
Procedural pain	53 (9.3%)	58 (10.1%)
Chills	20 (3.5%)	16 (2.4%)
Procedural hypotension	20 (3.5%)	16 (2.8%)
Constipation	18 (3.1%)	18 (3.1%)
Vomiting*	15 (2.6%)	19 (3.3%)

Data are n (%) unless otherwise indicated.
*Excluding nausea or vomiting events occurring in the 24-h period after the end of surgery.
TEAE = treatment-emergent adverse events.

from Acacia Pharma. All other authors declare no competing interests.

Reproducible Science

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

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

The French Connection of Somnoforme: Rolland and Rousseau of Bordeaux

For producing analgesia or general anesthesia, the Dental School of Bordeaux's Professor Georges Rolland pioneered the use in 1901 of "Soemnoforme." A 12:7:1 mixture of ethyl chloride, methyl chloride, and ethyl bromide, respectively, this unusual anesthetic was manufactured for worldwide distribution by chemist A. Roussseau, also of Bordeaux. To reassure purchasers and frustrate his competitors, that chemist supplied markets worldwide with a green-colored glass bottle for Rolland's eclectic mixture with raised letters (*middle bottle*) reading: LE SOEMNOFORME / ANESTHESIQUE GENERAL / A. ROUSSEAU DE BORDEAUX. Listing the trademark as Soemnoforme or Somnoforme, the front label (*upper bottle*) cites members of the de Trey family as sales agents worldwide by about 1904. While fairly lauding its contents as "agreable [*sic*] and sure," the back label (*lower bottle*) listed hyperbolic claims, such as Soemnoforme: (1) could be used on nonfasting patients, (2) allowed an immediate return to consciousness, and (3) presented "none of the dangerous inconveniences…[or risk of] shock by its use." (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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